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EDITORIAL

The cruel journey through the COVID-19 INFERNO

Dante Alighieri died in 1321. His three-part masterpiece, "The Divine Comedy",[1] tells about his journey through Inferno, Purgatory and Paradise, meeting famous and symbolic personalities along the way. After 700 years, are there similarities between the Divine Comedy and our times?

The COVID-19 pandemic has dragged the whole world's population down into the Circles of Hell. At the end of his journey, Dante "*came forth to see again the stars*" whereas we are still stumbling about "*in a gloomy wood*". All are living a suspended life, marked by anxiety and anguish, experiencing personal and collective human and professional dramas. This is especially so for us health professionals who are fully aware of the situation, or supposed to be, and have the duty to maintain the "*path which leads aright*".

Like Dante, the healthcare world is still on its own journey of knowledge through the painful and difficult events and ethical dilemmas caused by COVID-19. What happened worldwide in 2020 and still is happening is a real "health hurricane" that has put overwhelming pressure on the health system with an intense ongoing healthcare demand. The huge need for hospitalizations has led to a real assault on hospitals, the only places in such a crisis that can provide care.

Patients plummet down through the hell circles of COVID-19 in a long trail that begins with initial symptoms, then the discovery of virus positivity, then serious illness, hospitalization and isolation, and the need for acute medical treatment[2] including invasive or non-invasive support.[3] And finally, if and when they survive, there is a long process to recover mobility, lung function and the capacity to swallow, health status.

One of the most despicable sins in the COVID era has been the scorn — or, even worse, the hatred — poured out against Science. In the darkest night, as a retort to the Negationists, Reductionists, No Vax and/or No Mask people, why don't we quote to them Ulysses' words: "*Bethink you of the seed whence ye have sprung; for ye were not created to lead the life of stupid animals, but manliness and knowledge to pursue*"? In contrast to the *pursuers of knowledge*, the above COVID-19 *sinners* are all well represented in Dante's Inferno by figures like the heretic *Farinata degli Uberti*, the "*workers of magic"* and the *"sowers of discord* ".

Even more dismaying, what about the so-called "No Vax doctors"? They are represented in Dante's Inferno too, e.g. by *Boniface VIII*, a pope in hell who was supposed to fight for the truth and instead. . ., or by *Count Ugolino*, a traitor to his country (Science). Not to leave out the politicians (followers, not leaders) who, like *Celestinus V*, for a fistful of votes "*through cowardice the great Refusal made*", promoting, consenting to, or not sufficiently curbing inappropriate behaviors like mass shopping or the street cocktail crowding of people like the "*injurious guilty-of-gluttony Ciacco*".

Like Dante we, the health professionals, have been compelled to descend, with our personal protective equipment,[4] down through the hell circles of material and moral bewilderment in the awareness of our fragility and often impotence to fight against the ferocious claws of this new Lucifer. However, we are not alone in our fight. We have a Virgil, a "*teacher and authority*": Science with its principles and evidence. With the support of Science, we may hope to rise up and meet *Beatrix*, a "*teacher of truth*". To achieve this target, the vast majority of the medical and scientific community is giving of its best and paying a high cost in terms of lost lives of doctors, nurses and other professionals, making great organizational efforts and investing increasing energy into research.[5—7] Speaking of Pulmonology alone, last year we received almost 200 papers on COVID-19.

The Divine Comedy is Dante's first-person recall of an unbelievable journey. *Virgil and Beatrix* (to us: an allegory of Science and Health Care) have the ability to hear Dante's thoughts and they often answer his deep, unspoken questions. Dante's journey winds its way through Purgatory and Hell to "pool" his story with that of other humans. We also need to communicate, to share and reflect on what happened and still is happening.

What did Dante Alighieri learn after his journey? He rose up reborn and purified. And what will we learn from our present journey? That we need to make a fresh start, we need to "reason" our approach to healthcare to decide new

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priorities and care paths to follow once everything has "calmed down". A reflection on these dramatic times would enable us to avoid future mistakes by organizing new healthcare paths: this is a slow, tiring and methodical process requiring observation, data collection, measurement, description, analysis and evaluation. The call to the entire scientific community is to contribute with experience and ability in order to overcome this difficult moment. The challenge is, first, to completely rethink the different health systems, considering a wide range of flexibility and the strong need to develop new models of hospital organization, home care and telemedicine.[8] Secondly, to develop a specific "Recovery Plan" for health services, strong enough to cope with the devastating impact that the COVID-19 pandemic will have on human and economic resources.[9,10]

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Declaration of competing interest

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EDITORIAL

Rehabilitative practice in Europe: Roles and competencies of physiotherapists. Are we learning something new from COVID-19 pandemic?

Rehabilitation has been recognised as an essential intervention for the management of at least 25 clinical conditions that are highly prevalent and associated with disability.[1] Estimates have shown that in 2019, 2,41 billion people had conditions that would benefit from rehabilitative treatments.[1] Rehabilitation is part of the universal health coverage to which all individuals should have access, and is it is widely acknowledged that there is an urgently need for it to be disseminated and implemented around the globe.[1–3]

Physiotherapy promotes maximum functional ability throughout the life span of the general population when movement and function are threatened by ageing, injuries, diseases, and environmental factors.[4] Physiotherapists, therefore, play a key role in providing appropriate and personalised therapies for those patients needing rehabilitation, and are a well-established professional presence around the world.

Chronic respiratory diseases and/or occurrence of respiratory symptoms such as cough and shortness of breath are already common in those conditions with the highest disability risk and burden.[1]

From early 2020, we have known how essential rehabilitative activities are in caring for patients suffering from COVID-19, as clearly outlined by recently issued recommendations.[5] The demand for rehabilitation services is, therefore, fast increasing globally.[1]

To date, 65,000 (100.7/100,000 inhabitants) physiotherapists work in Italy[6] and approximately 14,000 (140/100,000 inhabitants) in Portugal.[7] An academic training programme of three (in Italy) or four (in Portugal) years, mainly focusing on the assessment and treatment of musculoskeletal and neurological diseases leads to graduation with a bachelor's degree in physiotherapy. For physiotherapists working in the clinical area of cardiorespiratory disorders and critical care, specific post-graduate programmes of education and training exist aimed at developing advanced skills and knowledge in line with the European Respiratory Society HERMES (Harmonised Education and Training in Respiratory Medicine for European Specialists).[8] Although almost 300 physiotherapists have already obtained a post-graduate certificate in this field in Italy, an internal survey conducted by the Associazione Riabilitatori dell'Insuffcienza Respiratoria about physiotherapists' engagement during COVID-19 pandemic in the Lombardy Region have highlighted that only 4,7% of responders were skilled in respiratory physiotherapy. The scenario in Portugal is worse, with little more than 1,000 physiotherapists working in the National Health Service, of whom 909 are integrated into hospitals and 150 in primary care.[9] The exact percentage of physiotherapists specialised in cardiorespiratory field is not available, but in an online survey conducted in 2016 with 375 Portuguese physiotherapists, of 54% possessing a cardiorespiratory post-graduate course, only 15% were working in that field.[10] In 2020, a nationwide web-survey with 551 physiotherapists showed that only 18% were working with COVID-19 patients. These are the figures that constitute an essential although minimal workforce to speed up the recovery of the individual.

There is no doubt that the current global crisis has highlighted even further (1) the need for greater involvement of physiotherapists in the health care systems across all settings; (2) that the perception of physiotherapists as healthcare professionals subordinated to a medical prescription is outdated, and a movement towards greater autonomy is overdue.

Moreover, from the COVID-19 pandemic, we have learned that physiotherapists have had a clear understanding of the procedures and treatments that should be carried out since the beginning of the SARS-CoV-2 outbreak; they were also deeply involved in the genesis of relevant research and have published key documents for proper management of patients with COVID-19.[11,12] There are several likely explanations for the way these professionals have responded to the needs of the pandemic. Among these, the main ones could be summarised as follows: 1) development of specialised educational programmes, including post-graduate courses, and production of high-quality research has contributed to

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expanding the borders of physiotherapy knowledge in the last 20 years; 2) overall, in the developed countries, physiotherapists are recognised as autonomous professionals and are responsible for planning and implementing therapeutic procedures in different types of clinical conditions and in heterogeneous care settings; 3) hierarchical relationships between healthcare professions (*i.e.*, physiatrists and physiotherapists) are today only anecdotal.

Sharing evaluations of patients with acute or chronic conditions among different healthcare professionals is fundamental to optimise outcomes across all clinical settings. Pulmonologists, anaesthetists, surgeons, general practitioners and nurses, among others, often deal with physiotherapists directly. This two-way collaboration is essential for addressing the new and urgent challenges such as the critical care of patients with COVID-19.[13,14] Such collaboration will also be crucial in the future demand for rehabilitation.[1]

Therefore, there is an urgent need to raise academic and public awareness of physiotherapy and its different areas of action and settings of work. A special emphasis should also be given to increased awareness of cardiorespiratory physiotherapy in light of the current challenges being faced (*i.e.* increasing number of lifestyle-related conditions, ageing of the population, still unpredictable sequelae of COVID-19).

The recent experience with the pandemic has taught all of us that interdisciplinary teams, in which all members are equally recognized, are strategic structures for addressing such an unprecedented situation. Recognising physiotherapists as autonomous professionals, with the freedom to exercise their professional judgement and decision making, within their knowledge, competence and scope of practice, is crucial for optimisation of patients' rehabilitative outcomes.

Consent to publish data

Not applicable

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Conflicts of interest

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ORIGINAL ARTICLE

The effects of hidden female smokers on the association between smoking and chronic obstructive pulmonary disease in Korean adults

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KEYWORDS
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Abstract
Objective: Smoking is an important causative factor of chronic obstructive pulmonary disease (COPD), and females are considered more susceptible to the effects of smoking than males. However, in previous Korean studies, the effects of sex differences on the association between smoking and COPD have been controversial. In this study, the effects of sex differences on the association between smoking and COPD and the effects of female hidden smokers on that association in Korean adults were investigated.
Methods: Data were acquired from the Korea National Health and Nutrition Examination Surveys (KNHANES).
Results: The multivariate logistic regression analysis showed that self-reported smoking status for ex-smoker and current smoker correlated with COPD (odds ratio, OR: 1.67 and OR: 2.41, respectively). Self-reported smoking status for ex-smoker and current smoker correlated with COPD in men (OR: 1.61, OR: 2.43, respectively). Female self-reported current smoking status correlated with COPD (OR: 2.52), but female ex-smoker status was not significantly correlated with COPD. The ratios of cotinine-verified to self-reported smoking rates were 1.95 for women and 1.07 for men.

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Conclusion: The results of this study were that sex differences might affect the association between COPD and smoking and that female hidden smoking might affect the association between smoking and COPD in Korean adults.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality[1] and the economic burden of COPD is increasing.[2]

Smoking is the most important causative factor of COPD. However, while more than 4000 chemical substances contained in a cigarette have adverse effects on various pulmonary diseases, the pathophysiological mechanisms underlying the association between smoking and COPD have not been fully elucidated.[3]

The effects of gender on COPD are well known, and women are widely considered more susceptible to the effects of smoking than men.[4,5] The suggested reasons for the increased susceptibility of women to the effects of smoking include a smaller airway size compared with men[6] and female sex hormone-mediated metabolism differences.[7]

In a Norwegian study, more women were current smokers. The authors hypothesized that females were more susceptible to the lung damaging effects of cigarette smoking.[4] In other studies based on larger reductions in forced expiratory volume in 1 second (FEV1) and after adjustment for smoking intensity, female smokers were shown to develop COPD more often than male smokers.[8,9]

However, the effects of sex on the association between current smoker status and COPD in Korean adults are controversial. In a community-based cohort Korean study, current smoker status was significantly associated with COPD in men (risk ratio, RR: 2.28, 95% confidence interval, CI: 1.86–2.80) and in women (RR: 4.04, 95% CI: 2.84–5.75).[10] However, in another population sample-based study in which a non-smoking group of Korean adults was used for comparison, the odds ratio (OR, 95% CI) for COPD in the current smoker group was 3.49 (2.44–5.00) in men and 3.45 (2.20–5.40) in women.[11]

In addition, one previous study showed the ratios of cotinine-verified to self-reported smoking rates were 2.36 for females and 1.12 for males in Korea,[12] and another study showed the effects of female hidden smoking on the association between smoking and hypertension in Korean adults.[13]

Therefore, in this study, we investigated the effects of sex differences on the association between smoking and COPD and the effects of female hidden smoking on the association between smoking and COPD in Korean adults.

Methods

Study population

This study was based on data obtained from the 2008 to 2016 Korea National Health and Nutrition Examination Surveys (KNHANES), a cross-sectional survey designed to examine the health and nutritional status of the non-institutionalized Korean population and conducted by the Division of Chronic Disease Surveillance at the Korea Centers for Disease Control and Prevention (KCDC).

The study included 76,909 KNHANES participants; 62,552 participants were excluded due to the following criteria: <40 years of age, no smoking history, no COPD information, no urine cotinine test results, no weights for the results of pulmonary function test, history of renal failure, or serum creatinine $\geq$1.5 mg/dL. The remaining 14,357 participants (6424 males and 7933 females) were included in the final analysis.

General characteristics, anthropometry, and laboratory tests

KNHANES includes well-established questions to determine the demographic and socioeconomic characteristics of the participants. The questions include sex, age, marital status, employment status, educational level, monthly family income, number of household members, residential area, body mass index (BMI), hypertension, diabetes, myocardial infarction, and stroke. The residential areas of respondents were categorized as urban (an administrative division of a city) or rural (not classified as an administrative division of a city). A city in Korea was defined as an area with >50,000 inhabitants. Monthly family income represents monthly equalized family income and was calculated by dividing the total family income by the square root of the number of household members. In KNHANES, monthly family income is classified into quartiles to determine the monthly household income level (1: low, 2: middle low, 3: middle high, and 4: high). Educational levels were defined as less than middle school, middle school, high school, or college or more. BMI was calculated as weight (kg) divided by height squared (m^2) and was categorized into three groups: underweight (<18.5 kg/m^2), normal (18.5–23 kg/m^2), and overweight ($\geq$23 kg/m^2).[14]

Table 1 Definition of survey cotinine-verified smoking status.

	Cotinine-verified smoking status	
	Non-smoker ($\leq$50 ng/mL)	Current smoker (>50 ng/mL)
Self-reported smoking status		
Non-smoker	Non-smoker (n = 8,289)	Current smoker (n = 317)
Ex-smoker	Ex-smoker (n = 2,919)	Current smoker (n = 207)
Current smoker	Current smoker (n = 65)	Current smoker (n = 2,560)

Cigarette smoking status was divided into three categories: smoker, ex-smoker, and never smoker. Respondents who reported having smoked $\geq$100 cigarettes in their lifetime or responded ''yes'' to the question, ''Do you smoke cigarettes now?'' were regarded as current smokers. Participants answering ''no'' to the same question were classified as ex-smokers. Respondents who consumed <100 cigarettes in their lifetime were regarded as never smokers.

Urinary cotinine was measured using tandem mass spectrometry (tandem mass API 4000; Applied Biosystems, Carlsbad, CA, USA) and gas chromatography/mass spectrometry (Perkin Elmer Clarus 600T; PerkinElmer, Turku, Finland). Respondents with urinary cotinine levels $\geq$50 ng/mL were considered cotinine-verified smokers, and those with cotinine levels <50 ng/mL were cotinine-verified non-smokers.[15]

COPD was defined as FEV1/forced vital capacity (FEV1/FVC, % FEV1) <0.7 on pulmonary function test in subjects >40 years of age. Hypertension was defined as elevated blood pressure (BP; systolic BP, SBP $\geq$140 mmHg and/or diastolic BP, DBP $\geq$90 mmHg) or taking anti-hypertensive medication. Diabetes was defined as fasting blood glucose (FBG) of 126 mg/dL or a diabetes diagnosis from a physician and taking diabetes medication or starting insulin therapy.

To better understand the link between COPD and smoking, a new variable was used to define smoking status (survey cotinine-verified smoking status, SCS; Table 1). In using this variable, we assumed smoking meant all kinds of smoking types, including light smoking, intermittent smoking, passive smoking, hidden smoking, and active heavy smoking (Table 1).

Statistical analysis

All statistical analyses were conducted using SPSS complex sample procedures because KNHANES data were collected through a representative, stratified, and clustered sampling method. Multivariate logistic regression analysis was performed to identify the relationships between risk factors and the prevalence of COPD. Multivariate logistic regression analysis was also used to evaluate the relationship between self-reported and cotinine-verified smoking status and the presence of COPD. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc. Chicago, IL, USA). For all analyses, p-values were two-tailed; a p-value <0.05 was considered statistically significant.

Results

Clinical characteristics

A total of 14,357 subjects from the KNHANES were included in this study. Mean age was 57.11 $\pm$ 10.71 years. The majority of participants were married (85.06%), employed (64.86%), and had an educational level of high school or less (74.16%). Most subjects lived in urban areas (80.21%; Table 2). The prevalence of self-reported smoking was 21.82% and the prevalence of cotinine-verified smoking in the overall population was 25.14% (Table 2).

Relationship between COPD and smoking

Based on univariate analysis, compared to subjects without COPD, subjects with COPD tended to be male (p < 0.01), older (p < 0.01), single (separated or divorced; p < 0.01), unemployed (p < 0.01), less educated (p < 0.01), and obese (p < 0.01). Those with COPD had a lower monthly family income (p < 0.01), had fewer household members (p < 0.01), lived in a rural setting (p < 0.01), were over or underweight (p < 0.01), and had higher prevalence of hypertension (p < 0.01) and diabetes (p < 0.01) compared to subjects without COPD.

Multivariate logistic regression analysis showed that for self-reported smoking status, ex-smoker and current smoker status correlated with COPD (OR: 1.67, 95% CI: 1.34–2.07 and OR: 2.41, 95% CI: 1.92–3.01, respectively). In addition, current smoking status correlated with COPD based on cotinine-verified smoking status (OR: 1.68, 95% CI: 1.44–1.95); ex-smoker status and current smoker status correlated with COPD in SCS (OR: 1.60, 95% CI: 1.29–1.99 and OR: 2.23, 95% CI: 1.81–2.75, respectively; Table 3).

To determine the effects of sex on smoking and COPD, sex differences were analyzed separately. For male participants, self-reported ex-smoker and current smoker status correlated with COPD (OR: 1.61, 95% CI: 1.25–2.07 and OR: 2.43, 95% CI: 1.86–3.18, respectively). Based on cotinine-verified smoking status, current smoker status correlated with COPD (OR: 1.65, 95% CI: 1.40–1.96), and, based on SCS, ex-smoker and current smoker status correlated with COPD (OR: 1.58, 95% CI: 1.22–2.05 and OR: 2.29, 95% CI: 1.76–2.99, respectively). Self-reported and SCS-based current smoker status in women also correlated with COPD (OR: 2.52, CI: 1.66–3.83 and OR: 2.13, 95% CI: 1.51–3.02, respectively). However, self-reported and SCS-based ex-smoker status were not significantly correlated with COPD.

Table 2 Demographic characteristics of study subjects.

Characteristics	Sample size	Estimate % (95% CI)
Sex (*n* = 14,357)		
Male	6,424	49.60 (48.79–50.41)
Female	7,933	50.40 (49.59–51.21)
Age (years; *n* = 14,357)		
40–49	4,187	35.75 (34.60–36.91)
50–59	4,432	31.25 (30.24–32.28)
60–69	3,644	19.79 (18.98–20.61)
≥70	2,094	13.22 (12.45–14.02)
Marital status (*n* = 14,276)		
Married	11,943	85.06 (84.23–85.86)
Single (separated or divorced)	2,104	12.78 (12.07–13.52)
Never married	229	2.16 (1.85–2.51)
Employment status (*n* = 14,088)		
Employed	8,805	64.86 (63.74–65.96)
Unemployed	5,283	35.14 (34.04–36.26)
Educational level (*n* = 14,084)		
<High school	6,345	41.04 (39.65–42.45)
High school	4,393	33.12 (32.06–34.19)
>High school	3,346	25.84 (24.48–27.25)
Monthly family income (*n* = 14,234)		
<25th	2,882	18.53 (17.52–19.58)
25–50th	3,645	24.97 (23.90–26.06)
50–75th	3,625	26.91 (25.82–28.02)
≥75th	4,082	29.60 (28.13–31.11)
Number of household members (*n* = 14,352)		
1	1,314	6.58 (6.08–7.12)
2	4,864	28.87 (27.86–29.91)
3	3,349	24.48 (23.51–25.47)
4	3,261	26.94 (25.84–28.08)
≥5	1,564	13.12 (12.26–14.03)
Residential area (*n* = 14,357)		
Urban	10,973	80.21 (77.84–82.39)
Rural	3,384	19.79 (17.61–22.16)
Smoking status		
Self-reported (n = 14,357)		
Non-smoker	8,606	55.84 (54.93–56.75)
Ex-smoker	3,126	22.33 (21.57–23.12)
Current smoker	2,625	21.82 (20.97–22.70)
Cotinine-verified (n = 14,357)		
Non-smoker	11,273	74.86 (73.95–75.76)
Current smoker	3,084	25.14 (24.24–26.05)
Survey cotinine-verified (n = 14,357)		
Non-smoker	8,289	53.52 (52.60–54.44)
Ex-smoker	2,919	20.80 (20.04–21.58)
Current smoker	3,149	25.68 (24.78–26.61)
BMI (*n* = 14,344)		
<18.5	133	0.89 (0.72–1.09)
18.5–23	5,016	34.58 (33.61–35.58)
≥23	9,195	64.53 (63.53–65.51)
Hypertension (*n* = 14,167)	5,509	37.80 (36.77–38.85)
Diabetes (*n* = 13,592)	1,851	13.19 (12.51–13.90)
COPD (*n* = 14,357)	2,006	13.08 (12.42–13.77)

Table 3 Adjusted OR and 95% CI for the prevalence of COPD.

Characteristics	Self-reported	Cotinine-verified	Survey cotinine-verified
Sex			
Male	3.29 (2.63–4.12)	4.68 (3.97–5.53)	3.50 (2.83–4.32)
Female	Reference	Reference	Reference
Age (years)			
40–49	Reference	Reference	Reference
50–59	2.42 (1.91–3.07)	2.42 (1.91–3.07)	2.43 (1.92–3.08)
60–69	6.19 (4.76–8.04)	6.22 (4.79–8.09)	6.19 (4.76–8.05)
≥70	11.84 (8.94–15.70)	11.84 (8.94–15.69)	11.82 (8.91–15.68)
Marital status			
Married	Reference	Reference	Reference
Single (separated or divorced)	1.14 (0.90–1.44)	1.17 (0.93–1.47)	1.14 (0.91–1.45)
Never married	0.96 (0.53–1.74)	0.96 (0.53–1.73)	0.98 (0.54–1.77)
Employment status			
Employed	Reference	Reference	Reference
Unemployed	1.09 (0.94–1.27)	1.11 (0.95–1.29)	1.09 (0.94–1.27)
Educational level			
<High school	1.54 (1.25–1.90)	1.56 (1.27–1.92)	1.54 (1.25–1.90)
High school	1.19 (0.97–1.47)	1.22 (0.99–1.50)	1.20 (0.97–1.47)
>High school	Reference	Reference	Reference
Monthly family income			
<25th	1.12 (0.90–1.40)	1.10 (0.88–1.37)	1.11 (0.89–1.39)
25–50th	1.02 (0.82–1.27)	1.02 (0.82–1.26)	1.02 (0.82–1.26)
50–75th	1.07 (0.88–1.31)	1.06 (0.87–1.30)	1.06 (0.87–1.30)
≥75th	Reference	Reference	Reference
Number of household members			
1	1.01 (0.73–1.39)	1.03 (0.75–1.42)	1.02 (0.74–1.40)
2	1.06 (0.84–1.35)	1.08 (0.85–1.37)	1.06 (0.84–1.35)
3	1.11 (0.86–1.44)	1.12 (0.86–1.44)	1.10 (0.85–1.43)
4	0.98 (0.75–1.29)	0.99 (0.75–1.29)	0.98 (0.75–1.28)
≥5	Reference	Reference	Reference
Residential area			
Urban	Reference	Reference	Reference
Rural	1.02 (0.87–1.20)	1.01 (0.86–1.19)	1.02 (0.87–1.19)
Smoking status			
Self-reported			
Non-smoker	Reference	–	–
Ex-smoker	1.67 (1.34–2.07)	–	–
Current smoker	2.41 (1.92–3.01)	–	–
Cotinine-verified			
Non-smoker	–	Reference	–
Current smoker	–	1.68 (1.44–1.95)	–
Survey cotinine-verified			
Non-smoker	–	–	Reference
Ex-smoker	–	–	1.60 (1.29–1.99)
Current smoker	–	–	2.23 (1.81–2.75)
BMI			
<18.5	1.24 (0.77–1.98)	1.28 (0.81–2.03)	1.25 (0.79–1.99)
18.5–23	Reference	Reference	Reference
≥23	0.72 (0.62–0.83)	0.72 (0.63–0.84)	0.72 (0.62–0.83)
Hypertension			
No	Reference	Reference	Reference
Yes	0.94 (0.83–1.08)	0.94 (0.82–1.07)	0.94 (0.82–1.08)
Diabetes			
No	Reference	Reference	Reference
Yes	1.04 (0.87–1.23)	1.05 (0.88–1.25)	1.04 (0.88–1.24)

Table 4 Adjusted OR and the associated 95% CI for the prevalence of COPD in males.

Characteristics	Self-reported	Cotinine-verified	Survey cotinine-verified
Age (years)			
40–49	Reference	Reference	Reference
50–59	2.61 (1.98–3.44)	2.60 (1.98–3.42)	2.62 (1.99–3.45)
60–69	7.06 (5.18–9.61)	7.04 (5.19–9.54)	7.02 (5.16–9.54)
≥70	14.52 (10.27–20.53)	14.21 (10.11–19.98)	14.40 (10.19–20.33)
Marital status			
Married	Reference	Reference	Reference
Single (separated or divorced)	1.11 (0.74–1.66)	1.14 (0.76–1.70)	1.12 (0.75–1.68)
Never married	1.24 (0.64–2.40)	1.24 (0.64–2.38)	1.27 (0.66–2.44)
Employment status			
Employed	Reference	Reference	Reference
Unemployed	1.18 (0.96–1.45)	1.21 (0.99–1.48)	1.18 (0.96–1.44)
Educational level			
<High school	1.60 (1.27–2.02)	1.62 (1.29–2.05)	1.59 (1.26–2.01)
High school	1.23 (0.97–1.55)	1.26 (1.01–1.59)	1.23 (0.98–1.55)
>High school	Reference	Reference	Reference
Monthly family income			
<25th	1.24 (0.94–1.63)	1.21 (0.91–1.59)	1.23 (0.93–1.62)
25–50th	1.04 (0.80–1.34)	1.03 (0.79–1.33)	1.03 (0.80–1.34)
50–75th	1.13 (0.89–1.43)	1.12 (0.89–1.42)	1.13 (0.89–1.42)
≥75th	Reference	Reference	Reference
Number of household members			
1	0.66 (0.41–1.06)	0.66 (0.41–1.06)	0.66 (0.41–1.06)
2	0.93 (0.70–1.23)	0.94 (0.70–1.25)	0.93 (0.69–1.23)
3	0.95 (0.70–1.29)	0.96 (0.70–1.30)	0.95 (0.70–1.29)
4	0.97 (0.70–1.34)	0.97 (0.70–1.34)	0.97 (0.70–1.34)
≥5	Reference	Reference	Reference
Residential area			
Urban	Reference	Reference	Reference
Rural	1.03 (0.85–1.24)	1.02 (0.85–1.24)	1.03 (0.85–1.24)
Smoking status			
Self-reported			
Non-smoker	Reference	–	–
Ex-smoker	1.61 (1.25–2.07)	–	–
Current smoker	2.43 (1.86–3.18)	–	–
Cotinine-verified			
Non-smoker	–	Reference	–
Current smoker	–	1.65 (1.40–1.96)	–
Survey cotinine-verified			
Non-smoker	–	–	Reference
Ex-smoker	–	–	1.58 (1.22–2.05)
Current smoker	–	–	2.29 (1.76–2.99)
BMI			
<18.5	1.16 (1.25–2.07)	1.20 (0.67–2.13)	1.17 (0.65–2.08)
18.5–23	Reference	Reference	Reference
≥23	0.83 (0.69–0.99)	0.83 (0.70–0.99)	0.82 (0.69–0.99)
Hypertension			
No	Reference	Reference	Reference
Yes	1.00 (0.85–1.18)	0.99 (0.84–1.17)	0.99 (0.84–1.17)
Diabetes			
No	Reference	Reference	Reference
Yes	1.10 (0.90–1.36)	1.12 (0.91–1.38)	1.11 (0.90–1.36)

Table 5 Adjusted OR and 95% CI for the prevalence of COPD in females.

Characteristics	Self-reported	Cotinine-verified	Survey cotinine-verified
Age (years)			
40–49	Reference	Reference	Reference
50–59	1.92 (1.23–3.02)	1.91 (1.21–3.02)	1.92 (1.22–3.03)
60–69	4.39 (2.76–6.98)	4.39 (2.72–7.08)	4.44 (2.75–7.15)
≥70	7.71 (4.68–12.70)	7.73 (4.63–12.92)	7.79 (4.67–13.02)
Marital status			
Married	Reference	Reference	Reference
Single (separated or divorced)	1.32 (0.98–1.78)	1.33 (0.99–1.79)	1.32 (0.98–1.78)
Never married	0.28 (0.06–1.33)	1.30 (0.06–1.42)	0.29 (0.06–1.38)
Employment status			
Employed	Reference	Reference	Reference
Unemployed	0.93 (0.74–1.17)	0.93 (0.74–1.17)	0.93 (0.74–1.17)
Education			
<High school	1.45 (0.93–2.26)	1.45 (0.94–2.26)	1.45 (0.93–2.26)
High school	0.97 (0.60–1.56)	0.97 (0.60–1.57)	0.97 (0.60–1.57)
>High school	Reference	Reference	Reference
Monthly family income			
<25th	0.80 (0.54–1.17)	0.79 (0.53–1.16)	0.78 (0.53–1.15)
25–50th	0.86 (0.60–1.25)	0.86 (0.59–1.24)	0.86 (0.59–1.24)
50–75th	0.86 (0.58–1.27)	0.85 (0.57–1.26)	0.85 (0.57–1.26)
≥75th	Reference	Reference	Reference
Number of household members			
1	1.74 (1.01–2.99)	1.78 (1.03–3.08)	1.77 (1.02–3.05)
2	1.39 (0.86–2.26)	1.41 (0.86–2.29)	1.40 (0.86–2.28)
3	1.52 (0.92–2.52)	1.51 (0.91–2.49)	1.51 (0.91–2.50)
4	0.99 (0.59–1.68)	0.99 (0.59–1.68)	0.99 (0.59–1.68)
≥5	Reference	Reference	Reference
Residential area			
Urban	Reference	Reference	Reference
Rural	1.01 (0.78–1.31)	0.98 (0.75–1.27)	0.99 (0.77–1.28)
Smoking status			
Self-reported			
Non-smoker	Reference	–	–
Ex-smoker	1.63 (0.94–2.85)	–	–
Current smoker	2.52 (1.66–3.83)	–	–
Cotinine-verified			
Non-smoker	–	Reference	–
Current smoker	–	2.11 (1.49–2.98)	–
Survey cotinine-verified			
Non-smoker	–	–	Reference
Ex-smoker	–	–	1.49 (0.80–2.79)
Current smoker	–	–	2.13 (1.51–3.02)
BMI			
<18.5	1.26 (0.66–2.39)	1.30 (0.68–2.45)	1.29 (0.68–2.45)
18.5–23	Reference	Reference	Reference
≥23	0.54 (1.66–3.83)	0.55 (0.43–0.70)	0.55 (0.43–0.70)
Hypertension			
No	Reference	Reference	Reference
Yes	0.86 (0.68–1.09)	0.86 (0.68–1.09)	0.86 (0.68–1.09)
Diabetes			
No	Reference	Reference	Reference
Yes	0.89 (0.63–1.27)	0.89 (0.63–1.26)	0.89 (0.63–1.26)

Based on cotinine-verified smoking status, current smoker was associated with COPD (OR: 2.11, 95% CI: 1.49–2.98; Tables 4 and 5).

Discussion

The main findings of this study were that ex-smoker and current smoker status were significantly associated with COPD in the overall population. In addition, sex effects were observed as well as an effect of female hidden smokers on the relationship between smoking and COPD in Korean adults.

The effects of sex on COPD are well established, and females are widely considered more susceptible to the effects of smoking than males.[4,5] There are several hypotheses that explain sex-related variation in COPD prevalence. First, women may experience greater exposure to cigarette smoke due to possessing smaller airways than men.[6] Second, female sex hormones may contribute to oxidative stress and, eventually, greater airway injury. During smoking, numerous smoking chemicals are metabolized in two phases. Phase I is mediated largely by cytochrome P450 (CYP) enzymes; these are responsible for detoxifying cigarette smoke into intermediate metabolites. Subsequently, these metabolites are conjugated by phase II enzymes and excreted. Because several intermediate metabolites are toxic, estradiol upregulates CYP enzymes without necessarily altering the expression of phase II enzymes. This causes the female lungs to be more susceptible to oxidant damage in response to cigarette smoke.[7,16]

Compared with other previous foreign studies, the results in previous Korean studies regarding the effects of sex on the association between current smoking status and COPD were controversial.[4,8–11] In a community-based cohort Korean study, current smoking was significantly associated with COPD in males (RR: 2.28, 95% CI 1.86–2.80) and in females (RR: 4.04, 95% CI 2.84–5.75).[10] However, in another population sample-based study, results showed that, compared with a non-smoking group of Korean adults, the OR (95% CI) for COPD in the current smoker group was 3.49 (2.44–5.00) in men and 3.45 (2.20–5.40) in women.[11]

Consistent with a previous study using similar data (2008–2016 KNHANES in this study and 2007–2015 KNHANES in the previous Korean study), we did not find sex differences in the association between COPD and current smoking.[11] In our study, male self-reported and cotinine-verified current smoking status were correlated with COPD (OR: 2.43, 95% CI: 1.86–3.18 and OR: 1.65, 95% CI: 1.40–1.96, respectively) and female self-reported and cotinine-verified current smoking status also correlated with COPD (OR: 2.52, 95% CI: 1.66–3.83 and OR: 2.11, 95% CI: 1.49–2.98, respectively).

Interestingly, in the association between COPD and ex-smoking, this study and previous studies showed ex-smoking was associated with COPD in men and not in women.[10,11]

We assumed the different effects of sex differences between COPD and current smoking in two previous studies might be due to selection bias associated with the sampling of different groups.[10,11] One study used a region-based sample, while the other used a nationally representative sample.[10,11]. In addition, a previous Korean study reported large geographic variation in the prevalence of COPD in Korea and emphasized the importance of nationally representative sampling.[17,18]

In a previous study, a significant number of female hidden smokers in Korea was reported compared with other countries.[12] Similar results were observed in this study. One hypothesis suggests that self-reported smoking in Korean females underestimates the true prevalence as a result of Confucianism. The adoption of Confucianism can result in a patriarchal culture in which female smoking is stigmatized.[19]

In a previous Korean study, the ratios of cotinine-verified to self-reported smoking rates were 2.36 for women and 1.12 for men,[12] indicating that women are more likely than men to be hidden smokers. Conversely, in a study from other countries, sex differences in underreporting the rate of past or present smoking was not observed.[20,21]

In this study, the ratios of cotinine-verified to self-reported smoking rates were 1.95 (632/325) for women and 1.07 (2452/2300) for men. These rates were similar to the findings in a previous Korean study.[12] Sex differences in underreporting the rate of past or present smoking were observed in this study: a greater number of hidden smokers were women. The discrepancy in the underreporting rates between the sexes could lead to statistical issues. In addition, a larger effect of hidden smokers was found in the association between COPD and smoking in females. In male participants, the adjusted OR for self-reported current smoking associated with COPD was 2.43 (95% CI: 1.86–3.18) and 2.29 (95% CI: 1.76–2.99) based on SCS. In women, the adjusted OR for self-reported current smoking status associated with COPD was 2.52 (95% CI: 1.66–3.83) and 2.13 (95% CI: 1.51–3.02) based on SCS.

The results from this study showed the risk of COPD associated with current smoking was lower in Korean adults than in those of other nationalities.[22,23] One hypothesis is that this result was due to different lung functions and genetic polymorphisms among nationalities.[22] In this study, an association between ex-smoker and COPD was observed; however, the association was not significant in women. These results might be due to lower amount of smoking by women than men, which was similar to results reported in a previous Korean study.[11,22]

Light and social smokers are often not detected because many of these individuals are self-reported non-smokers.[24,25] Recently, a report was published showing that light smoking was associated with COPD and amount of smoking was associated with progressively higher risk of COPD than never smoking.[22]

To better understand the association between COPD and smoking, a new variable, SCS, was used in this study to evaluate the effects of hidden smoking and other types of smoking. This new variable showed similar results compared with self-reported smoking status. Therefore, passive and light smoking may affect COPD development similar to active smoking.

Parental smoking was a major risk factor for second-hand smoke exposure in children; and maternal, not paternal, smoking was known as a risk factor for decreased lung function and COPD in children.[26–28] However, because there are many hidden female smokers in Korea, maternal hidden smokers should be considered when determining the impact of maternal smoking on lung function in Korean children.

This study had several limitations. First, because this study was based on a survey, selection and recall biases may have existed. Second, because this study was cross-sectional in design, the causal relationship between smoking and COPD could not be confirmed. Finally, potential confounding factors, including amount and duration of smoking, diet patterns, and genetic variations affecting nicotine metabolism were not evaluated. Further prospective studies are needed to clarify the effects of hidden female smokers on COPD by country.

However, the notable strength of our study is the use of national and widely sampled data to assess sex-specific relationships between smoking status and COPD. The other strength is the evaluation of the effects of sex and hidden smokers on the relationship between smoking and COPD.

Conclusions

This large population-based cross-sectional study showed that sex differences might affect the association between COPD and smoking status. Depending on country, hidden female smokers should be considered in the study on the relationship between smoking and COPD.

Authors' contributions

Ju Suk Lee conceived and supervised all aspects of this study. Hye Sung Ock contributed to the concept of study and wrote the final version of this manuscript. Sang Won Hwang analyzed data and contributed to design of our study. Hae Jeong Lee, Cheol Hong Kim, and Sung Hoon Kim collected data. Tae Hong Kim and Jun Hwa Lee collected data and carried out statistical analysis.

Conflict of interests

The authors have no commercial relationships or potential conflicts of interest to declare.

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ORIGINAL ARTICLE

The role of interventional bronchoscopy in the management of post-intubation tracheal stenosis: A 20-year experience

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KEYWORDS
Benign tracheal stenosis;
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Abstract
Purpose: Benign tracheal stenosis management is still controversial, and there is no international consensus on the best treatment option. Thus, we aimed to look into the history of PITS and the different strategies used in its treatment. The importance of bronchoscopic treatment was also defined, and its effectiveness and safety were assessed.
Methods: Retrospective study of patients diagnosed with PITS, who were referred to the Bronchology Department between January 1996 and December 2016.
Results: Of 115 patients enrolled (mean age 48.5 ± 17.6 years, 53% males), 66.1% had complex stenosis. The most common causes of intubation were respiratory (29.9%), neurological (26.8%) and surgical (19.6%). Complex stenosis was caused by longer intubation, and was more frequent among previously tracheostomized patients. The most common location was the upper third of trachea (60.9%). Most cases were initially treated by interventional bronchoscopy, and although serial dilations were effective in some complex PITS, a higher proportion of simple stenosis was successfully managed with this treatment option. Long-term recurrence after serial dilation was observed in 25.0% of cases. Stent placement was required (19.1%) only for complex PITS. Stent-related complications were frequent (61.9%) and linked to the stenting time ($p < 0.001$). Overall, there were no procedure-related complications. Surgical intervention was also performed (30.0%), always with complex PITS. Post-surgical recurrences were observed in 24.2% of cases.

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Conclusions: Interventional bronchoscopy is an efficient and safe modality in PITS management. Further studies are needed for better classification and improved knowledge of PITS pathogenesis, and to achieve international consensus of definition to guide clinicians in their practice.

Introduction

Benign tracheal stenosis is a debilitating and potentially life-threatening condition that, in most cases, is caused by iatrogenic events as a result of endotracheal intubation and tracheostomy.[1] The management of post-intubation tracheal stenosis (PITS) is still controversial and there is no international consensus about the best treatment option.[2] Surgical resection of the affected trachea followed by anastomosis is considered the definitive treatment for this condition.[1–3] Although surgery is still considered the first treatment option, especially in complex stenosis,[2,4] interventional bronchoscopy has shown promising results in selected patients with simple stenosis.[5] In fact, some authors have proposed bronchoscopic treatment as an alternative to surgery for patients who were not eligible and those awaiting surgery.[2,6,7] Moreover, recent data demonstrated the crucial role of bronchoscopic approach in the management of benign tracheal stenosis and suggests that, after a correct stenosis classification and careful patient selection, this treatment modality may represent a definitive strategy in most cases.[4,8,9]

In this context, the aim of the present study was to investigate how PITS has evolved and the several strategies used in its treatment, to define the importance of bronchoscopic treatment and to evaluate its effectiveness and safety among PITS patients.

Materials and methods

A retrospective study was performed including patients diagnosed with PITS referred to the Bronchology Department of Centro Hospitalar e Universitário de São João (CHUSJ), a tertiary hospital in Porto, Portugal between January 1996 and December 2016. Demographic and clinical data were reviewed. This study had the approval of the Ethics Committee of CHUSJ.

PITS evaluation and treatment decision

When a PITS was suspected (Fig. 1), patients underwent a flexible bronchoscopy to diagnose and evaluate stenosis characteristics, which are location, vertical extension and severity of obstruction and stenosis classification as simple or complex. A thoracic and cervical computer tomography (CT) was performed in non-emergency cases to help classification. Simple PITS were defined as web-like lesions with <1 cm in vertical extension, whereas complex ones were lesions with >1 cm in extension and/or with tracheomalacia or cartilage involvement.[10]

After stenosis assessment, symptomatic patients or those with >50% of airway obstruction were intubated with a rigid bronchoscope (RB) (Karl Storz, Tuttlingen, Germany). Patients with simple PITS underwent mechanical dilation using increasing RB sizes as the first treatment option, and a balloon, when appropriate. A diode laser (Multidiode endolaser 30, Intermedic Arfran, Barcelona, Spain) was used in selected cases for granulation tissue ablation and to assist mechanical dilation using the spare mucosal technique.[5]

Patients with complex PITS were always considered for surgical resection of the affected trachea and further end-to-end anastomosis.[11] Patients ineligible for surgery (severe comorbidities or more than 4 cm length) or symptomatic patients waiting for surgery underwent bronchoscopic treatment. In complex PITS, if dilation was ineffective ($\geq$50% of obstruction after procedure), a silicone stent (Novatech, La Ciotat, France) was placed as described by Dumon.[12]

Patients were regularly and exclusively followed-up in our department, according to their clinical status (Fig. 1), and were able to contact the team if symptomatic. In every visit a clinical assessment was performed and if symptoms or signs related with stenosis recurrence developed, a new bronchoscopic evaluation and appropriate treatment were performed. In patients whose stenosis was managed with a silicone stent, the stent removal decision was individualized for each case according to subsequent bronchoscopic evaluations. When stent-related complications occurred and the airway patency was reasonable (at least less than 50% of residual obstruction) after stent removal, the patient remained without stent. Otherwise, a new silicone stent was placed. The stenosis was considered solved when there was no recurrence after 12 months from the last intervention. After that, if any additional intervention was necessary, it was considered a long-term recurrence.[4]

Statistical analysis

Categorical and continuous variables were described as absolute (n) and relative frequencies, and as mean and standard deviation (SD), or median, and minimum and maximum values, when appropriate, respectively. Mann–Whitney test or t-test for independent samples were used to test a hypothesis on continuous variables, while for categorical variables, the chi-square and Fisher's exact tests were applied, as appropriate. Statistical Package for the Social Sciences (SPSS, IBM Corp.) software, v. 25.0, was used for all statistical analysis, with an alpha set at 0.05.

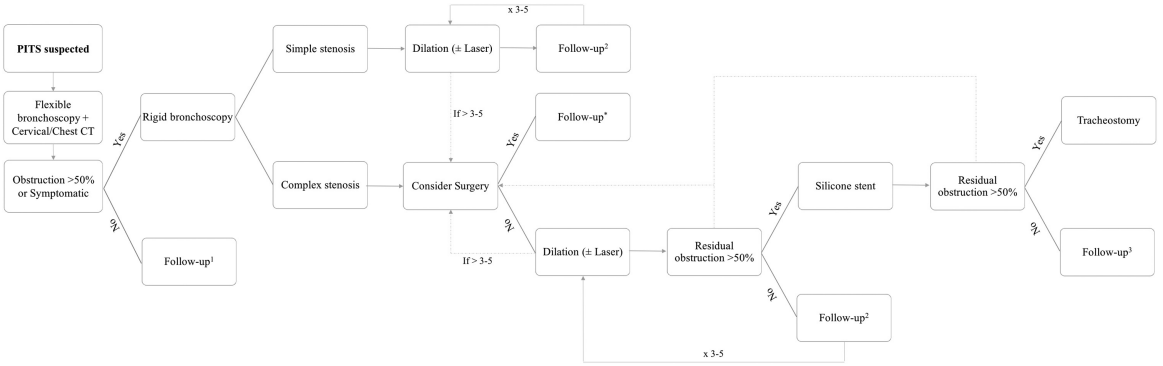

Fig. 1 PITS algorithm. *Follow-up by surgeons, refer if there is a need for interventional bronchoscopy;[1] every 6 months;[2] 1, 3, 6 and then every 6 months;[3] 1, every 3 months until the first year, and then every 6 months.

Table 1 Patients' characteristics.

Characteristics	Total (n = 115)
Age (years, mean ± SD)	48.5 ± 17.6
Gender, n (%)	
Men	61 (53.0)
Women	54 (47.0)
Comorbidities, n (%)	
Arterial hypertension	24 (20.9)
Diabetes mellitus type 2	14 (12.2)
Congestive heart failure	11 (9.6)
Dyslipidaemia	8 (7.0)
Previous stroke	5 (4.3)
Previous myocardial infarction	4 (3.5)
Atrial fibrillation	4 (3.5)
Valvular heart disease	3 (2.6)
Autoimmune disease	3 (2.6)
Down syndrome	2 (1.7)
Tetralogy of Fallot	2 (1.7)
OSA	1 (0.9)
Colonic diverticulosis	1 (0.9)
Depression	1 (0.9)
Neoplasia	1 (0.9)
Asthma	1 (0.9)
COPD	1 (0.9)
GERD	1 (0.9)
Previous deep vein thrombosis/pulmonary thromboembolism	1 (0.9)
HIV infection	1 (0.9)
Chronic liver disease	1 (0.9)

COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus; OSA, obstructive sleep apnoea.

Results

From a total of 115 patients enrolled in this study (Table 1), with a mean of 48.5 ± 17.6 years, 53% (n = 61) were males and 47% (n = 54) were females. The median follow-up time was 23 months (range, 0.2–130.8). Comorbidities were present in 46 (40%) patients.

Stenosis was classified as follows, 33.9% (n = 39) were categorized as simple and 66.1% (n = 76) as complex. Gender was the only patient-related characteristic that was associated to stenosis type (p = 0.008), simple PITS was more frequent in women (n = 25 vs. n = 14) and complex PITS more frequent in men (n = 47 vs. n = 29). This finding was independent of other patients or stenosis characteristics.

With regards to stenosis causes and features (Table 2), median intubation time was 15 days (range, 1.0–118.0) and the most common causes of intubation were respiratory (n = 29, 29.9%), neurological (n = 26, 26.8%) and surgical (n = 19, 19.6%). Thirty-three (28.7%) patients had been previously tracheostomized. Complex stenosis was caused by longer intubations compared with simple ones (16.5 vs 10.5 days, p = 0.011) and was more frequent among previously tracheostomized patients (34.2% vs 17.9%, p = 0.068). The most common location was the upper third of trachea (60.9%, n = 70), with a stenosis extension and severity of 2.0 cm (range 0.5–6.0) and 80% (range 20–100), respectively. Specifically, complex stenosis had a median 2.6 (range 1.0–6.0) cm of vertical extension.

Several treatment strategies and bronchoscopic procedures were necessary for PITS management (Fig. 2 and Table 2). Five patients were followed-up in other centre, even though the first bronchoscopic treatment was performed in our centre as an emergency procedure. The majority of cases were initially treated with a bronchoscopic procedure (n = 96), with a median 2.0 procedures (range 1.0–6.0) per patient. Four patients with simple stenosis had no significant obstruction and treatment was not necessary. The remainder (n = 35) were successfully treated with serial dilations alone. Despite serial dilations being effective in treating some complex PITS (n = 17, 23.9%), a greater proportion of simple stenosis was managed successfully with this treatment option (67.3% vs 32.7%, p < 0.001). Laser was used in 13.5% of cases. The number of dilations per patient was 2.0 (range 1–6) and the median time between dilations was 50 (range 14.0–327.5) and 30.6 (range 8.0–154.0) days, respectively, for simple and complex stenosis, with no statistically significant differences (p = 0.144) between groups (Fig. 3a and b). Procedure-related complications were not observed. Globally, 25.0% of cases treated with serial dilations presented a long-term recurrence; these recurrences were independent of the stenosis type. These cases consisted of seven simple and six complex stenoses and were successfully managed with additional mechanical dilations.

Table 2 PITS characteristics and treatment strategies.

PITS characteristics	Total n = 115	Simple n = 39	Complex n = 76	p Value
Reason for intubation, n (%)				0.197
Respiratory	29 (29.9)	6 (15.4)	23 (30.3)	
Surgical	19 (19.6)	8 (20.5)	11 (14.5)	
Neurological	26 (26.8)	12 (30.8)	14 (18.4)	
Cardiac	10 (10.3)	2 (5.1)	8 (10.5)	
Toxic	1 (1.0)	1 (2.6)	0	
Trauma	8 (8.2)	2 (5.1)	6 (7.9)	
Burns	1 (1.0)	0	1 (1.3)	
Infectious	3 (3.1)	0	3 (3.9)	
Intubation length, days (median, min–max)	15.0 (1–118)	10.5 (1–47)	16.5 (1–118)	**0.011**
Previous tracheostomy, n (%)	33 (28.7)	7 (17.9)	26 (34.2)	0.068
Location, n (%)				0.652
Subglottic	25 (21.7)	11 (28.2)	14 (18.4)	
Upper third of trachea	70 (60.9)	21 (53.8)	49 (64.5)	
Middle third of trachea	14 (12.2)	5 (37.5)	9 (11.8)	
Lower third of trachea	6 (5.2)	2 (12.8)	4 (5.3)	
Severity, % (median, min–max)	80 (20–100)	80 (20–100)	80 (40–100)	0.066
PITS treatment strategies	**Total n (%)**	**Simple n (%)**	**Complex n (%)**	**p Value**
Serial dilations alone	52 (47.3)	35 (67.3)	17 (32.7)	**<0.001**
Laser	7 (13.5)	6 (17.1)	1 (5.9)	0.264
Long-term recurrence	13 (25.0)	7 (20.0)	6 (35.3)	0.232
Stent	21 (19.1)	0	21 (100)	**<0.001**
Stent as 1st strategy	8 (38.1)	0	8 (38.1)	–
Stent removal	14 (66.7)	0	14 (66.7)	–
Long-term recurrence	7 (33.3)	–	7 (33.3)	–
Stent duration, months (median, min–max)	21.2 (0.03–71.3)	–	21.2 (0.03–71.3)	–
Surgery	33 (30.0)	0	33 (100)	**<0.001**
Surgery as 1st strategy	4 (12.1)	0	4 (12.1)	–
Long-term recurrence	8 (24.2)	–	8 (24.2)	–
Tracheostomy	6 (5.5)	0	6 (100)	0.062

Bold: $p < 0.05$.

Complex PITS required other treatment strategies. Stent placement was necessary in 21 (19.1%) patients, it was the first procedure in 8 cases. In the remainder (n = 13), mechanical dilation was unsuccessfully attempted prior to stent placement, with a median of 2.0 (range 1–4) dilations per patient (Fig. 3c). The stent was removed in most of cases (n = 14), with a median stent duration of 21.8 (range 0.03–69.2) months. Despite no procedure-related complications, long-term stent-related complications were registered in 61.9% (n = 13), namely mucostasis (n = 8), repetitive respiratory infections (n = 8), granulation tissue (n = 6) and stent migration (n = 5). Granulation tissue and stent migrations were also managed by interventional bronchoscopy. Patients who experienced stent-related complications had a longer median stent time compared to those without complications (42.6, range 16.6–71.3 vs 2.2, range 0.03–23.7 months, $p < 0.001$) (Fig. 3d). Half (n = 7) the patients whose stent was removed recurred afterwards. The treatment for these recurrences was diverse: three patients underwent mechanical dilation, two were surgically treated and two had a Montgomery T-tube inserted.

Surgery was performed in 30.0% (n = 33) of cases, all of them with complex stenosis. The majority needed other treatment options until surgery was performed: more commonly mechanical dilations (n = 23), but also stent placement (n = 5). A median of 2.0 (range 1–6) had bronchoscopic procedures until the ideal time for surgery (Fig. 3c). Post-surgical recurrences were observed in 24.2% (n = 8) of cases. In a subgroup analysis, there were no differences in patient or stenosis characteristics between patients who recurred and those who did not. Several strategies were used to manage post-surgical recurrences: 5 patients had serial mechanical dilations, 1 had a silicone stent placed (removed after 9 months, no further intervention required), 1 was managed with a Montgomery T-tube and another underwent a second resection surgery. Five patients with complex PITS were definitely tracheostomized. One case was first tracheostomized in emergency contextand then surgery was performed later.

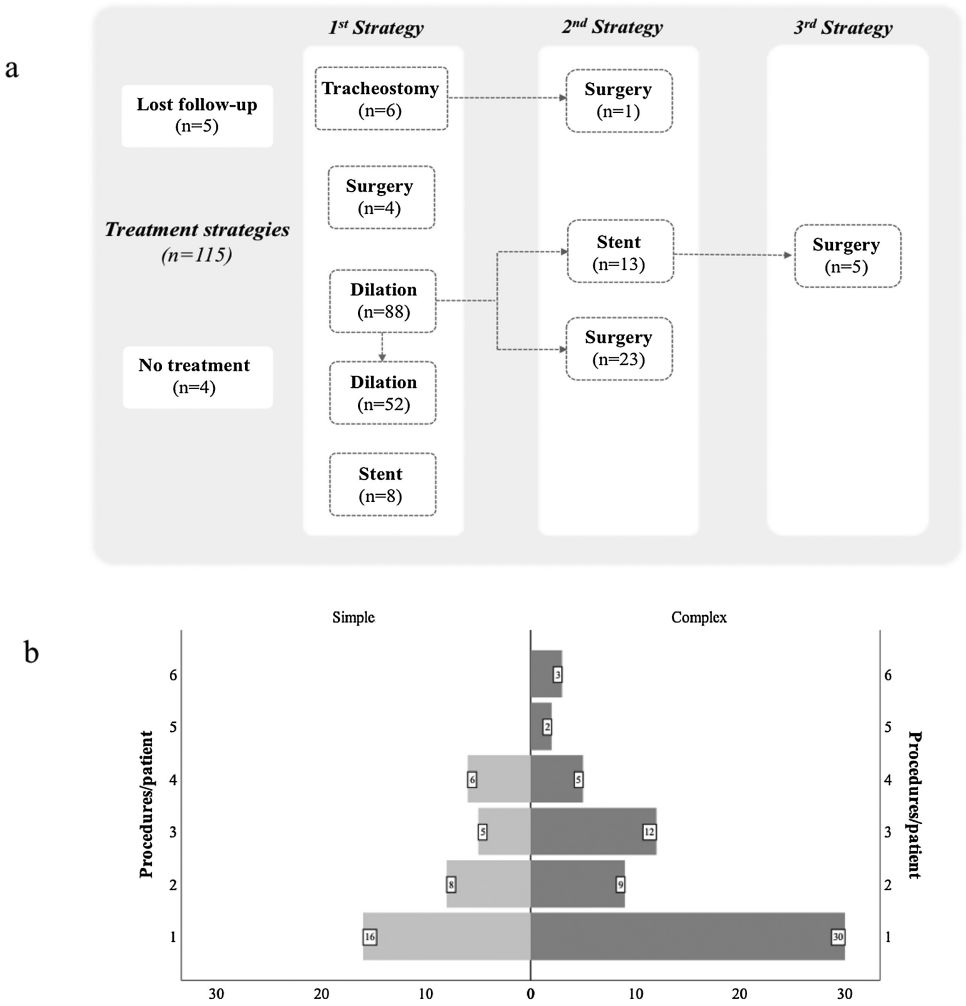

Fig. 2 (a) PITS treatment strategies; (b) Number of bronchoscopic procedures per patient.

Discussion

Benign tracheal stenosis is a rare but potentially fatal condition when acute. Once established it may cause a significant impact on patient quality of life. At present, there are no international guidelines for PITS management.[2] In general, surgical treatment is considered the gold standard for PITS.[1–3] However, there is evidence that interventional bronchoscopy may have a role in the management of this condition, not only in inoperable patients or as a bridge to surgery,[2,6,7] but also in selected patients as first treatment after a correct stenosis evaluation.[4,8,9] We aimed to demonstrate the role of interventional bronchoscopy in treating PITS and assess its efficacy and safety. To better understand PITS pathogenesis, we also analysed patients and stenosis characteristics.

Gender correlated with stenosis type, simple PITS was more frequent in women and complex more frequent in men. In a series of 209 patients with benign tracheal stenosis, although statistical significance was not presented by the authors, male/female ratio was reasonably similar between both types of stenosis.[4] To the best of our knowledge, there is no similar data reported in other studies. We suggest that inflammation and scarring may vary with individual patients' characteristics.

Patients with longer intubation time and prior tracheostomy tended to develop a greater proportion of complex PITS. An increased degree of tracheal wall injury promoted by either prolonged damage stimulus or presence of a second injury element, such as tracheostomy cannula, might explain these findings. It has been proposed that, while PITS typically result from an ischaemic lesion caused by cuff pressure followed by scar contracture,[13] post-tracheostomy tracheal stenosis lesions normally imply granulation tissue formation and scar contracture. Besides, additional cartilage damage from tracheal tube attachment at stoma site may occur,[14] increasing damage to tracheal wall structures. A retrospective study showed that post-tracheostomy tracheal stenosis patients had more complicated stenosis than those with post-intubation ones.[15] Up to 14% of patients requiring mechanical ventilation when admitted to the Intensive Care Unit (UCI) needed long periods of weaning and tracheostomy.[16] According to our data, difficult-to-wean patients may be at higher risk of developing complex tracheal stenosis. Evidence has shown that non-invasive ventilation (NIV) may be helpful during the weaning process in specific cases.[17–19] A prospec-

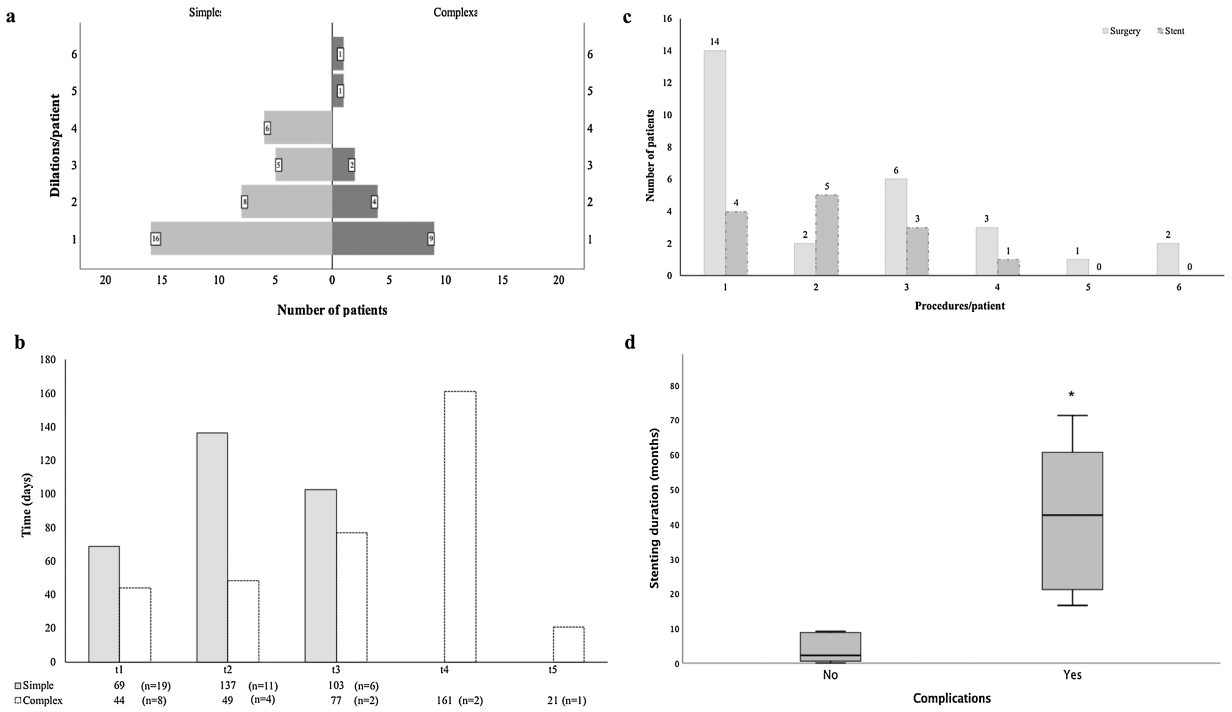

Fig. 3 (a) Serial mechanical dilations; (b) Time between serial dilations; (c) Number of bronchoscopic procedures before stent placement and surgery; (d) Duration time of stenting and stent-related complications occurrence. *p < 0.001.

tive study suggested that NIV may be helpful in achieving weaning in critically ill chronic patients who have hypercapnia after 24 h of spontaneous breathing or are unable to increase the duration of spontaneous breathing beyond 18 h.[20] Similarly, a more recent prospective study showed that in tracheostomised patients partially dependent on mechanical ventilation, decannulation is feasible and safe after switching to NIV.[21] Thus, combined NIV/decannulation protocols may represent a way to decrease the risk of developing tracheal stenosis in these patients, improving their quality of life. Furthermore, in the same study, upper airway endoscopy of these patients revealed a preserved respiratory space, with 30% of patients showing moderate mucosal introflection in tracheal cannula convexity and less than 10% had excessive dynamic airway collapse (EDAC) without tracheomalacia.[21] Although not analysed in our study, EDAC is a distinct type of airway obstruction, since there is no fixed stenosis, but a dynamic obstruction. Bronchoscopy plays an important role in identifying EDAC and its treatment includes non-invasive positive pressure ventilation, probably acting as a ''pneumatic stent''[22,23] or, in severe cases, a stent trial to assess whether the patient is a candidate for tracheobronchoplasty and long-term stent placement in selected inoperable patients should be considered.[24] As with other conditions associated with upper airway obstructive events, such as obstructive sleep apnoea (OSAS), neuromuscular diseases, exercise-induced laryngeal obstruction and bulbar dysfunction,[25] endoscopic evaluation during ventilation titration may be useful in reducing expiratory airway collapse to less than 50%.[23]

PITS management is complex and most patients need more than one procedure to achieve stabilization. For complex stenosis, several treatment options are necessary, and a combination has been shown to be the best strategy in most cases. Bronchoscopic approach is a safe and less invasive option which is able to manage most cases. According to published data, only a minority of patients experience complications related to rigid bronchoscopy, the diagnosis of benign stenosis being less prone to complications compared to malignant disease or foreign bodies.[26] In this study, serial dilations alone were effective in all simple PITS, as previously reported.[4,5,9,27]

Regarding complex PITS, 23.9% of cases were successfully treated with serial dilations alone, confirming that selected complex stenosis can be managed only with mechanical dilations, as previously described.[8] Also, according to other series,[4,8,9,28] most cases were treated with 1–3 dilations. In some extreme cases, as in 2 patients with complex stenosis, >3 serial dilations were performed. Excluding these two patients with complex PITS, for whom high subglottic location precluded stent placement, most cases were managed with an acceptable number of dilations. We also present some cases of simple PITS with >4 dilations. Unlike our study, most authors reported stent placement in these cases.[2,4,8,9] Instead, we avoided silicone stent placement in simple stenosis given the high rate of complications. Our practice resulted in a maximum of 4 dilations/patient to achieve stabilization.

Despite the high number of procedures in a few cases, stenosis stabilization was achieved by serial dilations alone in most of them, as can be seen by the low rate of long-term recurrences. In general, as the number of dilations increases so does the time until the next dilation, demonstrating stenosis stabilization along serial interventions. The number of dilations, time between procedures and even long-term recurrences did not differ, suggesting that com-

plex PITS are a heterogeneous group that responds distinctly to different treatment options. This might be related to stenosis characteristics, such as the degree of cartilage involvement and tracheomalacia. We believe that complex PITS, with lower grade of cartilage involvement or tracheomalacia, may behave similarly to simple PITS and, therefore, be treated as such.

Silicone stents may be used not only as a bridge to surgery, but also as a definitive long-term treatment of selected, inoperable stenosis.[29,30] Compared to other studies, a lower proportion of cases with complex PITS placed a stent in our series.[4,8,9] Instead, up to four dilations were performed before stent placement. Although it is known that stenosis <1 cm in vertical extension and those without malacia are more likely to be successfully treated by stent placement,[22] in our practice, we consider stent placement only for highly unstable stenosis, impossible to manage with serial dilations due to the high rate of stent-related complications. The exact timing for stent removal and, specifically in complex stenosis, the time of cartilage regeneration is unknown; thus, long-term stenting may be necessary.[22] Stenting time in our series was in line with the previously reported data.[4,8,31] Stent removal was impossible in 7 cases due to absence of alternative strategies. Stent-related complications, associated with longer stenting times, were frequent, but comparable to the previously reported data.[8,9,32] Hence, if long-term palliative silicone stents are necessary, these patients demand closer clinical and bronchoscopic surveillance. Recurrences after stent removal were disappointing. Data published are conflicting, with some studies reporting a lower proportion of recurrences[4,33] and others similar findings.[30,34] It is worth noting that Montgomery T-tubes are effective, either as an alternative to surgery or when other types of stents are unsuccessful among complex PITS patients.[35]

Surgery, as first treatment option, was performed only in a minority of cases. This data agrees with previous studies[4,9] and supports the fact that interventional bronchoscopy may represent an alternative.[2,4,6,7,9] Frequently, treatment of comorbidities is necessary to optimize surgical conditions and meanwhile, interventional bronchoscopy may be the only way to relief symptoms. Moreover, high subglottic stenosis as well as long vertical extent (>4–6 cm) represent limitations to surgery.[22] Post-surgical restenosis was higher than that reported in other studies,[36–40] however we found no patients or stenosis features that could explain these results. Given the small sample size of patients undergoing surgery, this analysis may not be representative. However, it seems that surgery improved stenosis characteristics, such as the degree of affected cartilage and malacia, as demonstrated by the success of mechanical dilations in most cases and the good results obtained with silicone stent placement. In fact, interventional bronchoscopy plays an important role in these cases, and is often the only way to improve patients' symptoms.

Data on topical mitomycin C application was not available, despite its rare use. However, the role of topical mitomycin C in PITS is not well-established. Although some retrospective studies reported positive results,[41–43] more recently, a randomized controlled trial suggested that its use brings no additional benefit.[44]

Overall, these data reflect the importance of interventional bronchoscopy in PITS management, demonstrating it to be efficient and safe. The main advantage of interventional bronchoscopy is that it is less invasive, avoids intra-operatory risks and provides treatment of patients with important comorbidities or longer stenosis. The retrospective design of the study limited access to important data and, subsequently, the statistical analysis. Thus, it was not possible to perform an objective measurement of symptoms, pulmonary function or the application of severity assessment tools, and it was impossible to quantify the conclusions about the success rate of interventions. Objective tools are needed to achieve a better classification and improve knowledge about PITS pathogenesis to ensure a correct stratification and treatment decision. Further studies with a larger, prospective and multicentre design are required as well as international consensus to guide clinicians in their practice.

Statement of ethics

This study was approved by Ethics Committee of Centro Hospitalar e Universitário de São João and conducted in accordance with the Helsinki declaration.

Conflict of interest

The authors declare no conflict of interests.

CRediT authorship contribution statement

C. Freitas: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **N. Martins:** Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **H. Novais-Bastos:** Validation, Visualization, Writing - review & editing. **A. Morais:** Resources, Validation, Visualization, Writing - review & editing. **G. Fernandes:** Resources, Validation, Visualization, Writing - review & editing. **A. Magalhães:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing.

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Glossary

PITS: Post-intubation tracheal stenosis
CT: Computed tomography
RB: Rigid bronchoscope
COPD: Chronic obstructive pulmonary disease
GERD: Gastroesophageal reflux disease
HIV: Human immunodeficiency virus
OSA: Obstructive sleep apnoea

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SPECIAL ARTICLE

Non-invasive respiratory support paths in hospitalized patients with COVID-19: proposal of an algorithm

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KEYWORDS
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Awake proning

Abstract COVID-19 related Acute Respiratory Failure, may be successfully treated with Conventional Oxygen therapy, High Flow Nasal Cannula, Continuous Positive Airway Pressure or Bi-level Positive-Pressure ventilation. Despite the accumulated data in favor of the use of different Non-invasive Respiratory therapies in COVID-19 related Acute Respiratory Failure, it is not fully understood when start, escalate and de-escalate the best respiratory supportive option for the different timing of the disease. Based on the current published experience with Non-invasive Respiratory therapies in COVID-19 related Acute Respiratory Failure, we propose an algorithm in deciding when to start, when to stop and when to wean different NIRT. This strategy may help clinicians in better choosing NIRT during this second COVID-19 wave and beyond.

Non-invasive respiratory therapies (NIRT) have become paramount interventions in the management of COVID-19 induced acute respiratory failure.[1] Patients developing COVID-19 related Acute Respiratory Failure may be successfully treated by means of Conventional Oxygen Therapy (COT), High Flow Nasal Cannula (HFNC), Continuous Positive Airway Pressure (CPAP) or Bi-level Positive-Pressure ventilation (Bilevel-PAP) with the avoidance of endotracheal intubation (ETI) and invasive mechanical ventilation (IMV).

Recent data from the worldś widest database[2] (International Severe Acute Respiratory and emerging Infections Consortium-ISARIC) suggests that 20% of patients with COVID-19 are admitted at some point of their illness into an intensive care unit (ICU) or high dependency unit (HDU). Non-invasive ventilation (including both CPAP and Bi-level PAP) was applied in 15% of cases, while High-flow nasal cannula (HFNC) in 14%.

Two main concerns dealing with the use of NRST are the risk of delaying intubation in case of failure and the fear of virus spreading among health care workers (HCW) during noninvasive respiratory treatment.

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The pragmatic implications for the clinical practice are respectively the applications of reliable models predicting NIRT failure[3] and the use of proper personal protective equipment (PPE) together with equipment and ventilator setting limiting viral particles dispersion.[4,5] Contactless monitoring can help minimize entry of HCW into rooms and so decrease their risk of viral load exposure.[6]

It is well known from pre-COVID 19 data, that the recipe for the success of NIRT include mandatorily the management of the carefully selected candidate in an expert setting by means of a well trained staff, with the choice of a proper equipment and bearing in mind that there is a tight window of opportunity warranting short-interval monitoring and considering timely intubation for worsening respiratory status. Ideally, NIRT, like interventional pulmonology procedures, should be performed in a dedicated negative pressure room with strict isolation precautions and sufficient ventilation to avoid aerosol contamination.[7]

Prolonging NIRT in absence of clinical-arterial blood gases improvement may expose the patient to the risk of an unduly delayed intubation with an increased mortality.

Since the SARS epidemic, some reservations have been raised about the benefits of NIRT, the risks of aerosolization and the consequent increase in infections among HCW. Recently, several publications report that NIRT are not actually aerosol generators, but aerosol dispersers.[8] And so, with the appropriate PPE,[4,5] and in the hands of experienced teams, it's possible to reduce the intubation rate without seriously increasing the risk of nosocomial infections.

Recent experience in COVID-19 related Acute respiratory failure (21 publications including 1553 patients)[9–27] with HFNC, CPAP and Bi-Level Ventilation (using negative pressure rooms in only one series[15]) shows average success of 60%, 55% and 59%, respectively, and an average infection rate in health professionals of 5.2%, less than the 12% reported in New York City among the staff not necessarily working with NIRT.[28]

However there is significant heterogeneity in the employed NIRT protocols followed in the published studies.

Recent data,[29] in invasively mechanically ventilated patients, demonstrated the existence of different phenotypes of COVID-19 induced ARDS depending on static compliance, ventilator ratio as surrogate of dead space, and D-Dimer levels (as surrogate of diffuse thrombo-embolic pulmonary disease). The phenotype showing higher D-Dimer levels and lower static lung compliance is associated with greater mortality rate. One could speculate that the likelihood of improvement in gas exchange (I.e. PaO2/FiO2 ratio) after NIRT is greater in the earlier phases of COVID-19 induced ARDS patients who are still on spontaneous breathing when lung mechanics is preserved and pulmonary vascular thrombo-embolic diseases is less like to have developed. However, further clinical large controlled studies are needed to demonstrate this issue.

Based on this current evidence we would like to propose an algorithm (Fig. 1 and Table 1) and specific criteria to start NIRT, when to escalate NIRT, when to wean NIRT and when to proceed to Intubation. We believe it could help clinicians uniformize their practice of the management of Hypoxemic Respiratory Failure of COVID-19 and help to homogeneously collect data for the forthcoming studies.

Surprisingly, no published studies took into consideration normalized PaO2 and normalized PaO2/FiO2 ratio in hypoxemic and hypocapnic patients.[30] As a great deal of COVID-19-related pneumonia patients show hypoxemic hypocapnic alkalosis, SpO2 values may underestimate the severity of lung damage because of the left-side shift of hemoglobin dissociation curve. We speculate that PaO2/FiO2 ratio may not be considered a reliable score of hypoxemia if we do not consider PaO2 values standardised to PaCO2 levels in hypocapnic patients (1,66*PaCO2- PaO2 − 66,4 mmHg). Again in this scenario the severity of lung impairment may be underestimated by stratifying patients according to conventional PaO2/FiO2 ratio with the consequent risk of delaying the time for starting or escalating a NIRT or for intubation.

Criteria to start conventional oxygen therapy (COT)

a) Start when SpO2 < 92% (Room air)
b) Use Venturi mask to target spO2 of 92−96%[31] (choose preferentially masks with filter media covering the exhalation ports like the *Intersurgical FiltaMask* ™-Fig. 2)
c) In case the patient needs a higher oxygen concentration, use a non-rebreather reservoir mask

Reevaluate after 4 h: If SpO2 and Respiratory rate-RR (<30) remain stable-Maintain COT (**Responder**)

If SpO2 drops ≥ 2% or RR > 30, proceed to Arterial Blood Gas (ABG) analysis (NON-Responder) » **escalate to HFNC**

Criteria to start HFNC

It is not clear if HFNC can be more beneficial if started earlier. Preliminary non-peer review experience seems to point into an earlier start.[32]

a) Early start: If PaO2:FiO2 < 300 or SpO2 < 93% on O2 > 5 L/min or SpO2 < 94% with FiO2 40%[33]
b) Late start: SpO2 < 92% under O2 at 15 L/min and or PaFiO2 < 150[23]
c) Start with: Ramp up from 30 L/min until 60 L/min to accustom the patient (40−50 if not tolerated); FiO2 to maintain spO2 > 93%; Temperature 31−37º according to patient's comfort
d) A surgical mask should be placed over the nose and mouth of a patient with a properly fitted nasal cannula before initiating therapy. It not only reduces droplet deposition[34] but also improves COVID-19 patient's oxygenation[35] without any clinically relevant side effect, except for a moderate reduction in CO2 clearance.[34] This may require increasing flow rate of HFNC if the patient is displaying increased work of breathing.

Follow ROX Index (SpO2/FiO2: RR) criteria[36,37]: In brief calculate ROX at 2 h, 6 and 12 h. If its value is increasing then the patientś respiratory status is improving.

If at 2 h: ROX is between 2,85−4.87 increase support and re-evaluate in 30 min aiming at an improvement in ≥0.5; if ROX is ≥4.88 continue treatment; if ROX is below 2.85

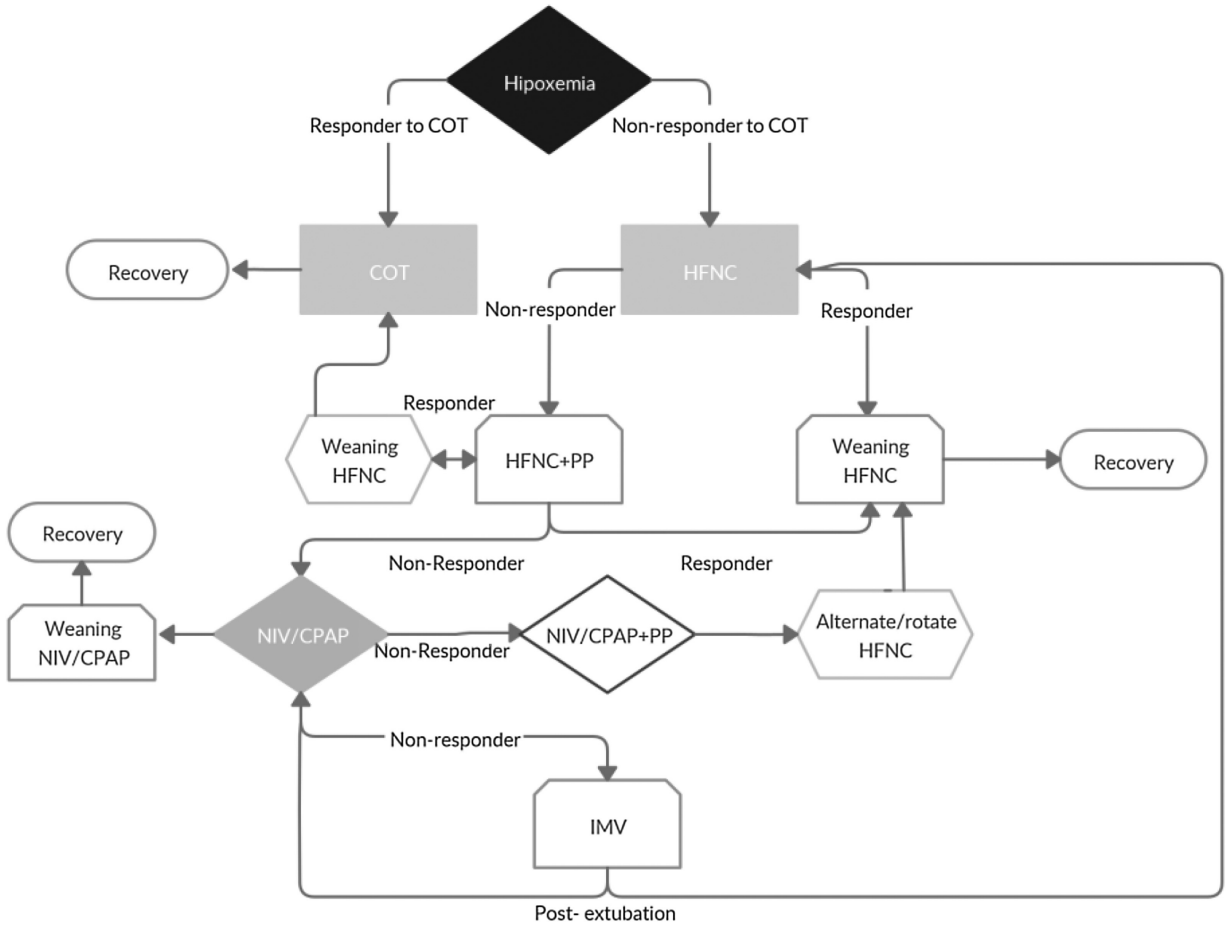

Figure 1 Legend: COT, Conventional Oxygen therapy; PP, prone positioning; HFNC, High Flow Nasal cannula; NIV, Non-Invasive Ventilation; CPAP, Continuous Positive Pressure Ventilation; Use short term trials (max 6 h); if OK maintain 2–3 days.

consider ETI or escalate to short trial of CPAP or NIV before (see steps 4—6).

If at 6 h: ROX is between 3.47–4.87 increase support and re-evaluate in 30 min aiming at an improvement in ≥0.5; if ROX is ≥4.88 continue; if ROX is below 3.47 consider ETI or escalate to short trial of CPAP or NIV before (see steps 4—6).

If at 12 h: ROX is between 3.85–4.87 increase support and re-evaluate in 30 min aiming at an improvement in ≥0.5; if ROX is ≥4.88 continue; if ROX is below 3.85 consider ETI or escalate to short trial of CPAP or NIV before (see steps 4—6).

Three recent studies applying the ROX index in COVID-19 patients, suggest different cut-off points like slightly higher values ≥4,94 at 2 and 6 h[38] and ≥5,37 at 4 h[39] and lower values ≥3,7 at 6 h.[23] Moreover other authors point to a daily significant decrease in the ROX index as a predictor failure within the first 3 days of HFNC treatment.[25]

Criteria of HFNC weaning

Decrease FiO2 hourly aiming at SpO2 92–98%. When you reach FiO2 of 40%, decrease flow until weaning.[40] However an ideal weaning protocol remains to be established. A current RCT[41] is studying 3 different protocols: 1) gradually wean flow by 10 L/min/h. When it reaches 20 L/min, FiO2 reduction will then begin at 0.1 /h until it reaches 0.3. 2) gradually reduce FiO2 by 0.1 /h until it reaches 0.3. At this point, flow will be reduced by 10 L/min/h until it reaches 20 L/min 3) both flow and FiO2 will be gradually reduced simultaneously at a rate of 10 L/min and 0.1 /h, respectively, until they reach the HFNC weaning off targets (20 L/min for flow and 0.3 for FiO2).

Criteria to start CPAP

a) If PaO2:FiO2 < 200 or PaO2 < 60 mmHg or RR > 30 (while on oxygen or HFNC)
b) If PaO2:FiO2 < 300 or SpO2 < 93% on O2 > 5 L/min- and Patient has BMI > 30 (OPTIONAL)[16]

If you start CPAP analyze improvement in PaO2:FiO2 in 1 h: a) if improves ≥15%[14] or ≥30%[20] consider existence of LUNG RECRUITABILITY

c) If you choose CPAP with HELMET or OroNasal Mask, start with 10 cmH20 (do not exceed 12–13 cmH20 to avoid barotrauma, Self-inflicted Lung Injyry (S-ILI) or negative hemodynamic impact) FiO2 to achieve SpO2 > 93%[14] or PaO2 ≥ 60 mmHg[26]

Table 1 Summary of the proposed algorithm.

Step 1-Start COT when SpO2< 92% Venturi mask to target SpO2 92-96%				
Step 2-Start HFNC when PaO2/FiO2 <300 on O2>5 L/min	Step 3-Wean HFNC	Step 2-HFNC Failure	Step 9-HFNC After extubation	Step 10-Wean HFNC After extubation
Ramp up from 30 L/min until 60 L/min of Flow; FiO2 to maintain SpO2>93%	Decrease FiO2 first; when you reach FiO2 40% decrease flow	If ROX is below 2.85 at 2h, below 3.47 at 4h; or below 3.85 at 12h	If PaCO2< 45 during SBT or intubation not associated with COPD	If Flow 30 L/min and FiO2 30%
Step 4-Start CPAP when PaO2/FiO2 <200	Step 5-Wean CPAP	-CPAP Failure	Step 8-NIV failure	
Apply 10 cmH20 and FiO2 to maintain SpO2 > 93%	When SpO2 > 94% with FiO2 < 50% and CPAP $\leq$ 5cmH20	If PaO2/FiO2 <100 or 20% increase in PaCO2	If HACOR Index > 5 1h or 12h after starting therapy	
Step 6-Start NIV when PaO2/FiO2 <100 and RR$\geq$30 and/or respiratory distress under CPAP Or PaCO2> 45mmHg	Step 8-NIV failure If HACOR Index > 5 1h or 12h after starting therapy	Step 9-NIV after extubation If PaCO2> 45 during SBT or intubation associated with COPD		
Consider Self-Proning after Step 1,2,4 and 6 as tolerated by the patient, and if efficacious extend it during 3—5 days.				

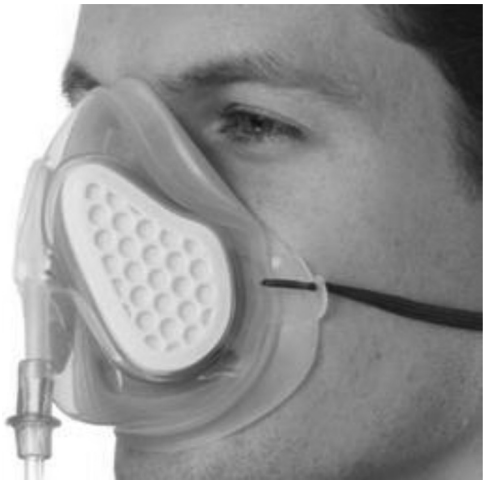

Figure 2 Fitta Mask™ Intersurgical.
Source: Intersurgical Ltd, Crane House, Molly Millars Lane, Wokingham, Berkshire, RG41 2RZ, UK; IS10.20_FiltaMask_INT_issue_5_web (2).pdf.

Criteria of CPAP weaning (a weaning trial should be attempted every day to avoid a delay in CPAP removal)

Patients on helmet CPAP who do not show signs of respiratory distress (e.g. RR < 25) and maintain a SpO2 > 94% with a FiO2 < 50% and a PEEP< = 5 cmH2O undergo a weaning trial. Patients maintaining a PaO2:FiO2 ratio >250 on Venturi mask with a FiO2 < 40% for at least 24 h are considered successfully weaned from helmet CPAP.[20]

OR

Reduce Helmet CPAP level to the minimum possible (5–6 cmH20) maintaining a FiO2 not higher than 50%. If de-recruitment is absent and the PaO2/FiO2 ratio is stable as compared with higher PEEP levels the patients is ready to undergo a CPAP weaning trial.[42]

Criteria to start NIV

a PaO2:FiO2 < 100 and RR $\geq$ 30 and or respiratory distress under CPAP
b Suggested parameters PEEP 12–16 cmH20 and PS set with the aim of VT 4—6 ml/kg and FiO2 aim of target SpO2 90–95%.[43]
c In patients with hypercapnic respiratory failure (PaCO2 > 45 mmHg)

Rotation of NIV/HFNC

Between NIV sessions, to allow for feeding and rest, HFNC could be delivered during 1 h with a flow of 50 L/min and a FiO2 to achieve adequate oxygenation (SpO2 $\geq$ 92%).

Table 2 HACOR Index.

Variables	Category (j)	Assigned points
Heart rate, beats/min	≤120	0
	≥121	1
pH	≥7.35	0
	7.30–7.34	2
	7.25–7.29	3
	<7.25	4
GCS	15	0
	13–14	2
	11–12	5
	≤10	10
PaO_2/FiO_2	≥201	0
	176–200	2
	151–175	3
	126–150	4
	101–125	5
	≤100	6
Respiratory rate, breaths/min	≤30	0
	31–35	1
	36–40	2
	41–45	3
	≥46	4

INTUBATION criteria after CPAP and NIV

Indication for intubation includes the presence of either ≥1 major or ≥2 minor criteria lasting for ≥1 h[20]:

Major criteria: respiratory arrest, respiratory pause with unconsciousness, severe hemodynamic instability (i.e., SBP < 90 mmHg instead of adequate volume resuscitation), and intolerance to helmet CPAP leading to discontinuation of the device.

Minor criteria: reduction of ≥30% of basal PaO2:FiO2 ratio, PaO2:FiO2 ratio <100, 20% increase of PaCO2 if basal PaCO2 was ≥40 mmHg, worsening of alertness, new onset or persistent respiratory distress, SpO2 < 90%, and exhaustion.

OR

According with Brusasco et al.,[26] If after 4 h of CPAP, PaO2/FiO2 decreasing, RR ≥ 30, PaO2 < 60 mmHg.

OR

A deterioration in oxygen saturation with a PaO2/FiO2 < 150 or 175 mm Hg after 1 h of NIV, a respiratory rate > 30/min, a high APACHE score, and a HACOR score >5.[44]

OR

Also HACOR Index (Heart rate, Acidosis (pH), Consciousness (GCS), Oxygenation, and Respiratory rate (HACOR)-Table 2) >5, 1 h or 12 h after Initiating CPAP/NIV.[45]

OR

Also if ROX is below 2.85 at 2 h, below 3.47 at 4 h; or below 3.85 at 12 h

NIV/CPAP/HFNC after extubation

If suspected hypercapnia (PaCO2 > 45 mmHg during SBT) or intubated with associated COPD (or other cause of Chronic Hypercapnic Respiratory Failure) extubate to NIV.[46] Also in case of failure of first Spontaneous Breathing Trial -SBT (with PEEP 6cmh20 FiO2 35% for 30 min, patients VT < 6 mL/kg of Predicted Body Weight, RR > 22 and SpO2 decreasing).[47]

According with the protocol of Thille AW et al.,[48] NIV will be immediately initiated after planned extubation by prolonged sessions during the 48 h following extubation: a first session of at least 4 h, and then sessions of at least 2 h, during all the night (continuous NIV from 10 P.M. to 6 A.M.) if it is possible, for a total duration of at least 12 h a day. NIV will be performed with a ventilator dedicated for NIV (ICU ventilator with NIV mode or NIV ventilator) in pressure-support ventilation using the following ventilator settings: Minimal pressure-support level of 5 cm H2O targeting a tidal volume around 6–8 ml/kg, a PEEP level between 5 and 10 cmH2O, a FiO2 adjusted to obtain adequate oxygenation (SpO2 ≥ 92%), a pressure ramp slope between 0.1 and 0.2 s and a cycling off criterion at 25–30% of peak inspiratory flow.

Rotation of NIV/HFNC[48]: To allow better tolerance, between NIV sessions, HFNC will be delivered with a flow of 50 L/min and a FiO2 to achieve adequate oxygenation (SpO2 ≥ 92%). The treatment including HFNC and NIV will be delivered for at least 48 h after planned extubation. NIV in this setting will offer better ventilator assistance, while HFNC better tolerance and humidification.

If there is no hypercapnia during SBT nor the intubation was associated with COPD (or other cause of Chronic Hypercapnic Respiratory Failure), extubate to HFNC.[46] If non-responsive to HFNC (see criteria of failure), rescue use of CPAP.

A recent case series report of a successful use of HFNC in extubating 4 COVID-19 patients and de-escalating from CPAP in 5.[49]

Moreover according with a recent meta-analysis,[50] HFNC reduces work of breathing to a similar extent as NIV, while keeping similar PaCO2 values in hypercapnic patients. So a strategy using HFNC as integrated management for patients with COPD exacerbation could be proposed, as a valid alternative to COT during breaks of NIV or to facilitate NIV discontinuation and prevent discomfort and NIV failure.[50]

Extubation failure criteria[51]: RR < 10 or >30/min; Rapid Shallow breathing index (RR: VT in Liters > 100); SpO2 < 90% with FiO2 ≥ 40%, PaO2:FiO2 < 200, HR 120, hemodynamic instability, GCS < 8, agitation, coma, no cough reflex, ph < 7,30, Respiratory Distress.

Criteria for HFNC discontinuation post-extubation

In the absence of ARF symptoms 48 h after planned extubation, treatment can be stopped and switched to standard oxygen therapy, after a weaning test using HFNC with a flow of 30 L/min and FiO2 of 30%. In case of occurrence or persistence of ARF symptoms at 48 h, HFNC will be continued or reinitiated by periods of 24 h until disappearance of symptoms.

Prone-Positioning as a complementary tool to improve oxygenation

Combination of early NIRT and prone position has been recently proposed as a measure to ''buy time'' and potentially improve outcomes.[52]

Self-proning can be tried with COT,[53–55] HFNC,[56–58] mask CPAP[59] or Helmet CPAP[60,61] to increase oxygenation.

These studies applied different frequency and duration of proning sessions, with one randomized prospective study aiming at 16 h/day having a non significant reduction in Intubation rate.[56] However the majority of studies show a significant improvement in oxygenation and respiratory rate, with no major adverse events. There is some suggestion that patients with a PaO2/FiO2 $\leq$ 150 have the best improvement and that for those with PaO2/FiO2 > 200 4 h/day may be enough while those with a PaO2/FiO2 < 200, 10 h/day may be needed.[62] Without a uniformized protocol it makes sense to apply self-proning as much as tolerated by the patient, and if efficacious extend it during 3—5 days.

Some authors suggest to encourage self-proning 2 times/day (at least 30 min until patient distress, monitoring SpO2 each 15 min) during the first 3 days.[63] Others propose 1—2 hours 3–4 times a day during more than 5 consecutive days,[64] and others to alternate every 2 h between prone and supine during the day and sleep in the prone position at night.[65]

According with Coppo et al., the best results come from early self-proning and patients with increase in inflammatory markers (LDH, CRP, Platelets).[61]

To increase tolerance some authors propose analgosedation with Alprazolam with or without hydroxizine[66] or even Dexmedetomidine.[67]

NIRT management of COVID-19 related pneumonia, like other severe Pneumonia, should be performed only in highly protected settings such as ICU, RICU or HDU where a close and continuous monitoring of cardiopulmonary parameters, a careful assessment of clinical and physiologic early response to NIRT, and the availability for a quick escalation to intubation and invasive ventilation as well as for the management of respiratory and non respiratory complications are feasible and easily applicable. Un-monitored ward-based COVID-19 areas are not safe and inadequate for managing such critically ill and complex patients. Pre-COVID-19 expertise of the team on NIRT should be the strongest driver to choose (when it's possible depending on the epidemiologic wave) the environment where allocate COVID-19 patients in the earlier stages of the diseases when the chance of success of NIRT in avoiding intubation is greatest.[68] Considering the still limited availability of ICU beds and the strategic need to keep as free as possible this precious environment reserved for the admission only of more severly ill patients to be supported by means of invasive ventilation and extra-pulmonary lung dysfunctions (ie. renal, cardiovascular replacement) and complications (i.e. septic shock), the majority of the patients should be managed in COVID-19 RICU or ICU COVID-19 area by Pulmonologists and/or other expert physicians in NIRT.[69] This is supported by the recent Italian experience, where the insufficient newtwork of RICU in pre-COVID-19 time may have caused the quick saturation of ICU beds during the tremendous outbreak in Lombardy. The following expanded network of pulmonologist units together with more restrictive national measures againts the virus dissemination has contributed to the mitigation of COVID-19 impact on mortality in the remaining Italian regions at the end of the first wave.[70]

In conclusion, protocolized use of NIRT through the proposed algorithm may help clinicians working in Respiratory Intermediate Care units to make choices and potentially decreasing admissions to the overwhelmed Intensive Care Units.

Conflicts of interest

The authors have no conflicts of interest to declare.

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SPECIAL ARTICLE

Reducing oral corticosteroids in severe asthma (ROSA Project): a nationwide Portuguese consensus

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Abstract
Introduction and objectives: We aimed to build a national consensus to optimize the use of oral corticosteroids (OCS) in severe asthma in Portugal.
Material and methods: A modified 3-round Delphi including 65 statements (topics on chronic systemic corticotherapy, therapeutic schemes, asthma safety and monitoring) was performed via online platform (October-November 2019). A five-point Likert-type scale was used (1-'strongly disagree'; 5-'strongly agree'). Consensus threshold was established as a percentage of agreement among participants $\geq$90% in the 1st round and $\geq$85% in the 2nd and 3rd rounds. The level of consensus achieved by the panel was discussed with the participants (face-to-face meeting).
Results: Forty-eight expert physicians in severe asthma (specialists in allergology and pulmonology) participated in the study. Almost half of the statements (28/65; 43.1%) obtained positive consensus by the end of round one. By the end of the exercise, 12 (18.5%) statements

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did not achieve consensus. Overall, 87% of physicians agree that further actions for OCS cumulative risk assessment in acute asthma exacerbations are needed. The vast majority (91.7%) demonstrated a favorable perception for using biological agents whenever patients are eligible. Most participants (95.8%) are more willing to accept some degree of lung function deterioration compared to other outcomes (worsening of symptoms, quality of life) when reducing OCS dose. Monitoring patients' comorbidities was rated as imperative by all experts.
Conclusions: : These results can guide an update on asthma management in Portugal and should be supplemented by studies on therapy access, patients' adherence, and costs.

Introduction

Asthma is a chronic inflammatory disease of the airways that leads to wheezing, dyspnea, cough, and breathing difficulties as a consequence of generalized airway obstruction. In Portugal, the overall prevalence of asthma is around 10.5% (95% CI 9.5–11.6) of the population.[1] There are different forms (phenotypes) of this condition, with different clinical features, including comorbidities, severity, treatment response and rates of acute exacerbations.[2]

Asthma control represents a main goal for the management of the disease and the impairment of patient's quality of life is now considered a serious outcome in clinical trials and thus should be routinely evaluated by validated questionnaires.[3] Patients with mild to moderate asthma are usually treated with inhaled corticosteroids (ICS), sometimes at higher doses and associated with long-acting beta-agonists (LABA) or other therapies. If necessary, in a flare-up where treated adults do not respond to a four-time increase in baseline dose of ICS, oral corticosteroids (OCS) may be used for short-term periods., this corresponds to 40—50 mg of prednisone or equivalent for 5–7 days.[4–6]

Severe asthma occurs in 5-10% of patients and is often characterized by an insufficient response to ICS (i.e. refractory to conventional therapy), especially in some subsets of patients (e.g. obese), where the severity might ameliorate with specific strategies.[7–10] These patients contribute to 50-60% of asthma costs and are responsible for most of the hospitalizations, admissions to emergency services and deaths from asthma.[4–6] In Portugal, the annual cost of patients with asthma has a significant impact on the National Health System which is mainly associated with emergency services (30.7%) and treatments (37.4%). For uncontrolled asthmatics, the annual cost exceeds twice the costs of controlled patients.[11]

Currently, in severe patients without disease control due to frequent asthma symptoms or frequent exacerbations despite optimal treatment, the additional use of OCS, or even biologic agents (monoclonal antibodies) represent therapeutic alternatives. As reported in the SANI registry and also in a French study, over 60% of patients with severe asthma are on regular oral corticosteroid treatment.[12–14] Low-dose OCS ($\leq$ 7.5 mg/day of prednisone equivalent) combined with other therapies can be effective for some adults with severe asthma (evidence level D); but it is often associated with considerable adverse effects (evidence level B), which may influence patient's quality of life and augment treatment costs.[4,5,15] A systematic review published by Cochrane Collaboration (18 clinical trials; n = 2438 patients), concluded that the evidence on the best treatment scheme is still weak (whether lower dose or short-term regimens of OCS in asthma are less effective/safe than those with higher doses or prolonged regimens).[16] Patients with severe asthma and T2-type inflammation respond to OCS and often require high and continuous dosages, contrary to T2-low asthma patients who have poor responsiveness to corticosteroid treatment. It was not until recently, in the era of widespread corticosteroid treatment for all patients with asthma, that it became evident that not all patients respond equally well to this treatment approach.[17,18] In this context, it can be assumed that the chronic use of OCS in asthma has been gradually replaced by therapies that target specific inflammatory pathways involved in the pathogenesis of asthma that are already available such as the biologic agents for patients with T2-type inflammation.[19,20]

Thus, given the severity of asthma along with an unclear treatment algorithm for patients with different phenotypes, the overuse of corticosteroids in practice and the diversity of healthcare settings dealing with asthma patients, we aimed to build a national consensus towards the optimization of the use of OCS in adults with severe asthma.

Material and methods

Study design

This study was designed as a modified 3-round Delphi exercise[21,22] to obtain possible agreement on the topic of optimizing the use of oral corticosteroids in adults with severe asthma, among a broad panel of medical experts in asthma.

The scientific committee comprised six experts with experience in the treatment of severe asthma, with different backgrounds, namely pulmonology and immunoallergology, and one epidemiologist. The expert panel selected by the scientific committee consisted of 48 physicians (specialists in allergology and pulmonology), from public and private institutions (with clinical and academic expertise in the management of asthma), and with a wide distribution at national level to capture any regional specific

aspects (North, Center and South Portugal). Because the survey was completed anonymously and no personal data were collected, institutional review board approval was not necessary. The research assistance team, which directed and oversaw the entire process, was responsible for the distribution and analysis of the questionnaires.

Delphi rounds and consensus meeting

The Delphi questionnaire was developed by the scientific committee and initially included 65 statements (items), formulated in Portuguese, grouped into three main topics: (1) Chronic Systemic Corticotherapy (CSC) in Asthma (n = 19 items); (2) Therapeutic Schemes of Systemic Corticotherapy in Crisis and Maintenance (n = 26 items); (3) Asthma Safety and Monitoring (n = 20 items).

The panel of experts should answer each statement with their degree of agreement, using a five-point, ordinal, Likert-type scale. The scale was rated as 1- 'strongly disagree', 2- 'disagree', 3- 'neither agree nor disagree', 4- 'agree' and 5- 'strongly agree'. Additionally, panel members during rounds 1 and 2 had the opportunity to add comments to each statement in free-text boxes. The modified Delphi study ran between October 2019 and November 2019. Panelists answered via an online survey platform for each round (Welphi Platform).

The research assistance team assessed and presented the overall results from each round to all participants (groups' responses and individual response) to facilitate comments and clarifications on the statements.

In 2nd and 3rd rounds, panel members contrasted their previous round personal opinion with other participants' opinions. When they decided, participants were allowed to reassess their initial opinion on those statements where consensus was not reached. In the 2nd round, relevant comments from 1st round could originate statement rephrasing, or addition of new statements, which were individually evaluated by the scientific committee before inclusion in Delphi. After the 3rd round, the scientific committee met face-to-face and, subsequently had a face-to-face meeting with the panelists to discuss the final results and gather more in-depth opinions.

Data analysis

For the purpose of the analysis, the answers given to categories 'strongly agree' and 'agree', or on the categories 'strongly disagree' and 'disagree' were aggregated into 'positive consensus' and 'negative consensus', respectively. As convergence indicators, the percentage variation of the concordance ratio between rounds was used.

Consensus threshold (cut-off concordance) was established as a percentage of agreement among the participants for each individual item equal or greater to 90% ($\geq$90%) in the 1st round; and equal or greater to 85% ($\geq$85%) in the 2nd and 3rd rounds. A statement that did not reach consensus on the 1st round was reconsidered in the following round and so on. After three rounds, the remaining statements were considered to have not reached consensus. The scores and the level of consensus achieved by panelists were used to analyze the group opinion for each item.[23]

Results

Overall, 46 of all 48 invited panelists completed the three rounds of the Delphi consensus (95.8% compliance). No new items were proposed during the exercise. Three items (two from topic 1 and one from topic 3) had their text reformulated after the 1st round by the scientific committee to improve interpretability, as suggested by the panelists.

Fig. 1 shows the flowchart of the Delphi exercise. In the 1st round, consensus was reached on 28 of the 65 items (43.1%), all of them due agreement (see Table 1). Ten statements had a concordance equal to 100% (statements 1, 2, 3, 9, 11, 20, 44, 54, 61, 62). Thirty-seven remaining items were iterated in the 2nd round, where 15 items (40.5%) reached consensus (14 in agreement and one in disagreement) (see Table 2). During the 3rd round, for the 22 remaining statements, 10 (45.5%) obtained consensus (nine in agreement and one in disagreement) (see Table 3). By the end of the Delphi exercise, twelve statements had not achieved consensus (18.5%) (items 5, 17, 22, 23, 31, 33, 39, 42, 46, 52, 63, 64) (see Table 4). See supplemental material (Tables S1) for complete analysis in the original language (Portuguese).

Topic 1: chronic systemic corticotherapy in asthma

This topic aggregated 19 statements. During 1st round, n = 10 statements (52.6%) obtained positive consensus (categories 'strongly agree' or 'agree') (see Table 1). The remaining nine items did not reach agreement and, thus, were launched again in the 2nd round, where n = 3 (33.3%) obtained positive consensus (Table 2). In the last round, n = 4 out of the six remaining items (66.7%) reached consensus; two items did not reach consensus (10.5%) (Tables 3 and 4).

Topic 2: therapeutic schemes of systemic corticotherapy in crisis and maintenance

This topic gathered 26 items, of which n = 8 (30.7%) obtained positive consensus in the 1st round (Table 1). The remaining statements were re-evaluated in the 2nd round, where n = 6 (33.3%) were positively consensualized (Table 2). The evaluation of the twelve items in 3rd round, resulted in consensus for n = 6 of them (50.0%), of which one obtained negative agreement (Table 3). Six other statements did not reach consensus in this topic (Table 4).

Topic 3: asthma safety and monitoring

This last topic comprised 20 statements. During 1st round, half of the items (n = 10) obtained positive consensus (Table 1), while the others followed to the next round. In the 2nd round, n = 6 were consensualized (60.0%) (Table 2), one of them with negative agreement. In the final round, none of the remaining four items (20.0%) reached consensus (Tables 3 and 4).

Some variations in the responses between rounds were observed. The median variation in agreement rates between 1st and 2nd rounds was 7.4% [IQR 3.7, 10.1], while between second and third rounds was 5.3% [IQR 2.2, 8.1]. Median variation in disagreement rates between the 1st and 2nd

Table 1 Results of the Delphi exercise: items reaching consensus in the 1st round.

Topic	Item	Statements	Positive agreement	Neutral opinion	Negative agreement	N. answers	Round of consensus
1	1	An objective evaluation and optimization of therapeutic noncompliance in patients with severe uncontrolled asthma are crucial for the correct diagnosis of severe asthma.	100.0%	0.0%	0.0%	48	***1 st***
1	2	Differential diagnosis and the identification and treatment optimization of comorbidities that interfere with asthma control are of major relevance for the correct diagnosis of severe asthma.	100.0%	0.0%	0.0%	48	***1 st***
1	3	Inhaled therapy should be maximized in severe asthma.	100.0%	0.0%	0.0%	48	***1 st***
1	4	Treatment of severe asthma should be driven by clinical criteria alongside with the evaluation of the mechanisms involved in the disease (with the aid of markers e.g. peripheral blood eosinophil count, total serum IgE, skin tests, nitric oxide (FeNO) and induced sputum cell count)	97.9%	0.0%	2.1%	48	***1 st***
1	7	Systemic corticosteroids may be used in moderate to severe asthma exacerbations, but NOT as front line to manage severe asthma in the long term.	95.8%	4.2%	0.0%	48	***1 st***
1	9	Chronic exposure to systemic corticosteroids is significantly associated with an increase of adverse events, such as infections, cardiovascular, metabolic, psychiatric, ocular, gastrointestinal and bone complications.	100.0%	0.0%	0.0%	48	***1 st***
1	11	Biologic agents allowing a reduction in systemic corticosteroids usage should be preferred as adjuvant therapy in eligible patients with severe asthma.	100.0%	0.0%	0.0%	48	***1 st***
1	12	Whenever eligible, asthmatic patients already dependent of systemic corticotherapy should be offered biologic agent therapy.	97.9%	2.1%	0.0%	48	***1 st***
1	16	A severe asthma patient with more than 2 severe asthma exacerbations treated with systemic corticosteroids, or an asthma related hospitalization in the last/past year, whenever eligible, should be treated with a biologic agent.	91.7%	8.3%	0.0%	48	***1 st***
2	19	Patients with uncontrolled severe asthma which are not eligible for biologics and treated with OCS, should have its effectiveness evaluated in 3-6 months. That evaluation should be based in the change of the outcomes previously defined for that specific patient.	93.8%	2.0%	4.2%	48	***1 st***

Table 1 (*Continued*)

Topic	Item	Statements	Positive agreement	Neutral opinion	Negative agreement	N. answers	Round of consensus
2	20	The lowest effective dose of systemic corticosteroids should be used in the control of asthma.	100.0%	0.0%	0.0%	48	***1 st***
2	21	An understanding about the best disease control should be pre-established with the patient, concerning various parameters to be considered, as exacerbations, symptoms, quality of life, respiratory function or adverse effects of therapy.	95.8%	2.1%	2.1%	48	***1 st***
2	26	In uncontrolled severe asthmatic patients, maximum daily doses of systemic corticosteroids should be the minimum needed dose to reach symptom relief and to reduce annual exacerbations	93.8%	2.0%	4.2%	48	***1 st***
2	36	Sudden interruption of chronic systemic corticosteroid therapy is not recommended.	93.8%	4.2%	2.0%	48	***1 st***
2	38	In stable patients receiving high doses of ICS / LABA and oral corticosteroids, a reduction in the dose of chronic systemic corticosteroids is recommended.	95.8%	2.1%	2.1%	48	***1 st***
2	41	The use of depot injectable corticosteroids should be avoided.	97.9%	2.1%	0.0%	48	***1 st***
2	43	The decision to treat asthma with chronic systemic corticosteroids should be assessed on the therapy benefit/risk balance.	95.8%	0.0%	4.2%	48	***1 st***
2	44	Continuous development of alternative therapies for the management of asthma exacerbations and severe asthma are necessary to reduce exposure to systemic corticosteroids.	100.0%	0.0%	0.0%	48	***1 st***
3	47	Sudden reduction in the dose of chronic systemic corticosteroids may be associated with symptoms of adrenal suppression, a side effect that must be avoided.	95.8%	2.1%	2.1%	48	***1 st***

Table 1 (*Continued*)

Topic	Item	Statements	Positive agreement	Neutral opinion	Negative agreement	N. answers	Round of consensus
3	50	Adverse events related to the use of chronic systemic corticosteroid therapy are dose dependent and cumulative over time.	97.9%	2.1%	0.0%	48	***1 st***
3	53	The use of systemic corticosteroids for short periods of time MAY be associated with serious adverse events, particularly in the presence of comorbidities.	95.8%	4.2%	0.0%	48	***1 st***
3	54	Patients on continuous use of systemic corticosteroid therapy should be regularly monitored regarding the assessment of weight gain, diabetes, dyslipidemia, hypertension, glaucoma, osteoporosis, cataracts, or neuropsychiatric disorders.	100.0%	0.0%	0.0%	48	***1 st***
3	58	Patients treated with chronic systemic corticosteroids should be screened for diabetes every 3 to 6 months in the first year and thereafter every year.	93.8%	4.1%	2.1%	48	***1 st***
3	59	Patients treated with chronic systemic corticosteroids should be screened for hypertension every 3-6 months.	93.8%	2.0%	4.2%	48	***1 st***
3	60	Patients treated with chronic systemic corticosteroids should undergo weight control assessment every 3-6 months.	91.7%	6.2%	2.1%	48	***1 st***
3	61	Patients treated with chronic systemic corticosteroids maintain indication for pneumococcal and flu vaccines.	100.0%	0.0%	0.0%	48	***1 st***
3	62	Patients who begin dose reduction/progressive dose reduction aiming chronic systemic corticosteroids discontinuation should do so with a slow and progressive decrease.	100.0%	0.0%	0.0%	48	***1 st***
3	65	In the presence of normal morning serum cortisol levels and symptoms of adrenal suppression (i.e. fatigue, nausea, vomiting, diarrhea, arthralgia, hypotension, psychiatric symptoms), patients should be referred to endocrinology for complementary evaluation.	93.8%	4.1%	2.1%	48	***1 st***

Table 2 Results of the Delphi exercise: items reaching consensus in the 2nd round.

Topic	Item	Statements	Rounds	Positive agreement	Neutral opinion	Negative agreement	N. answers	Round of consensus
1	6	So far, cumulative risk of systemic corticosteroids use in acute exacerbations of asthma has not been properly valued.	1 st 2nd	81.2% 87.0%	6.2% 4.3%	12.7% 8.7%	48 46	***2nd***
1	10	Exposure to systemic corticosteroids, even in short-term administration, i.e. without considering chronic exposure, is associated with an increased risk of adverse events, such as infections, cardiovascular, metabolic, psychiatric, ocular, gastrointestinal and bone complications.	1 st 2nd	81.3% 91.3%	10.4% 6.5%	8.3% 2.2%	48 46	***2nd***
1	13	A nitric oxide (FeNO) above 20 ppb or a peripheral blood eosinophil count above 150 cells per μl is suggestive of type 2 inflammation.	1 st 2nd	87.5% 91.3%	2.0% 4.4%	10.6% 4.3%	48 46	***2nd***
2	24	Corticosteroid-resistant asthma or insensitivity to corticosteroids, which might occur in severe asthma, is related to several factors.	1 st 2nd	87.5% 91.3%	10.4% 6.5%	2.1% 2.2%	48 46	***2nd***
2	28	In case of significant adverse events with clinical harm, chronic systemic corticosteroids dose should be reduced, being acceptable some worsening of asthma control, as long as it does not IMPLY FURTHER EXACERBATIONS.	1 st 2nd	81.2% 89.1%	10.4% 6.6%	8.5% 4.3%	48 46	***2nd***
2	34	In patients with the ability to self-manage asthma, in the face of an exacerbation, the timely initiation of therapy with a short cycle of systemic corticosteroids is usually effective in preventing the progression of the exacerbation and reducing symptoms.	1 st 2nd	77.1% 93.5%	12.5% 0.0%	10.4% 6.5%	48 46	***2nd***
2	35	The dose reduction of chronic systemic corticosteroids should be carried out under the direct supervision of a respiratory specialist.	1 st 2nd	89.5% 91.3%	2.1% 2.2%	8.4% 6.5%	48 46	***2nd***

Table 2 (*Continued*)

Topic	Item	Statements	Rounds	Positive agreement	Neutral opinion	Negative agreement	N. answers	Round of consensus
2	40	The dose of slow-release systemic corticosteroids is, in most cases, higher than the one needed to control the exacerbation.	1 st 2nd	81.2% 89.1%	8.3% 4.4%	10.4% 6.5%	48 46	***2nd***
2	45	Chronic systemic corticosteroids administration in asthmatics can anticipate in decades the appearance of comorbidities such as diabetes mellitus and cardiovascular disease in patients with susceptible genetic background.	1 st 2nd	87.5% 93.5%	6.5% 4.3%	6.5% 2.2%	48 46	***2nd***
3	48	There are no differences in the frequency of adverse events between intramuscularly or orally administered corticosteroids.	1 st 2nd	16.7% 8.7%	8.3% 4.3%	75.0% 87.0%	48 46	***2nd***
3	49	Adverse events related to the use of chronic systemic corticosteroid therapy are dose dependent.	1 st 2nd	77.1% 89.1%	14.6% 6.6%	8.3% 4.3%	48 46	***2nd***
3	51	Systemic corticotherapy is associated with an increase in health expenditure, partly due to related adverse events management.	1 st 2nd	87.5% 95.7%	10.4% 2.1%	2.1% 2.2%	48 46	***2nd***
3	55	Patients under chronic systemic corticosteroid therapy should perform bone densitometry every 2 years.	1 st 2nd	85.4% 89.1%	10.4% 10.9%	4.7% 0.0%	48 46	***2nd***
3	56	Patients treated with chronic systemic corticosteroids should undergo annual eye screening.	1 st 2nd	89.6% 93.0%	8.3% 7.0%	2.1% 0.0%	48 46	***2nd***
3	57	Patients treated with chronic systemic corticosteroids should be screened for lipid disorders after the first month and thereafter every 6 to 12 months.	1 st 2nd	87.6% 87.0%	6.2% 6.5%	6.2% 6.5%	48 46	***2nd***

Table 3 Results of the Delphi exercise: items reaching consensus in the 3rd round.

Topic	Item	Statements	Rounds	Positive agreement	Neutral opinion	Negative agreement	N. answers	Round of consensus
1	8	Systemic corticosteroids are one of the adjuvant therapies for severe asthma.	1 st	66.7%	10.4%	22.9%	48	
			2nd	80.4%	6.5%	13.1%	46	*3rd*
			3rd	89.1%	0.0%	10.9%	46	
1	14	Asthmatic patients treated with systemic corticosteroids or high dose inhaled corticosteroids may have a deceivingly reduction on type 2 inflammation signals.	1 st	85.4%	10.4%	4.2%	48	
			2nd	84.8%	10.8%	4.4%	46	*3rd*
			3rd	95.7%	4.3%	0.0%	46	
1	15	Even with the availability of biologic agents, a proportion of patients will still need systemic corticosteroids to control their severe asthma.	1 st	75.0%	14.5%	10.5%	48	
			2nd	84.8%	8.7%	6.5%	46	*3rd*
			3rd	91.3%	4.3%	4.3%	46	
1	18	In patients with uncontrolled severe asthma which are not eligible for biologics (e.g. non type 2 asthma), systemic corticosteroids may be attempted in order to achieve control.	1 st	81.2%	12.5%	6.3%	48	
			2nd	82.6%	10.9%	6.5%	46	*3rd*
			3rd	89.1%	8.7%	2.2%	46	
2	25	In corticosteroid-insensitive asthma, effective treatment with oral systemic corticosteroids might only be achieved with higher doses.	1 st	63.9%	19.1%	17.0%	47	
			2nd	71.7%	15.2%	13.0%	46	*3rd*
			3rd	87.0%	4.3%	8.7%	46	
2	27	Titration of systemic corticosteroids dose, in order to control severe asthma, should not exceed 40 mg prednisone or equivalent daily, since it is unlikely that higher doses have further benefits	1 st	72.9%	14.5%	12.7%	48	
			2nd	80.4%	8.7%	10.9%	46	*3rd*
			3rd	87.0%	6.5%	6.5%	46	
2	29	In case of significant adverse events with clinical harm, chronic systemic corticosteroids dose should be reduced being acceptable some worsening of asthma control, as long as it does not IMPLY WORSENING OF SYMPTOMS	1 st	68.7%	16.6%	14.8%	48	
			2nd	84.8%	4.4%	10.8%	46	*3rd*
			3rd	89.1%	0.0%	10.9%	46	
2	30	In case of significant adverse events with clinical harm, chronic systemic corticosteroids dose should be reduced, being acceptable some worsening of asthma control, as long as it does not IMPLY A QUALITY OF LIFE DETERIORATION.	1 st	68.7%	14.5%	16.7%	48	
			2nd	82.6%	4.4%	13.0%	46	*3rd*
			3rd	88.9%	0.0%	11.1%	45	
2	32	In severe asthma there is no need to escalate the chronic systemic corticosteroids dose	1 st	8.3%	16.7%	75.0%	48	
			2nd	4.4%	10.8%	84.7%	46	*3rd*
			3rd	2.2%	10.8%	87.0%	46	
2	37	Gradual dose reduction of chronic systemic corticosteroids avoids exacerbations, as the minimum necessary dose can be titrated.	1 st	72.9%	16.7%	10.4%	48	
			2nd	84.8%	13.0%	2.2%	46	*3rd*
			3rd	89.1%	8.7%	2.2%	46	

Table 4 Results of the Delphi exercise: items without consensus.

Topic	Item	Statements	Rounds	Positive agreement	Neutral opinion	Negative agreement	N. answers	Round of consensus
1	5	So far, chronic maintenance therapeutic with systemic corticosteroids in severe asthma has been avoided.	1 st 2nd 3rd	58.3% 63.0% 65.2%	9.8% 6.5% 2.2%	31.9% 30.5% 32.6%	48 46 46	Not reached
1	17	In patients with biologic criteria, systemic corticosteroid therapy should not be initiated because of the risk of incurring complications inherent to systemic corticosteroid therapy.	1 st 2nd 3rd	54.2% 76.1% 82.6%	8.3% 0.0% 0.0%	37.5% 23.9% 17.4%	48 46 46	Not reached
2	22	Doses until 5 mg prednisone or equivalent a day are considered low chronic systemic corticosteroid doses	1 st 2nd 3rd	70.8% 78.3% 82.6%	16.5% 13.0% 10.9%	12.7% 8.7% 6.5%	48 46 46	Not reached
2	23	Doses above 5 mg of prednisone or equivalent a day are considered high chronic systemic	1 st 2nd 3rd	56.2% 60.8% 69.6%	20.8% 19.6% 17.4%	23.0% 19.6% 13.0%	48 46 46	Not reached
2	31	Facing relevant side effects with serious clinical damages, chronic systemic corticosteroids dose should be reduced although with some acceptable worsening of asthma control, as long as it does not IMPLY THE DECLINE OF PULMONARY FUNCTION.	1 st 2nd 3rd	52.0% 67.4% 76.1%	18.8% 8.7% 4.3%	29.2% 23.9% 19.6%	48 46 46	Not reached
2	33	Monitoring inflammation biomarkers (e.g., exhaled nitric oxide, peripheral blood eosinophil count) is useful for titrating the chronic systemic corticosteroids dose in the long term.	1 st 2nd 3rd	37.5% 36.9% 37.0%	33.3% 41.3% 43.4%	29.2% 21.7% 19.6%	48 46 46	Not reached

Table 4 (*Continued*)

Topic	Item	Statements	Rounds	Positive agreement	Neutral opinion	Negative agreement	N. answers	Round of consensus
2	39	Intramuscular injections of depot corticosteroids are as effective as oral corticosteroids in preventing asthma exacerbations.	1 st	22.9%	14.6%	62.5%	48	Not reached
			2nd	21.7%	10.9%	67.4%	46	
			3rd	21.7%	8.7%	69.6%	46	
2	42	Titration of chronic systemic corticosteroids dose based on biomarkers results in a larger reduction of exacerbations, when compared to the dose titration solely based on clinical markers.	1 st	47.9%	37.5%	14.6%	48	Not reached
			2nd	52.2%	37.0%	10.8%	46	
			3rd	52.2%	41.3%	6.5%	46	
3	46	A patient treated with chronic systemic corticosteroids is at risk of being on long-term prednisone, as therapy may not be able to be stopped due to adrenal suppression.	1 st	56.2%	18.8%	25.0%	48	Not reached
			2nd	65.2%	8.7%	26.1%	46	
			3rd	67.4%	8.7%	23.9%	46	
3	52	The use of systemic corticosteroids for short periods of time is NOT associated with serious adverse events.	1 st	22.9%	20.8%	56.3%	48	Not reached
			2nd	17.4%	17.4%	65.2%	46	
			3rd	8.7%	8.7%	82.6%	46	
3	63	Whenever physiological doses are reached, plasmatic levels of ACTH and plasmatic cortisol should be measured	1 st	64.6%	22.9%	12.5%	48	Not reached
			2nd	73.9%	21.7%	4.4%	46	
			3rd	82.6%	17.4%	0.0%	46	
3	64	Morning serum cortisol levels should guide the reduction of chronic systemic corticosteroids below physiologic dose	1 st	50.0%	29.2%	20.8%	48	Not reached
			2nd	60.8%	26.1%	13.1%	48	
			3rd	63.0%	34.8%	2.2%	46	

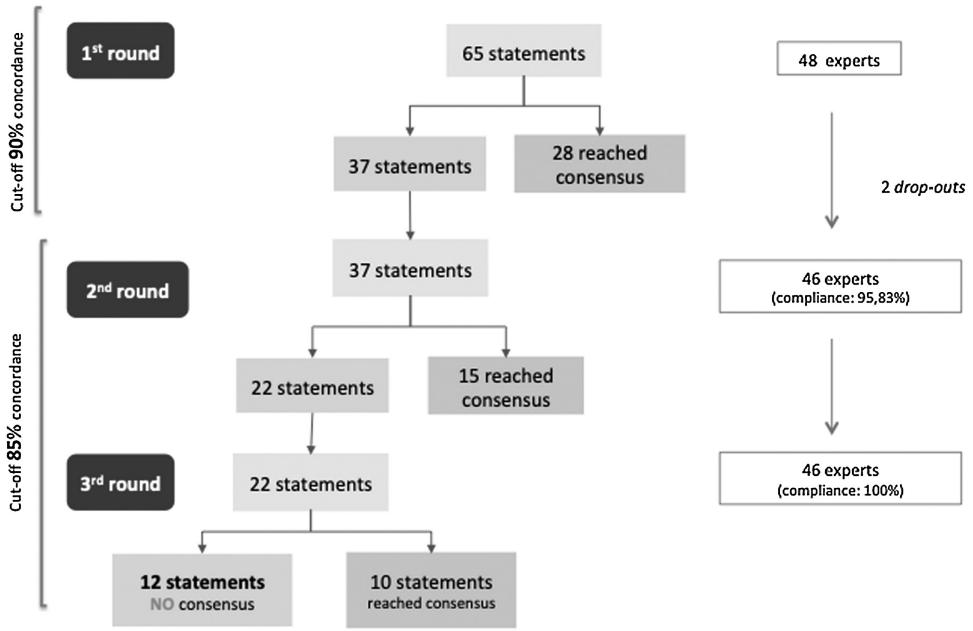

Figure 1 Flowchart of the consensus obtained in the Delphi study.

rounds was -3.7% [IQR -4.2, 0.1]; and between 2nd and 3rd rounds was -2.2% [IQR -4.4, -0.5]). Statements n. 17 (topic 1) and 34 (topic 2) presented the highest changes in agreement rates, expressed in percentage points (pp): 21.9 pp and 16.4 pp, respectively, between 1st and 2nd rounds. Between 2nd and 3rd rounds, statements 14 (topic 1) and 25 (topic 2) were those with highest variation (10.9 pp and 15.2 pp respectively). Statements n. 17 (topic 1) and 52 (topic 3) showed more variation in the disagreement rates: -13.6 pp (between 1st and 2nd rounds) and 17.4 pp (between 2nd and 3rd rounds), respectively (see supplemental material Table S2).

Discussion

We were able to perform a nationwide and multidisciplinary Delphi consensus with the participation of experts from the different clinical specialties that daily treat adult patients with severe asthma in Portugal. The high level of compliance among panelists with this exercise (over 95% in all rounds) may reveal the perception of relevance of the topic for clinical practice.

The Delphi technique has the advantage of avoiding the dominant personality effect by using anonymous responses, and allows for the re-evaluation of panelists opinions in the light of group answers, without losing the gains from face-to-face discussions.[24–26] Studies also stress the added value of comments along with personal interaction as a way of supporting the change on the level of agreement between rounds or to detail the reasons behind a lack of consensus.[27,28]

Almost half of the statements enrolled in this Delphi questionnaire obtained positive consensus by the end of round one; ten of them with a concordance equal 100%. By the end of the exercise, 12 statements had not reached consensus.

The lack of consensus in statement 5 ''*So far, chronic maintenance therapeutic with systemic corticosteroids in severe asthma has been avoided*'' may be due to lack of clarity of the text, leading to misinterpretation. Nevertheless, almost two-thirds of the panelists considered that there is no overuse of OCS in the maintenance therapeutics of severe asthma, which is far from the reality in our country,[29] and therefore should be addressed in future educational actions. On the other hand, there was a consensus (87% of positive agreement) that further actions for the assessment of the cumulative risk of OCS use in acute asthma exacerbations are needed (statement 6 ''*So far, cumulative risk of systemic corticosteroids use in acute exacerbations of asthma has not been properly valued*'').

For some statements, such as item 9 (''Chronic exposure to systemic corticosteroids is significantly associated with an increase of adverse events, such as infections, cardiovascular, metabolic, psychiatric, ocular, gastrointestinal and bone complications'') the full agreement in the 1st round was expected given the generic non-specific text. Nevertheless, statement 10 (''Exposure to systemic corticosteroids, even in short-term administration, i.e. without considering chronic exposure, is associated with an increased risk of adverse events, such as infections, cardiovascular, metabolic, psychiatric, ocular, gastrointestinal and bone complications'') only achieved consensus in the 2nd round. We might speculate that awareness of short-term OCS side-effects is lower but also, we should recognize that the statement did not quantify the increase in the number of adverse events nor define the meaning of short-term administration.

The positive consensus (91.3%) obtained for statement 15 in the last round (''Even with the availability of biologic agents, a proportion of patients will still need systemic corticosteroids to control their severe asthma'') demonstrated the ongoing debate on the substitution of OCS by

other therapies. During the face-to-face meeting, the committee highlighted that even with the availability of new biologic agents, physicians may still consider the use of OCS for severe asthma. Indeed, an important percentage of severe asthma patients are not eligible for the already available biological agents and so, probably given the clinical experience with OCS in type 2 asthma, these therapies might still have a role.[20,30] However, the positive consensus (91.7%) achieved for the statement 16 at the 1st round (''A severe asthma patient with more than 2 severe asthma exacerbations treated with systemic corticosteroids, or an asthma related hospitalization in the last/past year, whenever eligible, should be treated with a biologic agent'') demonstrated a favorable perception for using biologic agents. This emphasizes an especially important message for all physicians who face severe asthma patients (both in acute and chronic settings) that must increase their awareness for the availability of these novel therapies, reinforcing the need for a timely referral.

Consensus was not reached for statement 17: ''In patients with biologic criteria, systemic corticosteroid therapy should not be initiated because of the risk of incurring complications inherent to systemic corticosteroid therapy''. This may have occurred given the existing delays for the approval of use of biologic agents in our country, which contributes to increasing the number of untreated patients who need to initiate OCS. The discussion with the experts revealed that OCS should usually be avoided before biologics, but when justified, they can be initiated at a minimum effective dosage for a short period of time. This means, biologic agents are now viewed as the first line of treatment for severe asthma, and OCS should be withdrawn as soon as possible once a biologic is initiated.

Patients that do not respond to treatment with biologics may also be unresponsive to OCS,[31,32] especially because there are clear unmet needs requiring novel therapeutic approaches for non-type 2 asthma.[19,20] This was highlighted by both statements 18 (''*In patients with uncontrolled severe asthma which are not eligible for biologics (*e.g. *non type 2 asthma), systemic corticosteroids may be attempted in order to achieve control''*) and 19 (''*Patients with uncontrolled severe asthma which are not eligible for biologics and treated with OCS, should have its effectiveness evaluated in 3–6 months. That evaluation should be based in the change of the outcomes previously defined for that specific patient*''). In this context, treatment with OCS still appears to be an important alternative for asthmatic patients, but periodic re-evaluation and tailored treatment towards patients' needs are paramount to demonstrate the added value of this approach. If the added value is not reached, therapeutic strategies must be reconsidered. Asthma control encompasses objective clinical outcomes (e.g. pulmonary function and exacerbations), but also patient-reported outcomes (PROs), such as asthma symptoms, activity levels, health-related quality of life (HRQoL) and patient satisfaction. PROs are important complementary measures of the patient's health care experience which should be considered when selecting treatment, because they supplement physiologic and clinical assessments of asthma and may influence compliance with therapy.[33,34]

The high positive agreement (95.8%) for statements 21 in the 1st round (''An understanding about the best disease control should be pre-established with the patient, concerning various parameters to be considered, as exacerbations, symptoms, quality of life, respiratory function or adverse effects of therapy''), together with the lack of consensus for statement 31 (''Facing relevant side effects with serious clinical damages, chronic systemic corticosteroids dose should be reduced although with some acceptable worsening of asthma control, as long as it does not IMPLY THE DECLINE OF PULMONARY FUNCTION'') may reveal that some degree of lung function deterioration may be more acceptable compared to outcomes such as worsening of symptoms or quality of life (HRQoL).

The lack of consensus in statements 22 and 23 (''Doses until 5 mg prednisone or equivalent a day are considered low chronic systemic corticosteroid doses'' and ''Doses above 5 mg of prednisone or equivalent a day are considered high chronic systemic'', respectively), may have occurred given the differences in the definition of 'low dose'. Although a daily dose of 5 mg of prednisone or equivalent is usually assumed a low dose,[4,5] further evidence on these thresholds may be necessary.

Statements 25 (''In corticosteroid-insensitive asthma, effective treatment with oral systemic corticosteroids might only be achieved with higher doses'') and 27 (''Titration of systemic corticosteroids dose, in order to control severe asthma, should not exceed 40 mg prednisone or equivalent daily, since it is unlikely to have further benefits with higher dose''), both of them with positive consensus in the 3rd round (87.0%), conceptualize the OCS plateau effect for anti-asthmatic efficacy. However, higher doses than 40 mg prednisone daily, or equivalent, should be avoided because there is an increased risk of adverse events without any evidence of added benefits.[4,5,35]

The lack of consensus in statement 39 ''Intramuscular injections of depot corticosteroids are as effective as oral corticosteroids in preventing asthma exacerbations.'' should be interpreted alongside statements 40 (''The dose of slow-release systemic corticosteroids is, in most cases, higher than the one needed to control the exacerbation'') and 41 (''The use of slow-release injectable corticosteroids should be avoided'') which obtained positive agreement in the 2nd and 1st rounds, respectively. These results indicate, as perceived in the face-to-face panel meeting, that item 39 should clearly state 'in the treatment' instead of 'in prevention'. Additionally, long acting OCS should be avoided as stated in the rule: lowest dose, shortest treatment duration. Studies highlight the relevance of the cumulative steroid dose.[36]

The discussion of inflammation monitoring in asthma (statement 33 - ''Monitoring inflammation biomarkers (e.g., exhaled nitric oxide, peripheral blood eosinophil count) is useful for titrating the chronic systemic corticosteroids dose in the long term'') further demonstrates a lack of consensus, probably due to access constraints to these evaluation methods rather than the lack of perception of relevance of the topic by the experts. Still, as shown by the debate from statement 42 (''Titration of chronic systemic corticosteroids dose based on biomarkers results in a larger reduction of exacerbations, when compared to the dose titration solely based on clinical markers'') the literature is ambiguous on the role of inflammation monitoring.[5,37,38] On the other hand, monitoring patient

comorbidities secondary to OCS side effects was rated as imperative by the experts with 100% positive consensus in the 1st round (statement 54 ''Patients on continuous use of systemic corticosteroid therapy should be regularly monitored regarding the assessment of weight gain, diabetes, dyslipidemia, hypertension, glaucoma, osteoporosis, cataracts or neuropsychiatric disorders''), revealing the need for standardized clinical protocols of data collection and evaluation.

The absence of consensus in statement 46 (''A patient treated with chronic systemic corticosteroids is at risk of being on long-term prednisone, as therapy may not be able to be stopped due to adrenal suppression'') may be due to different reasons. OCS withdrawal is sometimes associated with adrenal suppression and some studies find that roughly 20% of patients develop adrenal suppression.[15,30,38] Nevertheless, as no protocols to routinely evaluate these cases exist, this might correspond to an underestimate percentage. Keeping in mind the lack of guidance not only on OCS use in asthma context but also on how to monitor therapies side effects and withdrawals, it is important to develop protocols for daily practice.

The different interpretations of the concept of 'physiological dose' as well as the evaluation methods may justify the lack of consensus for both statement 63 *(''Whenever physiological doses are reached, plasmatic levels of ACTH and plasmatic cortisol should be measured'')* and statement 64 *(''Morning serum cortisol levels should guide the reduction of chronic systemic corticosteroids bellow physiologic dose'')*. Based on the discussion with the experts, the steering committee stated that morning serum cortisol test should be carried out whenever possible because it is an easy, low-cost and accessible test which assists, among other things, the evaluation of adrenal insufficiency.

Despite evident strengths our study has some limitations. Our discussion is based on expert opinion rather than patient data; however, the Delphi technique is a widely used and accepted method for achieving convergence and is well recognized as a qualitative technique for data elicitation. The Delphi panel included only clinical specialists in asthma, selected as key opinion leaders, with the ability to describe clinical practice in Portugal, in secondary specialized care level. However, other healthcare professionals, in other healthcare settings, may have different opinions.

Conclusions

The results of this study could be considered as a first step towards providing updated consensus of OCS use for asthma management in Portugal, and should be supplemented by additional studies, exploring treatment algorithms, therapy access, patient's adherence, and costs.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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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.2020.10.002.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pulmoe.2020.10.002.

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REVIEW

Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis

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Meta-analysis

Abstract
Background: Evidence suggests lungs as the organ most affected by coronavirus disease 2019 (COVID-19). The literature on previous coronavirus infections reports that patients may experience persistent impairment in respiratory function after being discharged. Our objective was to determine the prevalence of restrictive pattern, obstructive pattern and altered diffusion in patients post-COVID-19 infection and to describe the different evaluations of respiratory function used with these patients.
Methods: A systematic review was conducted in five databases. Studies that used lung function testing to assess post-infection COVID-19 patients were included for review. Two independent reviewers analysed the studies, extracted the data and assessed the quality of evidence.
Results: Of the 1973 reports returned by the initial search, seven articles reporting on 380 patients were included in the data synthesis. In the sensitivity analysis, we found a prevalence of 0.39 (CI 0.24–0.56, $p < 0.01$, $I^2 = 86\%$), 0.15 (CI 0.09–0.22, $p = 0.03$, $I^2 = 59\%$), and 0.07 (CI 0.04–0.11, $p = 0.31$, $I^2 = 16\%$) for altered diffusion capacity of the lungs for carbon monoxide (DL_{CO}), restrictive pattern and obstructive pattern, respectively.

Abbreviations: ARDS, Acute respiratory distress syndrome; COVID-19, Coronavirus disease 2019; CT, Chest computed tomography; DL_{CO}, Diffusion capacity of the lungs for carbon monoxide; FEV_1, Forced expiratory volume in the first second; FVC, Forced vital capacity; MERS, Middle East respiratory syndrome; MEP, Maximal expiratory pressure; MIP, Maximal inspiratory pressure; MMEF, Maximal mid-expiratory flow; MVV, Maximal voluntary ventilation; NHLBI, National Heart, Lung and Blood Institute; PFT, Pulmonary Function Test; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; PROSPERO, International prospective register of systematic reviews; R5, Airway resistance at an oscillation frequency of 5 Hz; R20, Airway resistance at an oscillation frequency of 20 Hz; RCT, Randomised controlled trial; SARS, Severe acute respiratory syndrome; TLC, Total lung capacity; VC, Vital capacity.

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Conclusion: Post-infection COVID-19 patients showed impaired lung function; the most important of the pulmonary function tests affected was the diffusion capacity.

Introduction

On March 11, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) to be a pandemic, with approximately 20% of patients infected requiring hospitalisation and 6% in critical care and needing invasive ventilatory assistance.[1] Early epidemiological reports showed that 8.2% of total cases presented with rapid and progressive respiratory failure, similar to acute respiratory distress syndrome (ARDS).[2]

Recent evidence suggests that the lungs are the organ most affected by COVID-19[3] with different pathophysiological events that include diffuse alveolar epithelium destruction, hyaline membrane formation, capillary damage and bleeding, alveolar septal fibrous proliferation, and pulmonary consolidation.[4] A characteristic of COVID-19 is the extensive injury to alveolar epithelial cells and endothelial cells with secondary fibroproliferation,[5] indicating a potential for chronic vascular and alveolar remodelling leading to lung fibrosis and/or pulmonary hypertension.[6] These findings generate concerns regarding the assessment of lung injury for discharged patients.[4]

Different types of functional respiratory evaluations can be carried out objectively, the most commonly used are pulmonary function tests (PFTs), such as spirometry, diffusion capacity and lung volumes,[7] However, other tests that complement lung function tests, such as the evaluation of respiratory muscles or airway resistance, can help to improve the study of the properties of the lung and allow us to determine the consequences of acute or chronic respiratory disease objectively.

The abnormalities of chest computed tomography (CT), as described in the epidemiological reports, can lead to pulmonary fibrosis and, for this reason, can be analysed together with pulmonary function.[3,8] Recent clinical guidelines suggest following up patients with severe pneumonia due to COVID-19 with full PFTs 12 weeks after discharge.[9] In the case of mild to moderate pneumonia, the PFTs must be conducted after abnormal chest x-rays. In both cases, if any abnormality in lung function, together with a CT abnormality, is found, the patient must be referred to a specialist in interstitial lung disease.[9]

The first reports on lung function related to COVID-19 indicated that patients have a restrictive defect and a small airways dysfunction that can be persistent and not related to the disease severity.[10] Additionally, Mo et al. reported an impairment of diffusion capacity followed by restrictive ventilatory defects, which are both associated with the severity of the disease.[4] The literature on previous coronavirus infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), is concordant with these reports and suggests that patients may experience persistent impairment lasting for months or even years after being discharged.[11,12]

Because it is essential to detect alterations in pulmonary function for the diagnosis and follow-up of patients with respiratory and functional sequelae produced by COVID-19, we decided to carry out a systematic review and meta-analysis aimed to determine the prevalence of restrictive pattern, obstructive pattern and altered diffusion in patients post-COVID-19 infection and to describe the different evaluations of respiratory function used with these patients.

Methods

Protocols and registration

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The meta-analysis was designed and performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE).[14] The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020198178).

Criteria for considering studies in this review

We included randomised controlled trials (RCTs) and observational studies (cross-sectional, longitudinal, case-control and cohort) of patients with a confirmed diagnosis of COVID-19. The studies included aimed to determine the use of PFTs to assess post-infection COVID-19 patients. The selected studies had to follow the ATS / ERS clinical guidelines.[7] In the case of studies that include spirometry, the restrictive pattern had to be confirmed by lung volumes. To analyse the obstructive and restrictive pattern, the studies had to be based on clinical guidelines, such as the ATS / ERS.[7] However, in clinical practice, an FEV_1 / FVC ratio of less than 0.7 has been used, so this relationship was also considered.[15]

Search strategies and data resources

We reviewed the Embase, PubMed/MEDLINE, Web of Science, CINAHL, and Cochrane Register of Clinical Trials (CENTRAL) databases on July 15, 2020. We conducted manual searches with the followings terms for condition: ''SARS-CoV-2'' OR ''COVID-19'' OR ''2019 novel coronavirus infection'' OR ''COVID19'' OR ''coronavirus disease 2019'' OR ''coronavirus disease-19'' OR ''2019-nCoV disease'' OR

''2019 novel coronavirus disease'' OR ''2019-nCoV infection''. We used the following search terms for the main outcome: ''respiratory assessment'' OR ''lung function'' OR ''pulmonary function'' OR ''spirometry'' OR ''total lung capacity'' OR ''vital capacity'' OR ''forced expiratory volume'' OR ''forced vital capacity'' OR ''maximal voluntary ventilation'' OR ''diffusing capacity for carbon monoxide'' OR ''transfer factor of the lung for carbon monoxide'' OR ''forced oscillation technique'' OR ''maximal inspiratory pressure'' OR ''maximal expiratory pressure'' OR ''TLC'' OR ''VC'' OR ''FVC'' OR ''FEV'' OR ''DLCO'' OR ''TLCO'' OR ''MIP'' OR ''MEP'' OR ''MVV'' (Supplementary file S1). We imposed no language or publication restrictions.

The terms selected were combined using Boolean logical operators (OR, AND, NOT). We also conducted a manual search of the references included in the selected articles. All references were analysed using Rayyan web software.[16]

Reviewing procedure and data extraction

The selected articles were reviewed independently by investigators with experience in meta-analysis and training in literature review. First, the titles and abstracts of all identified studies were reviewed by two investigators (LSN, LVC). Studies deemed not relevant based on the review of the title and abstract were excluded. Any disagreements were solved by a third reviewer (RTC). Second, the full-text versions of the articles selected in the first stage were read and checked against the eligibility criteria (RTC, LVC) again. Any disagreements were solved by a third reviewer (JV). Additional unpublished data were obtained from study authors when possible.

Methodological quality assessment

An assessment of the methodological quality of the primary articles was carried out using the Quality Assessment Tools from the National Heart, Lung and Blood Institute (NHLBI).[17] Each tool contains criteria against which internal validity and risk of bias are evaluated. The criteria were evaluated as ''Yes'', ''No'', or ''Other'' (not reported, not applicable, or not determinable), and an overall rating was provided for each study based on the items rated with an affirmative answer: $\geq$ 75% = good, 50–75% = fair, < 50% = poor. Two authors carried out this evaluation independently (XAR, LVC), and discrepancies were resolved by consensus. For discrepancies that could not be resolved, a third author (HP) was consulted.

Data synthesis and analysis

We used MetaXL software version 5.3 (EpiGear International, Sunrise Beach, Queensland, Australia) for our meta-analysis and generation of a forest plot that showed combined estimates with a 95% confidence interval. We pooled the prevalence of the studies structured around individual outcomes using the double arcsine transformation method.[18] We obtained combined measurements of effect for each primary outcome through meta-analysis under a random-effect model due to the expected heterogeneity between studies in prognostic reviews.[19] Statistical heterogeneity was measured through the I^2 statistic and classified as low (I^2 < 25%), moderate (I^2 25–50%), or high (I^2 > 50%).[20] Subgroup analysis, according to the outcome assessment and severity, was carried out. Sensitivity analysis was also carried out to assess the change in pooled prevalence due to the selective exclusion of studies.

Results

Study selection

The initial search yielded 1973 potential studies (1971 from selected databases and 2 from manual searches). In total, 228 duplicate records were deleted. We screened 1745 titles and abstracts and excluded 1677 records which did not meet our inclusion criteria. Sixty-nine of these were assessed as full-text. Of these, 30 studies were excluded for being wrong publication type, 16 for wrong study design, nine for wrong outcome, six for being wrong protocol and one for wrong population. Ultimately, seven studies met the criteria for eligibility and were included in the review.[4,6,10,21–24] The flow chart of the study selection process is shown in Fig. 1.

Characteristics of the included studies

Six studies were conducted in China[4,10,21–24] and one in France.[6] The designs of the studies included one RCT,[21] three retrospectives,[6,22,24] and three prospectives (Table 1).[10,21,23]

Participants

In total, 380 post-infection COVID-19 patients were enrolled in the included studies. Sample sizes varied between 18[10,23] and 110[4] participants. The studies included 162 females and 190 males with mean age varied between 46.7 ± 13.7 and 69.1 ± 7.8 years. One study did not report the gender and mean age of the patients.[23] Five studies reported that between 6% and 18% of patients had a history of smoking,[4,6,22–24] while two studies did not report this.[10,21] Three studies reported respiratory comorbidities,[4,6,23] including emphysema,[6] asthma,[4,6] sarcoidosis,[6] tuberculosis,[23] chronic bronchitis[4] and bronchiectasis.[4]

Time of assessment

There was a wide range in the time of assessment. Two authors reported that respiratory assessment were conducted one month after symptom onset.[4,6] a further two authors reported that they were conducted one month after discharge,[10,22] One author reported that they were conducted three months after discharge.[24] another reported two assessment times, close to discharge and two weeks after discharge,[23] and one author did not report the time of assessment.[21]

Table 1 Description of included articles.

Author	Country	Design	Participants Male/Female	Age (years)	BMI (kg/m^2)	Smoking	Respiratory comorbidities	Time of assessment	Quality rating*
Frija-Masson et al, 2020	France	Retrospective	50 28 M/22F	54 (46–62)	27 (24.6–32.5)	Active 5 (10%) Former 9 (18%)	Emphysema 2 (4%) Asthma 2 (4%) Sarcoidosis 1 (2%)	30 days after symptoms onset	Fair
Huang et al, 2020	China	Retrospective	57 26 M/31F	46.7 ± 13.7	23.9 ± 3.5	History of smoking 9 (15.7%)	No patient was reported having chronic respiratory diseases	30 days after discharge from the hospital	Poor
Li et al, 2020	China	Prospective	18 NR	NR	NR	History of smoking 3 (16.6%)	History of tuberculosis 1 (5.5%)	Near to discharge and two weeks after	Poor
Liu et al, 2020	China	RCT	72 49 M/23F	69.1 ± 7.8	23 ± 3.7	NR	NR	NR	Fair
Mo et al, 2020	China	Prospective	110 55 M/55F	49.1 ± 14.0	23.5 ± 2.8	Smoker 13 (11.8%)	Asthma 1 (0.9%) Chronic bronchitis 1 (0.9%) Bronchiectasis 1 (0.9%)	27.9 ± 7 days after the onset of disease	Fair
You et al, 2020	China	Prospective	18 10 M/8F	50.7 ± 12.1	26.4 ± 2.8	NR	No patient was reported having chronic respiratory diseases	38 ± 13.4 days after hospital discharge	Poor
Zhao et al, 2020	China	Retrospective	55 22 M/23F	47.7 ± 15.5	NR	Active 2 (3.6%) Former 2 (3.6%)	No underlying pulmonary diseases were observed on admission	3 months after hospital discharge.	Fair

Abbreviations: BMI: Body mass index; NR: Not reported; RCT: Randomised controlled trial.
Data are shown as Mean ± standard deviation, Median (Inter-quartile range), n (%).
* NHLBI Study Quality Assessment Tools.

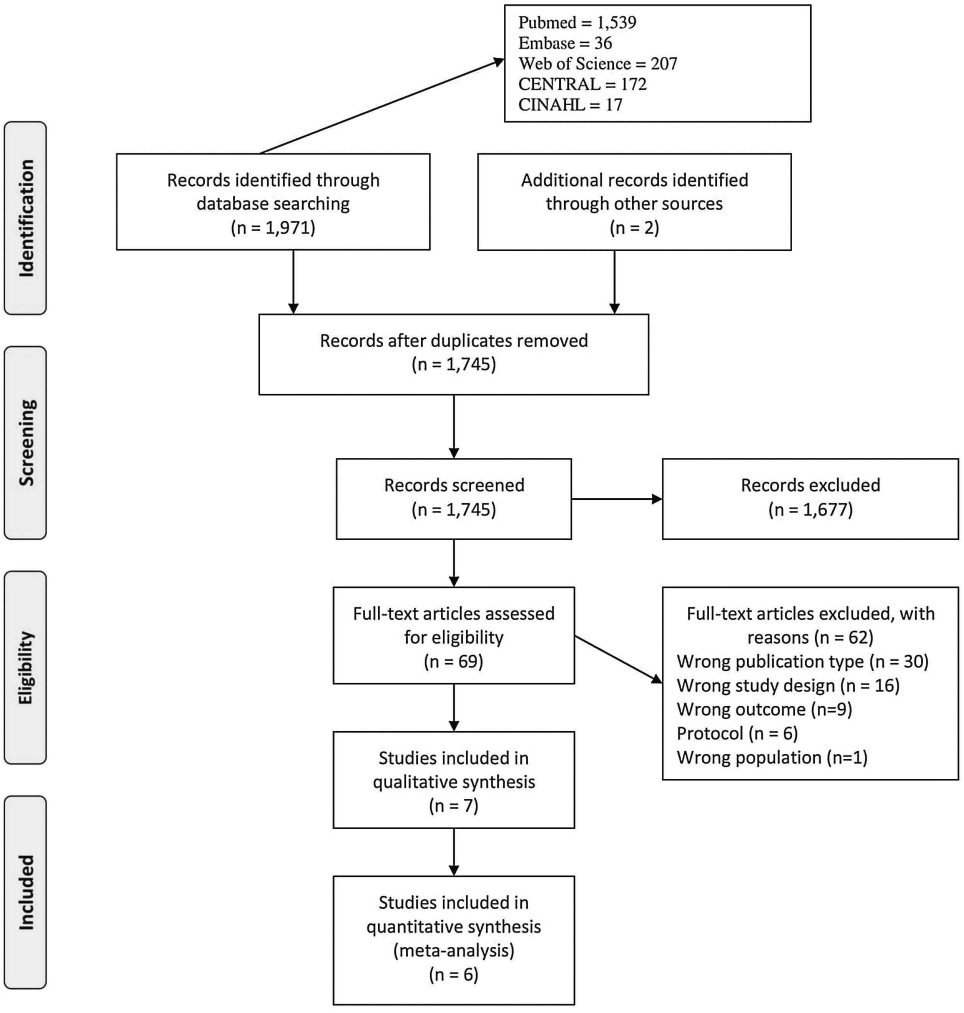

Figure 1 Study selection process.

Methodological quality assessment

The methodological quality of the studies was determined to be ''fair'' in four studies[4,6,21,24] and ''poor'' in three studies[10,22,23] (Supplementary file S2). In our analysis of design, we used the NHLBI's Quality Assessment of Controlled Intervention Studies tool in one study rated as ''fair''.[21] We used the NHLBI's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies in six studies, with three being rated as ''fair''[4,6,24] and three being rated as ''poor''.[10,22,23]

Main findings

Spirometry and lung volumes

Seven studies reported the spirometry test (Table 2, Supplementary file S3).[4,6,10,21–24] All studies showed forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and FEV_1/FVC ratio.[4,6,10,21–24] The interpretation by severity of COVID-19 is shown in Table 3. Three studies indicated maximal mid-expiratory flow (MMEF)%,[4,10,23] and one reported maximal voluntary ventilation (MVV).[10] Six studies reported lung volumes.[4,6,10,22–24] The most-reported parameters were TLC,[4,6,22,24] residual volume (RV)[4,22] and vital capacity (VC).[10,23] Only one study reported tidal volume, expiratory reserve volume, inspiratory reserve volume and inspiratory capacity.[10]

One study did not report patterns of PFT abnormality;[21] therefore, in sensitivity analysis, we analysed six studies[4,6,10,22–24] and found a prevalent restrictive pattern of 0.15 (CI 0.09–0.22, $p = 0.03$, $I^2 = 59\%$) (Fig. 2). In the case of obstructive pattern, prevalence was 0.07 (CI 0.04–0.11, $p = 0.31$, $I^2 = 16\%$) (Fig. 3). We did not analyse severity for restrictive and obstructive patterns because there were insufficient articles.

Diffusion capacity

Five studies reported diffusion capacity of the lungs for carbon monoxide (DL_{CO}) (Table 2, Supplementary file S3).[4,6,21,22,24] Two studies reported DL_{CO}/VA.[4,6] The interpretation by severity is shown in Table 3. In sensitivity analysis, we include three studies[4,6,22] and found a prevalence of altered diffusion capacity of 0.39 (CI 0.24–0.56, $p < 0.01$, $I^2 = 86\%$) (Fig. 4). In the analysis of severity, we excluded one study that had not performed this sub-analysis.[24] The prevalence found was 0.66 (CI 0.31–0.94, $p < 0.01$, $I^2 = 82\%$)

Table 2 Pulmonary function tests of included studies.

	Frija-Masson et al, (n = 50)	Huang et al, (n = 57)	Li et al, (n = 18)	Liu et al, (n = 72)	Mo et al, (n = 110)	You et al, (n = 18)	Zhao et al, (n = 55)
Spirometry							
FVC, L	NR	NR	NR	1.78 ± 0.58	NR	NR	NR
FVC, % of predicted	93 (85–99)	101 ± 15.9	91.5 ± 17.3	NR	93.6 ± 12.3	105.1 ± 23.3	NR
FEV_1, L	NR	NR	NR	1.11 ± 0.11	NR	NR	NR
FEV_1, % of predicted	93 (83–100)	97.9 ± 14.9	89.4 ± 15.7	NR	92.7 ± 11.6	101 ± 19.5	NR
FEV_1/FVC	0.81 (0.75–0.87)	81.2 ± 6.1	80.5 ± 7.0	60.5 ± 6.2	80.7 ± 5.8	77.9 ± 8.1	NR
Lung volumes							
TLC, % of predicted	91.5 (81–103)	93.9 ± 12.8	NR	NR	86.3 ± 11.3	NR	NR
Diffusion capacity							
DL_{CO}, % of predicted	80 (70–92)	78.4 ± 13.6	NR	60.5 ± 11.7	78.2 ± 14.3	NR	NR
DL_{CO}/VA, % of predicted	94 (78–108)	NR	NR	NR	92.1 ± 16.7	NR	NR
PFT Interpretation							
Restrictive, n (%)	13 (26)	7 (12.3)##	5 (27.7)	NR	10 (9.09)# 27 (25)##	3 (16.7)#	6 (10.9) 4 (7.3)
Obstructive, n (%)	2 (4)	6 (10.5)	1 (5.5)	NR	5 (4.55)*	3 (16.7)*	NR
Altered difusion, n (%)	22 (44)	30 (52.6)**	NR	NR	51 (47.22)**	NR	9 (16.4)**
Time of assessment	30 days after symptoms onset	30 days after discharge from the hospital	Near to discharge and two weeks after	NR	27.9 ± 7 days after the onset of disease	38 ± 13.4 days after hospital discharge	3 months after hospital discharge

Abbreviations: DL_{CO}: Diffusion capacity of the lungs for carbon monoxide; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in the first second; NR: Not reported; TLC: Total lung capacity. Data are shown as Mean ± SD, Median (Inter-quartile range), n (%).
#Author reported values lower 80% predicted FVC.
##Author reported values lower 80% predicted TLC.
*Author reported values lower 70% predicted FEV_1/FVC.
**Author reported values lower 80% predicted DL_{CO}.

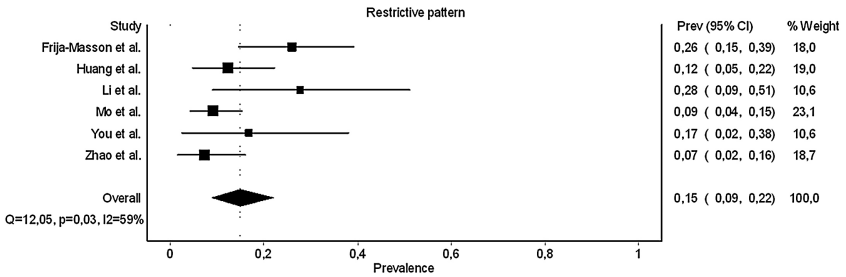

Figure 2 Prevalence of restrictive pattern.

for severe patients and 0.36 (CI 0.28–0.46, $p = 0.27$, $I^2 = 25\%$) for non-severe patients.

Other respiratory measures

One study reported the use of an impulse oscillation system.[22] The parameters reported were airway resistance at an oscillation frequency of 5 Hz (R5) and of 20 Hz (R20).[22] The values obtained were 126.6 ± 29.5%pred and 132.8 ± 30.9%pred for R5 and R20, respectively. One study reported on respiratory muscle strength.[22] In this study, the parameters reported were maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP).[22] The MIP and MEP were 76.2 ± 24.3%pred, and 102.7 ± 32.7%pred, respectively (Supplementary file S3).

Table 3 Pulmonary function tests (PFT) interpretation by severity.

	Frija-Masson et al, 2020[&]		Huang et al, 2020		Mo et al, 2020		You et al, 2020	
PFT Interpretation	Non-severe	Severe	Non-severe	Severe	Non-severe	Severe	Non-severe	Severe
	n = 29	n = 16	n = 40	n = 17	n = 91	n = 19	n = 12	n = 6
Restrictive, n (%)	5 (17.2)	8 (50)	2 (5)[#]	4 (23.5)[#]	8 (8.8)[#]	2 (10.53)[#]	1 (8.3)	2 (33.3)
			3 (7.5)[##]	4 (23.5)[##]	18 (19.8)[##]	9 (47.37)[##]		
Obstructive, n (%)	NR	NR	NR	NR	5 (5.5)*	0 (0)*	3 (16.7)	0 (0)
Altered difusión, n (%)	7 (24.2)	5 (31.25)	17 (42.5)**	13 (76.5)**	35 (38.5)**	16 (84.21)**	NR	NR
Time of assessment	30 days after symptoms onset		30 days after discharge from the hospital		27.9 ± 7 days after the onset of disease		38 ± 13.4 days after hospital discharge	

[#]Author reported values lower 80% predicted FVC.
[##]Author reported values lower 80% predicted TLC.
*Author reported values lower 70% predicted FEV_1/FVC.
**Author reported values lower 80% predicted DL_{CO}.
[&]Only 45 patients were classified by severity.

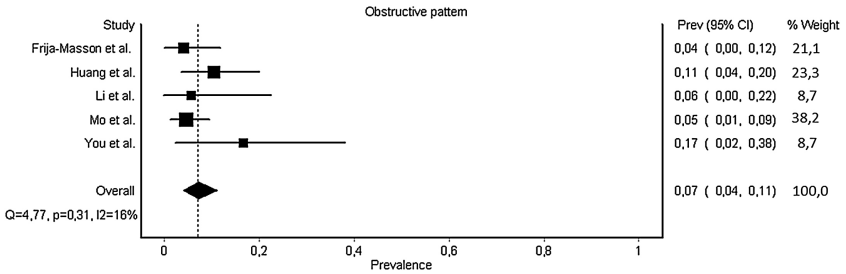

Figure 3 Prevalence of obstructive pattern.

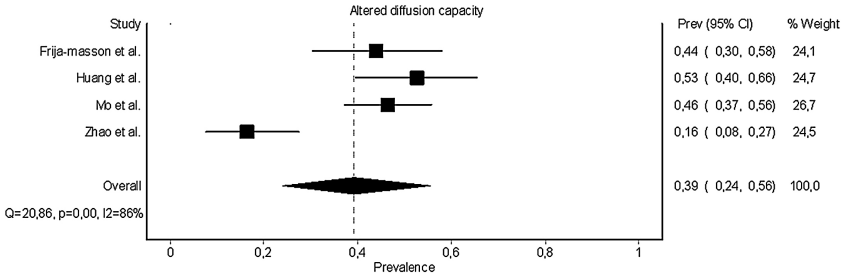

Figure 4 Prevalence of altered diffusion.

Discussion

Altered diffusion capacity, restrictive pattern and obstructive pattern were found in 39%, 15% and 7% of patients, respectively. The assessments most commonly used to assess the respiratory function of patients with COVID-19 were spirometry, lung volumes and diffusion capacity.

We found a high prevalence of altered diffusion capacity. Similar data were found in three studies.[4,6,22] in one of which the prevalence was nearly a third smaller than in the other studies.[24] A possible explanation for this difference is the time of assessment. Zhao et al., who reported a 16% prevalence, performed the PFTs three months after COVID-19 patients were discharged from hospital.[24] Three other studies, which reported a prevalence of between 44% and 56%,[4,6,22] performed the PFTs during the first month post-infection.

An important aspect to consider is the ideal time to perform respiratory assessment tests. The British Thoracic Society (BTS) guide recommends the evaluation of PFTs at three months post-discharge, especially at follow-up with patients suspected of having an interstitial disease.[9] However, in the reviewed studies, most PFTs were conducted one month after the onset of COVID-19 or one month after

discharge. Haste of evaluation may lead to errors in functional diagnosis since we cannot determine how much of this limitation is a result of the disease and how much is due to inflammation from the acute event.

Autopsies of COVID-19 patients revealed different degrees of destruction in alveolar structure, and pulmonary interstitial fibrosis was observed.[25] Pathological changes in the lungs could explain the impaired diffusion capacity. This finding, added to the initial reports of lung damage evidenced by CT,[8] confirms the need to follow these patients, looking for interstitial diseases specifically, as recommended by some clinical guidelines.[9] We found a very high prevalence of altered diffusion capacity (66%) in severe patients, especially those with high inflammatory indicators who are more likely to develop pulmonary fibrosis.[26]

We found a prevalence of restrictive patterns in 15% of patients. The current guidelines suggest a restrictive pattern if the FEV_1/FVC ratio $\geq$ lower limit normal (LLN) and the FVC is < LLN, which should be confirmed by evaluating the TLC.[7] Despite the higher heterogeneity ($I^2 = 59\%$), all studies that assessed spirometry also performed lung volumes. The heterogeneity can probably be explained by the different evaluation times and different methodological designs.

Regarding the obstructive pattern, we found a prevalence of 7% in the sensitivity analysis with low heterogeneity (16%). However, the authors of all studies reviewed, reported differences in criteria at the cut-off point of the obstructive alteration: Frija-Masson et al. used the LLN of GLI values[6]; Mo et al. and You et al. used the FEV_1/FVC ratio as the cut-off point in 70%[4,10]; and Huang et al. used the FEV_1/FVC ratio as the cut-off point in 80% and reported mild impairment in 44% of patients, but later reported only 10.5% of patients had an obstructive pattern, without indicating the method used.[22] The use of the LLN of reference values to homogenise obstructive pattern findings should be reinforced so that results can be more reliable.[7]

An important confounding in our obstructive pattern analysis is the presence of chronic respiratory diseases as comorbidities. Frija-Masson found only two patients with obstructive patterns, but these patients had underlying respiratory diseases (one had asthma and one had sarcoidosis).[6] Other authors also reported the presence of respiratory comorbidities that could influence PFTs.[4,23] For this reason, we analysed this outcome with caution as the data may be overestimated.

We identified other respiratory function assessments, such as respiratory muscle strength, that provide essential information about the state of respiratory pumps and airway resistance, which is important for the confirmation of lung obstruction.[22] All these assessments help to improve the respiratory characterisation of COVID-19 patients and have been recommended to characterise the functional limitations generated by this disease.[27]

Given the heterogeneity of the clinical presentation of COVID-19, it is essential to have simple tools to assess and monitor the impact of symptoms on the respiratory function of patients.[28] Considering the large number of COVID-19 survivors who require follow-up, the use of reproducible instruments to identify patients suffering from slow or incomplete recovery will help guide the reasonable use of medical resources.[28]

Potential biases in the review process

The systematic review process was rigorous. The review was preceded by the publication of a protocol with all review methods described and all review authors were appropriately trained and had experience in review preparation.

Completeness of evidence

We conducted a comprehensive search of the literature, including full-text publications, without language restrictions or the use of filters in the search strategy. Although we only included studies published between December 2019 and July 2020, it is unlikely that any have been missed, given that publications on the topic only began to appear in December 2019.

Quality of evidence

This systematic review followed the standard recommended methodology and was constructed in line with PRISMA guidelines.[13] Two independent review authors assessed the inclusion criteria for the studies, extracted data and assessed the risk of bias of the included studies, thus reducing the risk of performance bias in the review and data extraction errors.

Sources of heterogeneity

We found wide heterogeneity in the designs. We were only able to analyse seven studies, and these were not necessarily of good quality. The majority were qualified as ''poor''. The most significant concern was the time of assessment. Haste in evaluation may lead to errors in functional diagnosis since we cannot determine how much of this limitation is a result of the disease and how much is due to inflammation from the acute event.

Limitations

The most important limitation of this study is the high heterogeneity of the selected studies, particularly among the different evaluations used. The criteria for determining the severity of pneumonia differ according to the literature; variations such as based on CT findings, guidelines of COVID-19, or use of ventilatory support. Assessing the methodological quality in the studies reviewed was difficult because different designs were identified. Another significant limitation is that the studies did not report the previous lung function of the patients, so it is not possible to know the real affect generated by the infection. This limitation can be partially remedied since it is compared with reference values; however, it should be considered that there may be a reduction in lung function due to previous respiratory diseases, effects of smoking or environmental pollution.

Finally, the assessment times were different. Although the PFTs follow specific guidelines given by the clinical guidelines of respiratory societies, it is necessary to establish standard evaluation times to facilitate comparison between different populations. In this way, we will be bet-

ter able to know the real impact on respiratory function generated by COVID-19.

Conclusion

Post-infection COVID-19 patients showed altered respiratory function. The most important of the PFTs affected was the diffusion capacity in close to 40% of patients. The results of PFTs must be analysed with caution and considering the respiratory comorbidities and the possible impairment generated by smoking and air pollution. Well-designed studies conducted in post-COVID-19 infection patients, taking into consideration the infection severity and based on the pulmonary function guidelines are required. Future research should be focused on the characterisation of short and long-term respiratory function sequelae to optimise the decision-making in clinical practice. The data collected to date in this systematic review could be a useful starting point for further studies.

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Conflicts of interest

FB belongs to Scientific Advisory Board (Medical Graphics Corporation Diagnostics). The other authors declare to have no conflict of interest.

CRediT authorship contribution statement

R. Torres-Castro: Conceptualization, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **L. Vasconcello-Castillo:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **X. Alsina-Restoy:** Writing - original draft, Writing - review & editing. **L. Solis-Navarro:** Data curation, Writing - original draft, Writing - review & editing. **F. Burgos:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **H. Puppo:** Conceptualization, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **J. Vilaró:** Conceptualization, Writing - original draft, Writing - review & editing.

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.2020.10.013.

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THEMATIC SERIES

Different disease, same challenges: Social determinants of tuberculosis and COVID-19

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KEYWORDS
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Abstract Infectious diseases, such as tuberculosis (TB) and the novel coronavirus (COVID-19) relate to environmental factors, understanding of which is essential to inform policy and practice and tackle them effectively.

The review follows the conceptual framework offered by the World Health Organization Commission on Social Determinants of Health (defined as ''all those material, psychological and behavioural circumstances linked to health and generically indicated as risk factors' in the conventional epidemiological language''). It describes the social factors behind TB and COVID-19, the commonalities between the two diseases, and what can be learned so far from the published best practices.

The social determinants sustaining TB and COVID-19 underline the importance of prioritising health and allocating adequate financial and human resources to achieve universal health coverage and health-related social protection while addressing the needs of vulnerable populations. Rapid and effective measures against poverty and other major social determinants and sources of inequality are urgently needed to develop better health in the post-COVID-19 world.

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Introduction to social factors

Infectious diseases may be conceptualized as ecological, biological and social events given their ability to influence life at several levels and dimensions.[1] Some of the social and economic factors that concur to shape human behaviour pose considerable challenges for preventing and controlling infectious diseases.[2] Among the most described and explored are population density, setting (urban/rural), and population growth.[3–5] Like other well-established infectious diseases, such as tuberculosis (TB), the prevention and control of 2019 novel coronavirus (COVID-19) also relates to environmental factors. To identify these and to assess their association with the features of the COVID-19 pandemic it is essential to inform policy and practice and address this problem in more practical terms.

In the present article, we follow the conceptual framework offered by the World Health Organization (WHO) Commission on Social Determinants of Health, which defines them as ''all those material, psychological and behavioural circumstances linked to health and generically indicated as risk factors' in the conventional epidemiological language''.[6] We describe the social factors behind TB and COVID-19, commonalities between the two diseases, and what we can learn so far from the published best practices.[7]

Methods

A non-systematic search of the English-written scientific literature was carried out on PubMed using the following keywords: 'social determinants', 'COVID-19' and 'tuberculosis'. No time restrictions were applied and the selected publication types included clinical trials, observational studies, cohort studies and literature reviews. The information retrieved from the above search was used in the compilation of the present article.

Social factors and TB

TB is a chronic infectious disease and is one of the leading causes of mortality worldwide. Over a century ago, Virchow recognized it as a social disease[7] and, although TB rates worldwide are declining, they remain very high.[8] Thus, in this sense, TB continues to be a social disease inextricably linked with poverty.[7,9,10]

Global TB control and the respective research strategy have during long periods focused mainly on a biomedical approach rather than a socioeconomic response to the epidemic. Even though it may cure millions of people, an exclusively biomedical response has not been enough to eliminate TB. A more holistic approach, addressing not only biomedical responses but also the broader environmental determinants of this disease, is required.[11–14]

Personal experiences, perceived aetiology of the disease, stigma, beliefs and attitudes associated with TB are meaningful in health-seeking behaviour.[15] Many studies have assessed what factors may affect it in different sociocultural settings. Poor perception of health problems, care-associated costs, and physical distance to healthcare facilities are obstacles to seeking care among TB patients.[16–18] Furthermore, socioeconomic status, poor housing and environmental conditions, food insecurity and malnutrition, alcohol consumption, smoking, drug consumption, comorbidities (e.g., HIV/AIDS, diabetes, mental disease), and incarceration seem to predispose people to developing TB.

These social factors have been described as influential on the access to TB diagnostic and treatment. A modelling study published in 2018 to support the WHO End TB Strategy demonstrated that reducing extreme poverty and expanding social protection is estimated to reduce TB incidence by up to 84.3%.[10]

Social factors and COVID-19

The outbreak and rapid global diffusion of the COVID-19 continue to occupy prominent positions in social media, research, and policy agendas worldwide.[19–21] As expected, and based on previous infectious disease outbreaks, such impacts have been especially dire in particular contexts and particular groups, with broad-ranging and systemic consequences.[22–26] In countries everywhere, infection rates of certain diseases are disproportionately high in socially disadvantaged and underserved groups, negatively impacting health and well-being and driving individuals and communities into cycles of illness and poverty.[27]

Issues such as inadequate health care, especially for poor and low-wage workers without paid sick days or insurance; lack of proper sanitation and infrastructure; and exposure to other diseases, pests, and environmental pollutants, constitute obstacles that can increase vulnerability to infection. Regarding the consequences of the pandemic on individuals and communities, not to mention societies at large, healthcare access, quality, and capacities are fundamental considerations. Protection against income loss is an important enabler for following public health advice, such as staying home when sick or quarantine after exposure, and people living in the context of insecure employment with poor social security have increased risk of both infections and social impact of disease.[7,28] Demographic, socioeconomic, and geographical factors that characterize different populations are significant predictors of disease transmission and effects.

Many social determinants of health – including poverty, physical environment (e.g., smoke exposure, homelessness), and racial and ethnic discrimination – can considerably affect COVID-19 outcomes.[29] This way, social determinants have an impact on health by affecting those who get sick and the community as a whole. Not everyone has been equally affected by the COVID-19 pandemic, and the same can be affirmed about TB or other infectious disease pandemics. The COVID-19 pandemic exacerbates the impact of previous inequalities (Fig. 1), particularly among those already experiencing different types of barriers, like those with TB (Fig. 2). Therefore, mitigating social determinants - such as improved housing, reduced overcrowding, improved nutrition and increased economic and social resilience – diminishes the impact of infectious diseases, such as TB and COVID-19, even before the advent of effective medications.[25,30–34]

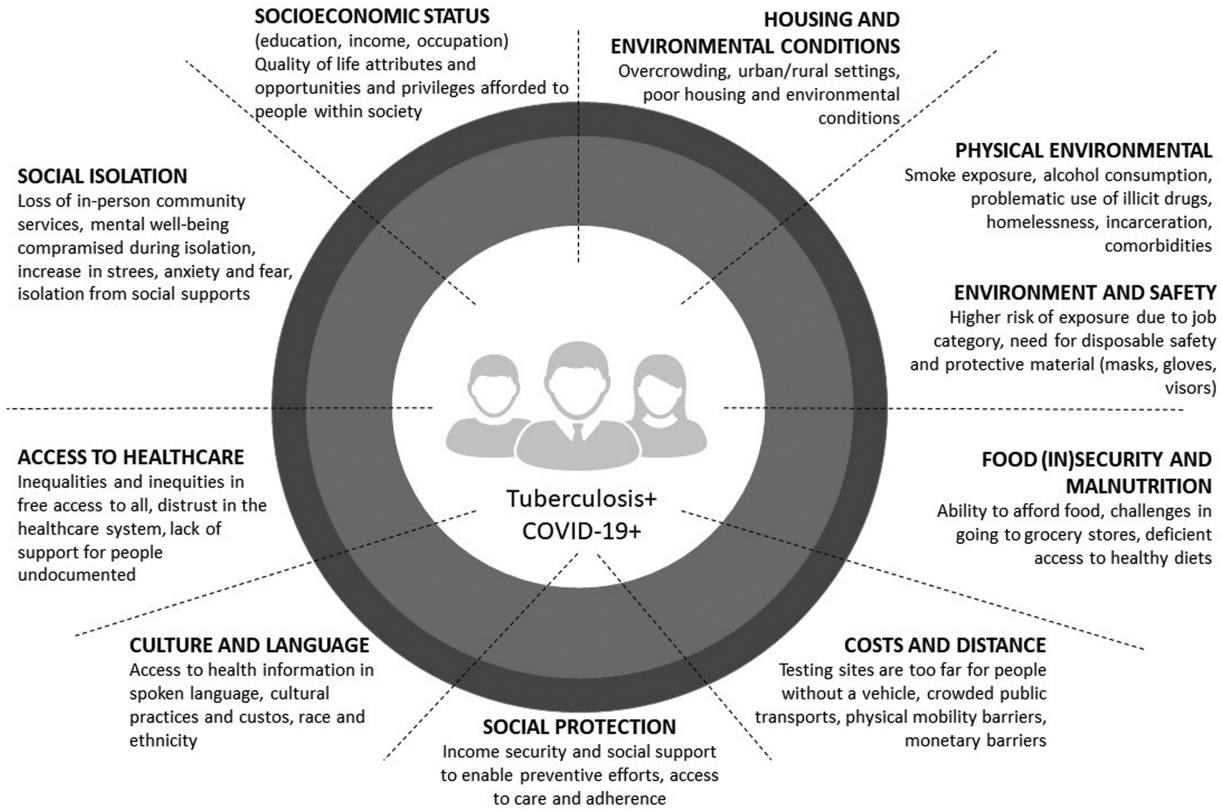

Figure 1 Social determinants for TB and COVID-19.

What is there in common between tuberculosis and COVID-19

Much had been written in both social media and the scientific literature[35–46] before the first cohorts of patients with TB and COVID-19 had been finally evaluated and described.[47–51] We are still on the learning curve for COVID-19, while we know more about TB, which has affected mankind for a long time.[25] A year into the beginning of the pandemic, COVID-19 has been responsible for roughly the same number of deaths caused by TB annually (approximately 1.8 million for the first vs 1.5 million for the latter in 2019) although COVID-19 as of January 10 2020, had 8 times more cases than TB (approximately 86 million vs 10 million new TB cases in 2019).

They are both airborne-transmitted diseases, although SARS-CoV-2 is more infectious, and therefore needs very careful management of individual protection devices, as well as social distancing.[25]

Signs and symptoms are largely the same, potentially challenging differential diagnosis. SARS-CoV-2 is also transmitted by asymptomatic individuals, a feature which makes it very transmissible and harder to control.[25]

For both diseases, co-morbidities lead to increased vulnerability (including cancer; chronic lung and kidney diseases; smoking; alcohol use disorders; depression; HIV and other immunocompromising diseases and diabetes, among others).[25]

Whilst, for TB, curative strategies are available, with success rates above 85% in drug-susceptible individuals (lower for those who are multidrug-resistant, in the order of 60%), several drugs are under evaluation to define an effective treatment for COVID-19.[8,25]

Finally, both diseases have significant impact on health and social services and important economic implications, which for COVID-19 still need to be quantified.[25] Additionally, scientific literature on the relevance of sequelae following the acute phase of COVID-19[51,52] is emerging and those can also be combined with the post-TB treatment sequelae.[53–56]

Their impact on quality of life, the potential need for pulmonary rehabilitation, and long-term socioeconomic support are future challenges needing further evaluation.

How and what can we learn from good practices

COVID-19 represents an unprecedented challenge in modern public health practice. Having spread across most of the countries and having infected millions of individuals, this pandemic requires a coordinated, effective response without sacrificing quality or availability of other essential medical services.[57] At first glance, COVID-19 transcends the traditional boundaries of socioeconomic and demographic status, with everybody seemingly at risk of falling ill. In reality though, COVID-19 is, like most infectious disease outbreaks, a pandemic that accelerates and compounds existing inequities.

TB infection and prevention programmes, as well as correlative health professionals, are uniquely prepared for this

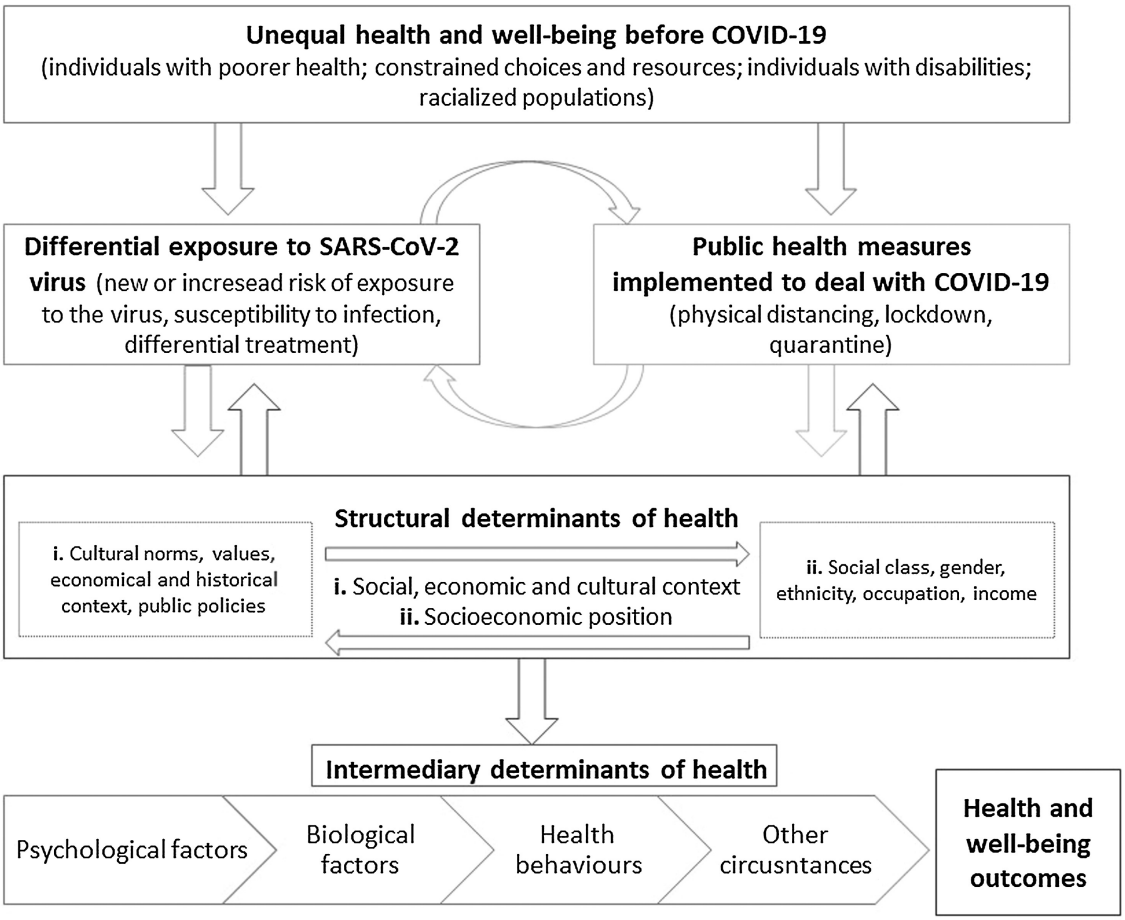

Figure 2 Comprehensive action flow for the social determinants of COVID-19.

challenge due to all the previous years fighting against this disease. Thus, these resources can and should be leveraged to mobilize already-trained health care workers to adapt existing TB programmes' guidance; to implement the already available administrative and environmental controls; and to improve practices around the use of personal protective equipment.

Effective epidemic surveillance systems such as increasing mass testing capacity to self-isolate infected patients or implementing effective contact tracing through Bluetooth and/or GPS tracking (as for example Singapore, Portugal and South Korea did) can enable knowledge of infection among asymptomatic individuals.[58–60]

Individuals need to follow healthy hygiene practices; stay at home when sick; observe physical distancing to lower the risk of disease spread; and use a cloth face-covering or mask in community settings when physical distancing cannot be maintained.[32–34] Many countries quickly put in place economic support models to facilitate this, although coverage of such measures is still very limited.[61] Here we can see that the concept of community vs individual is really important – if we as individuals comply with the rules, we can protect others.

Another great achievement that needs to be addressed as good practice and capability to response in a time like this is related to the health system preparedness and capacity: building new hospitals; increasing intensive care unit bed numbers; resort to medical and nursing students and/or to retired health care workers.[20,24,33] The improvement of community care capacity with hospital at home, distance monitoring with oximeter and home oxygen, are good examples of the capacity and resilience to fight against COVID-19 crisis.

In this sense, both diseases would gain from the use of capacity building efforts; improved surveillance and monitoring systems; and robust programmes and infrastructure already developed over many years of investment.[33] An example is one of the TB outpatient centres in the Portuguese Northern Region that actively engaged with the premise of not leaving anyone behind, assembling a significant and rapid response to COVID-19, while ensuring that TB and other essential health services were maintained.[62]

Lessons learned and global health response

In recent years, the role of risk factors and social determinants of TB have been more intensively studied and the role of some highly prevalent determinants such as Human Immunodeficiency Virus (HIV), smoking, diabetes mellitus, alcohol use and under-nutrition have been highlighted. Others include overcrowding, housing conditions and economic deprivation. It has been shown that the highest TB incidence

geographic areas are also those with highest incidence of HIV infection, incarceration, overcrowding, unemployment and immigration.

Although TB outbreaks occur everywhere, available diagnosis and treatment ensure that people in richer countries mostly recover from the disease.[63] COVID-19, with its current rate of spread, lack of treatment and natural immunity, is exploiting many of the same health, economic, and social inequities that TB has been doing for centuries. Additionally, the prioritization of human and material resources to fight the COVID-19 pandemic and the increased danger of co-infection with SARS-CoV-2 to those with TB pose further threats to TB control efforts.[64] If those concerns are not addressed soon, COVID-19 could substantially reverse the gains achieved in TB control and worsen the epidemic in the coming months or years.[65,66]

To date, the COVID-19 response has demonstrated that, with political will, prioritization and investments, it is possible for the international community to mobilize resources, accelerate scientific discovery, and deploy new public health tools to fight a pandemic.[67] These same strategies can thus be employed for TB. However, the COVID-19 response, especially strict lock-downs and mobility restrictions, have also caused immense social and economic suffering and highlighted the need to strike a careful balance between immediate public health gains and unintended health and social side effects.

We have now a rare opportunity to seize the moment and use the attention garnered by this novel virus pandemic to ensure that new investments contribute, not only to the control of COVID-19, but also to strengthen the control of older challenges. Lessons learned from previous relevant public health programs would certainly benefit those at risk for COVID-19.

Final notes

Despite the rapidly increasing number of cases, the data needed to predict the impact of the COVID-19 pandemic on patients with TB infection and TB sequelae and to guide management in this particular context still lies ahead.

COVID-19, like TB, reminds us of the importance of prioritising health and allocating financial and human resources for universal health and social protection coverage and addressing the needs of vulnerable populations. The link between infectious disease and poverty is further recognised as such; increased investment in their control results in societal structural changes that benefit all if carefully planned and executed.

We need to get ready for the post-COVID-19 world, where people-centred health systems with community-driven interventions will become vital instruments towards achieving better health, economic and moral outcomes.

Authors' contributions

All authors contributed substantially to the interpretation of the articles in analysis, critical discussion and revision of the manuscript, and approved its final version.

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Conflict of interest

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LETTER TO THE EDITOR

Anatomic lung recruitment in the early phase of severe COVID-19-pneumonia

To the Editor,

Lung recruitment of patients suffering from severe acute respiratory syndrome Corona-Virus 2 (SARS-CoV-2)-associated acute respiratory distress syndrome (ARDS) has been assessed functionally e.g. by electrical impedance tomography (EIT), determining compliance and right-to-left-shunt fraction or calculating the recruitment-to-inflation ratio,[1] methods all of which demonstrated a varying degree of functional recruitability. By comparing the CT images obtained at two different airway pressures one can visualize recruitable areas in the lungs of patients with ARDS anatomically.[2] Significant lung recruitability determined in this manner usually predicts a beneficial effect of positive end-expiratory pressure (PEEP) on oxygenation, relates inversely to the severity of lung injury and has prognostic implications.[2] Here, we amend such anatomic recruitment data from dynamic chest CTs of two increasingly invasively ventilated male patients (59- and 67-years of age) in the early phase of severe SARS-CoV-2-associated ARDS.

Following a first chest CT under myorelaxation at a lower pressure (10 cmH_2O) and a subsequent recruitment maneuver (PEEP 15 cmH_2O; inspiratory pressure 35 cmH_2O for one minute, then PEEP 25 cmH_2O and inspiratory pressure 45 cmH_2O for another minute) a second chest CT was performed with a 45 cmH_2O inspiratory hold. CT image processing, lung segmentation and quantitative analysis were performed with custom-designed software (Maluna®).[3] For each 0.0025 ml (2.5 mm^3) voxel we determined the density in Hounsfield units (HU) from −1000 to +100, subdivided the density range into quantiles of five HU (giving 220 segments) and calculated the corresponding volume of each segment. Each voxel was classified as non- (−100 to +100 HU), poorly- (−500 to −101 HU), normally- (−900 to −501 HU), or over-aerated (−1000 to −901 HU).[2] Overall recruitment potential was defined as the total change in the percentage of lung volume (in liters) classified as non-aerated between the two pressures. Lung weight was estimated as follows: Lung-volume (ml) × (mean density [HU] + 1000 [HU])/1000. Written informed consent for publication was obtained for both patients.

Chest CTs at 10 cmH_2O showed a radiological picture compatible with severe viral pneumonia with multifocal, bilateral, subpleural, and peribronchovascular pure ground-glass opacities, air bronchogram, traction bronchiectasis as well as subtotal consolidations in the dorsal lower lobes (Fig. 1). The latter nearly disappeared with an inspiratory pressure of 45 cmH_2O, while the percentage of non-aerated lung decreased from 35% and 36% (10 cmH_2O) to 4% and 13% (45 cmH_2O) for patients 1 and 2, respectively (Fig. 1). Likewise, the overall mean densities decreased from -375 ± 17 HU (standard error of the mean (SEM)) and -259 ± 20 HU (10 cmH_2O) to -620 ± 9 HU and -488 ± 13 HU (45 cmH_2O) while calculated lung weights amounted to nearly 3000 and 2500 g in patients 1 and 2, respectively. However, neither a fairly high PEEP (15 cmH_2O — guided by continuous transpulmonary pressure measurements) nor rotational therapy were able to bring about relevant near-term change in the paO_2/FiO_2 ratio, which remained almost constantly below 100 (Fig. 2).

The observed clearing of dorsal consolidations under high PEEP during CT is well in line with the common recommendation to apply a hypoxemia-driven high PEEP, which should theoretically induce a pressure-dependent fluid transfer from the bronchioli and alveoli into the surrounding parenchyma,[4] but also brings about possible detrimental effects like barotrauma, impairment of hemodynamics, and retention of carbon dioxide. Likewise, prone positioning is a well-established treatment option in severe ARDS and reduces the risk of gravity-dependent alveolar collapse and inflammatory pulmonary edema. However, contradicting the anatomic recruitment potential neither higher PEEP nor prone positioning significantly improved our patients' condition in the short-term.[2] This finding could relate to the severe and dynamic lung edema that is partially refractory to high ventilatory pressures or gravitational forces, and whose radiologic expression is the weak effect of high pressure on transparency in the CT in areas in which ground-glass opacities predominated. Accordingly, calculated lung weights were particularly high.[2] Additionally, high extents of lung microvascular thrombosis and dysfunction causing a severe imbalance between ventilation and perfusion are increasingly reported in COVID-19-associated ARDS.[5] In line with our observation, recent evidence indeed supports the application of low PEEP especially in the early stages of severe COVID-19-associated ARDS.[6] On the other hand, prone positioning currently is generally recommended for treatment of patients with severe COVID-19-associated ARDS.[6,7] However, its efficacy may be reduced in most severe forms of the disease.

In conclusion, anatomic recruitment of lung parenchyma was well preserved in two patients in the early phase of severe COVID-19-associated ARDS while functional recruitment was not. Severe hypoxemia, primarily good

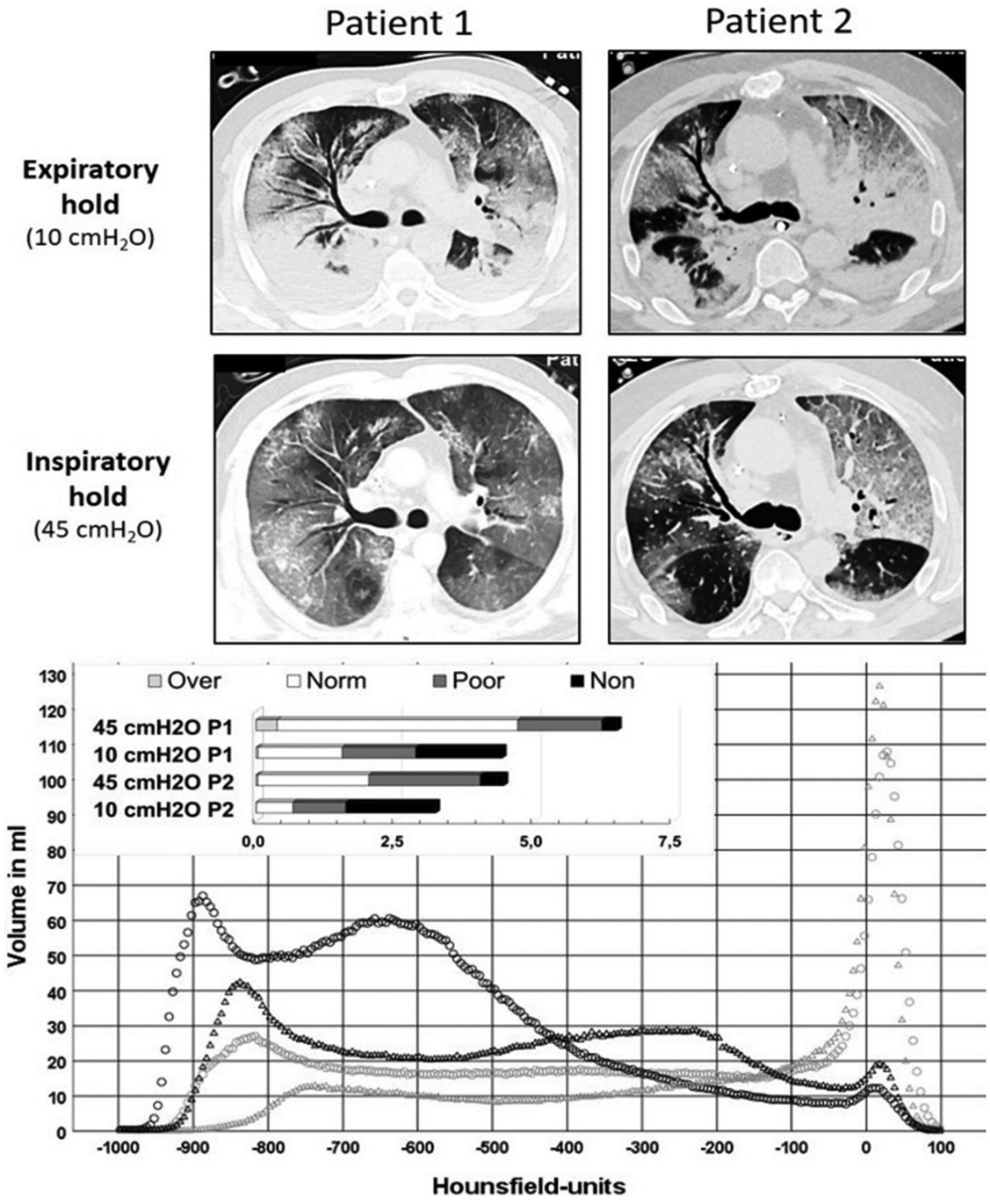

Figure 1 Upper part: sections from low-dose, native chest CTs of both patients during expiratory hold with PEEP 10 cmH_2O, as well as during inspiratory hold (airway pressure 45 cmH_2O). Although both patients exhibited a distinct recruitability of the lungs, the underlying COVID-19 pattern explains the poor functional effect of higher PEEP levels in improving oxygenation. Lower part: this graph displays the volumes determined in the chest CTs (y-axis) per a range of 5 Hounsfield units (x-axis) at 10 cmH_2O (light grey) and 45 cmH_2O (black). Circles represent data from patient 1, triangles data from patient 2. The insert at the upper left shows the absolute lung volumes in liters classified as non-aerated, poorly aerated, normally aerated and overaerated again comparing the two pressures in both patients. Note the differences between the absolute lung volumes at both pressure levels (at 45 cmH_2O about 6.5 l for patient 1, about 4.5 l for patient 2).

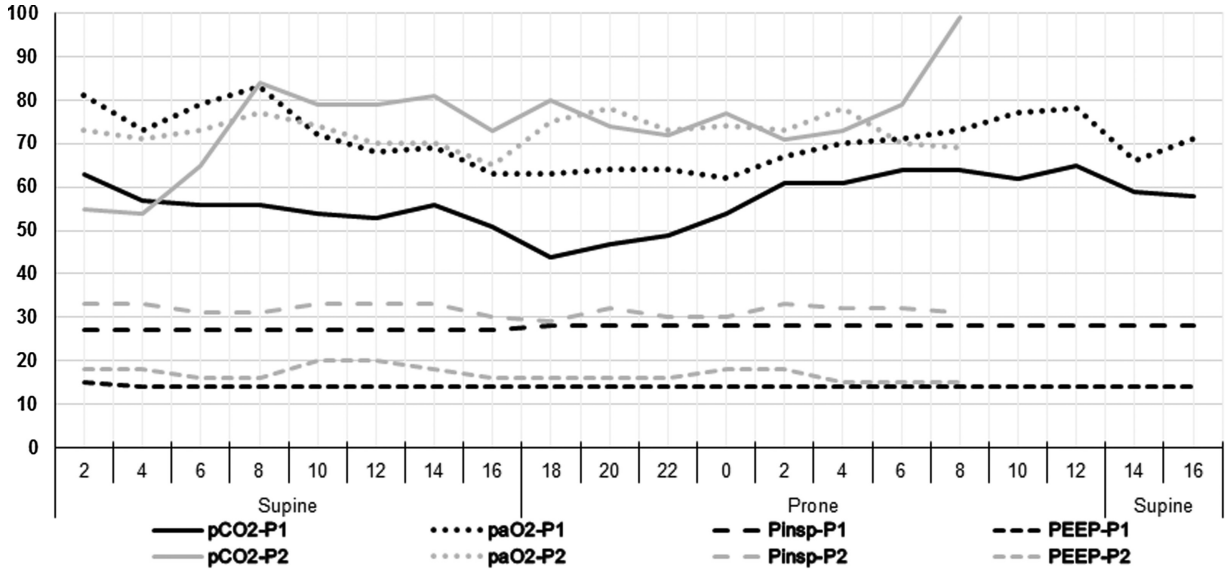

Figure 2 Blood gases and concurrent ventilator settings during a two-day course. As both patients had a nearly identical time course regarding recruitment CT and begin of prone positioning, the data for both are shown in the same diagram. The x-axis shows two-hour time intervals approximatively corresponding to the times of the blood gas analyses. In addition, the x-axis indicates how the patient was positioned (supine or prone). The numbers on the y-axis refer to both the arterial oxygen (paO_2) and carbon dioxide (pCO_2) partial pressures in mmHg, as well as to the positive end-expiratory (PEEP) and the inspiratory (Pinsp) pressures in cmH_2O. The inspiratory oxygen fraction (FiO_2) was kept between 75 and 80% for most of the time period of the diagram. The data sets of patient 2 (light grey) end at 8 am on day 2 as extracorporeal membrane oxygenation was initiated at that time.

compliance, and increased lung weight may be typical features of the early phase of severe COVID-19-associated ARDS and these patients may therefore benefit more from a higher FiO_2, a lower PEEP, and strict attention to fluid balance.

Conflicts of interest

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Pulmonary embolism detected by CT pulmonary angiography in hospitalized COVID-19 patients

Dear Editor,

Besides pneumonia, the most frequent serious manifestation of COVID-19, another prominent manifestation is venous thromboembolism (VTE).[1] Data on the prevalence/incidence of pulmonary embolism (PE) in COVID-19 are still limited and often focused on patients in intensive care units (ICU).[2–4] Moreover, few data are available on the severity of PE and on the severity of parenchymal involvement in those who develop PE. Here, we present our data in 157 consecutive COVID-19 patients, hospitalized at Bichat Hospital, who underwent CT pulmonary angiography (CTPA) for suspected PE.

From March 6 to April 20 2020, 1097 patients were hospitalized for COVID-19 at Bichat Hospital, one of the reference centers for infectious diseases in Paris. Of the 157 patients who had CTPA, all with positive SARS-CoV-2 PCR results, 30 were hospitalized in the ICU, with 23 (76.7%) requiring invasive mechanical ventilation. The remaining 127 patients were hospitalized in the general ward for serious COVID-19 manifestations but without critical illness.

For patients hospitalized for COVID-19, the general policy at our institution is to recommend use of anticoagulant therapy based on low-molecular-weight heparin or unfractionated heparin, the intensity varying from low-prophylactic doses to curative treatment via high-prophylactic doses according to the severity of the respiratory condition, the presence of obesity or other risks factors of VTE. In all cases, CTPA was performed to exclude the responsibility of superimposed PE in patients hospitalized for severe COVID-19 and presenting stagnation or worsening of their respiratory condition. CT-angiography scans were acquired with 64-row or greater scanners after injection of 70–90 mL of contrast material with a high concentration of iodine. Imaging was performed with use of a bolus-tracking technique and a threshold of 200 HU in the main pulmonary artery. Images were reconstructed with a slice thickness of 1 mm in mediastinal and parenchymal windows. We retrospectively analyzed the CTPA results as well as the clinical and biological data for the patients. The quality of the examinations was sufficient to assess the presence or absence of PE up to the segmental level. One reader (AK, with 25 years of experience) classified PE location as proximal, lobar, or segmental. The study received approval from the ethics committee of the French Language Society of Pulmonology ''Comité d'évaluation des protocoles de recherche observationnels (CEPRO)''.

The incidence of PE detected by CTPA in the 157 patients was 27% (8 of 30) in ICU patients and 12% (15 of 127) in ward patients. PE was proximal, lobar, segmental, and bilateral in 0%, 12.5%, 87.5%, and 25% and 7%, 33%, 60%, and 47% of cases in the ICU and general ward, respectively. CTPA revealed a concomitant evidence of worsening of pneumonia in 75% and 67% of ICU and ward patients with PE, respectively. When using an already published CT severity index (range 0–25),[5] the CT score was 14 on the initial CT and 18 [14–19] at the time of PE ($p = 0.0883$). Interestingly, the CT severity index of patients with and without PE showed no significant difference (18 [14–19] versus 14.5 [10–20]; $p = 0.2561$).

Clinical and biological data are in Table 1.

D-Dimers levels were significantly higher in ward patients with PE than those without; there was no difference in ICU patients. Using the age-adjusted D-dimers cut-off levels, the sensitivity, specificity, negative predictive value, and positive predictive value of D-dimers for the diagnosis of PE was 100%, 26%, 100%, and 21% respectively (Table 2). The ROC curve for D-dimer in hospitalized COVID patients with suspected PE is shown in Fig. 1.

Overall, 94.3% of patients received anticoagulant therapy (at least low-prophylactic doses) at the time of CTPA (100% in ICU patients and 93% in ward patients). For patients with PE, the proportion receiving anticoagulant therapy (at least a low-prophylactic dose) at the time of diagnosis was 100% and 86.7% in the ICU and general ward, respectively.

There is mounting evidence that COVID-19 patients, particularly critically ill patients, are at increased risk of VTE.[2–4,6,7] The underlying mechanism involves factors related to COVID-19, such as inflammatory state, hypercoagulability, and endothelial damage, along with classical risk factors of VTE (older age, obesity, dehydration, immobilization, mechanical ventilation) which are often present with severe COVID-19.

A high incidence of PE in COVID-19 patients hospitalized in ICUs has been already reported[3,4,6,7] but data in non-ICU patients remain limited.[6–9] Our data confirm the high incidence of PE in COVID-19 patients hospitalized in ICU but also indicate that PE is also frequently observed in COVID-19 patients hospitalized in the general ward, justifying a high degree of awareness by clinicians.

Not surprisingly, we found that COVID-19 is associated with an hyperinflammatory state that contributes to the hypercogulability and in turn to the risk of VTE but the levels of CRP and fibrinogen did not differ between those with and without PE. Overall, D-dimers levels were significantly higher in those with PE than in those without PE, in line with the results of other COVID-19 studies.[2,6,8–10] However, D-dimers were not able to predict thrombotic events, especially in ICU patients.

COVID-19 patients hospitalized in general wards because of severe illness are at risk of worsened condition leading, in the most severe cases, to admission to an ICU because of critical symptoms (respiratory failure, shock, multiple organ dysfunction). Likewise, in the ICU, physicians caring for COVID-19 patients are used to facing a general deterioration, with respiratory symptoms at the forefront. In both cases, progression of pneumonia is most often responsible for the observed worsening of the respiratory condition but the latter could also be related to the occurrence of PE or to PE superimposed on extending pneumonia.

From a clinical point of view, the fact that, along with the diagnosis of PE, CTPA also demonstrated a worsening of pneumonia in the majority of cases is informative. Performing thoracic CT without angiography instead of CTPA would have led to missing a significant number of embolic events. With worsening or non-improvement in patients hospitalized for COVID-19, our results argue for (1) increased awareness by clinicians of the possible responsibility of superimposed PE, even though progression of pneumonia may also be documented on chest CT, and (2) use of CTPA, whenever pos-

Table 1 Characteristics of COVID-19 patients with and without pulmonary embolism (PE) hospitalized in the intensive care unit (ICU) or general ward (GW).

Variable	Total ($n = 157$)	With PE ($n = 23$)	Without PE ($n = 134$)	p
GW patients	127 (80.9%)	15 (65.2%)	112 (83.6%)	
ICU patients	30 (19.1%)	8 (34.8%)	22 (16.4%)	
Clinical characteristics				
Age (years)	63 [52–74]	59 [52–79]	63 [52–73.25]	0.9185
BMI (kg/m^3)	27.08 [24.5–30.73]	28.11 [24.52–33.57]	26.83 [24.5–30.65]	0.5455
History of VTE	12 (7.6%)	1 (4.3%)	11 (8.2%)	0.4912
Diabetes	48 (30.6%)	6 (26.1%)	42 (31.3%)	0.6132
Dyslipidemia	37 (23.6%)	6 (26.1%)	31 (23.1%)	0.7579
Arterial hypertension	78 (49.7%)	11 (47.8%)	67 (50%)	0.8472
Active malignancy	5 (3.2%)	3 (13%)	2 (1.5%)	0.0036
Smoking status				
Never smoker	109	18	91	0.427
Former smoker	41	5	36	
Active smoker	7	0	7	
Chronic cardiac insufficiency	10 (6.4%)	2 (8.7%)	8 (6%)	0.621
Chronic respiratory insufficiency	1 (0.6%)	0	1 (0.7%)	0.6777
Anticoagulant therapy				
No anticoagulant	9 (5.7%)	2 (8.7%)	7 (5.2%)	0.1232
Low prophylactic dose	39 (24.8%)	5 (21.7%)	34 (25.4%)	
High prophylactic dose	90 (57.3%)	10 (43.5%)	80 (59.7%)	
Curative dose	19 (12.1%)	6 (26.1%)	13 (9.7%)	
Time between symptoms onset and CTPA (days)	13 [10–18]	16 [12–23]	12 [9–18]	**0.0164**
Time between hospitalization and CTPA (days)	5 [2–9.5]	8 [4–15]	5 [2–8]	**0.0134**
Radiological characteristics				
Parenchymal evaluation by comparison with the previous chest CT scan				
Worsening	107 (68.1%)	16 (69.6%)	91 (67.9%)	0.2420
Stability	29 (18.5%)	2 (8.7%)	27 (20.2%)	
Improvement	5 (3.2%)	2 (8.7%)	3 (2.2%)	
NA (no previous CT available)	16 (10.2%)	3 (13%)	13 (9.7%)	
Biological characteristics[a,b]				
D-Dimers (ng/ml)	1249 [566–3394]	7638 [2179–27544]	1064 [497.5–1767]	**<0.0001**
GW	1055 [491–1852]	27544 [7448–76306]	870 [478–1573]	**<0.0001**
ICU	2179 [1280–7638]	3898 [1556–16117]	1747 [1089–6981]	0.3074
Fibrinogen (g/l)	5.17 [4.325–11.81]	4.94 [4.010–6.675]	5.19 [4.34–6.21]	0.9855
GW	5.15 [4.335–6.19]	4.94 [3.045–6.41]	5.19 [4.545–6.14]	0.6511
ICU	5.23 [4.22–6.743]	5.52 [4.46–7.043]	5.23 [3.978–6.548]	0.6047
H-s troponin (μg/l)	0.015 [0.015–0.032]	0.015 [0.015–0.028]	0.015 [0.015–0.032]	0.44
GW	0.015 [0.015–0.0255]	0.015 [0.015–0.0355]	0.015 [0.015–0.026]	0.7024
ICU	0.015 [0.015–0.06475]	0.015 [0.015–0.03450]	0.017 [0.015–0.1048]	0.2341
NT-proBNP (ng/l)	324 [95–1335]	253 [111.5–3096]	329.5 [93.75–1307]	0.7062
GW	244 [83–804.5]	160 [82–520.5]	307 [82–809]	0.4165
ICU	1360 [392–3901]	3096 [350.5–9674]	1069 [392–3647]	0.4815
CRP (mg/l)	52 [21–108.5]	109.5 [31.25–181]	47 [20.5–96.5]	**0.0292**
GW	50 [21–96.5]	117 [32.25–181]	46 [20.5–93.5]	0.0532
ICU	63.5 [21.25–189.8]	99 [31.25–189.8]	59.5 [17.25–191.3]	0.5574

Data are presented as median [interquartile range] or number (percentage) where appropriate. Groups with and without PE were compared by Mann–Whitney U test or chi-square test, for quantitative and categorical variables, respectively. $p < 0.05$ was defined as statistically significant.

Bold values signifies values are statistically significance.

[a] Biological data from samples obtained within 48 h before or after CT pulmonary angiography in the ICU and within 5 days before or after CT in the GW.

[b] Missing data in ICU: D-dimers $n = 3$, NT proBNP $n = 3$, CRP $n = 2$; missing data in GW: D-dimers $n = 59$, fibrinogen $n = 33$, troponin $n = 39$, NT proBNP $n = 39$, CRP $n = 6$.

Abbreviations: PE: pulmonary embolism; GW: general ward, ICU: intensive care unit; BMI: body mass index; VTE: venous thromboembolism; CTPA: CT pulmonary angiography; H-s troponin: high sensitivity troponin; BNP: brain natriuretic peptide; CRP: C reactive protein.

Table 2 Age-adjusted D-dimers for predicting pulmonary embolism in hospitalized COVID-19 patients with suspected pulmonary embolism: contingency table for sensitivity and specificity calculation.

Age-adjusted D-dimers	Total ($n = 157$)	PE ($n = 23$)	No PE ($n = 134$)
Positive	73	15	58
Negative	20	0	20
D-Dimers non available	64	8	56

Data are presented as numbers.
Age-adjusted D-dimers cut-off level (ng/ml) was age multiplied by 10. D-Dimers were considered positive if they were above this threshold.
Abbreviation: PE: pulmonary embolism.

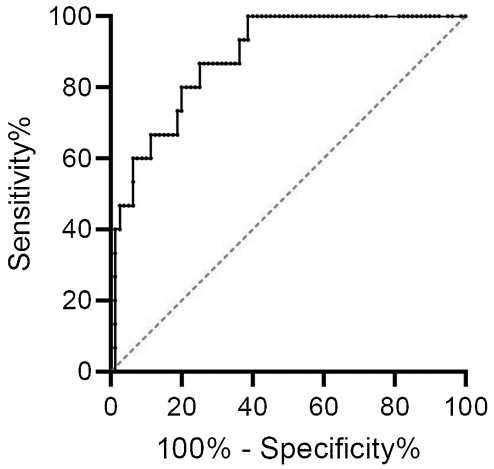

Figure 1 ROC curve for D-dimer in hospitalized COVID patients with supected PE. The area under the curve was 0.885 (95% CI 0.807–0.963). The best cut-off value seemed to be 1274 ng/ml, corresponding to a sensitivity of 100% (95% CI 79.6–100%) and a specificity of 61.3% (95% CI 50.3–61.2%).

sible. New diagnostic techniques of PE have been recently investigated.[11] Given the high incidence of PE in hospitalized COVID patients, they could be useful in this setting.

Ethics approval and consent to participate

The study received approval from the ethics committee of the French Language Society of Pulmonology ''Comité d'évaluation des protocoles de recherche observationnels (CEPRO)''.

Consent for publication

Not applicable.

Availability of data and material

All data are available for reviewers on demand.

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Contributions of the authors

VB and HM wrote the manuscript.

GW provided assistance for statistical analysis.

XL, JFT, AD, BLJ, JG, SN, NA retrieved the clinical and biological data from the files.

AK and LS analyzed the CTPAs.

All the authors have checked the manuscript.

Conflict of interest

Dr. Mal reports grants from Pfizer, personal fees from Boehringer, non-financial support from Novartis, outside the submitted work. Dr. Timsit reports personal fees from Merck, personal fees from Pfizer, personal fees from Gilead, personal fees from Paratek, personal fees from Medimmune, outside the submitted work. The other authors have no conflicts of interest to declare.

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High-resolution CT features in patients with COVID-19 pneumonia and negative nasopharyngeal and oropharyngeal swabs

To the Editor:

In response to the SARS-CoV-2 outbreak, rapid and accurate diagnosis of COVID-19 pneumonia is essential for controlling the spread of the disease and optimizing patient treatment. Although nasopharyngeal and oropharyngeal (NP/OP) swab tests are commonly used for laboratory confirmation of suspected COVID-19 cases, RT-PCR for detection of the virus has been reported to have very high specificity, but sensitivity as low as 70–80%. Reasons for initial false-negative NP/OP swab tests may include inadequate sampling techniques and/or low patient viral burden.[1]

Chest imaging is indicated for patients with moderate to severe symptoms of COVID-19 infection, regardless of NP/OP swab results and/or for those with confirmed diagnosis and evidence of worsening respiratory status.[2] Recently, it has been reported that patients who initially tested negative for COVID-19 by RT-PCR were less likely to exhibit pulmonary consolidation by CT.[3]

This study aimed to describe the chest CT findings in patients with COVID-19 pneumonia who had initially tested negative by NP/OP swab. The final goal is to assist physicians to avoid missed or delayed diagnoses of SARS-CoV-2 infection.

Our study was conducted in accordance with the Declaration of Helsinki and approved by the Padova Hospital ethics committee. De-identified CT scans were assessed by on-site radiologists at the Department of Radiology of Padova University. All CT scans were from patients admitted to the emergency department (ED) for suspected COVID-19 pneumonia, according to exposure history and clinical data, between February 17 and May 5, 2020.

The following inclusion criteria were used: (1) Laboratory confirmed SARS-CoV-2 infection; (2) No previous known underlying lung disease; (3) CT examination performed 1–3 days from admission to the ED. All patients included in the study group initially tested negative for COVID-19 by NP/OP swab test. All results were compared with those in the group of patients who initially tested positive for COVID-19. Two radiologists with over 5 years' experience analysed all CT images in consensus. The following CT features were assessed: distribution pattern (peripheral or central); number of lobes involved (one, two, or more); main radiological feature (ground-glass opacity [GGO], consolidation, or GGO with consolidation); concomitant lung abnormalities (crazy paving pattern, fibrous stripes); and extrapulmonary manifestations (mediastinal lymph node enlargement, pleural effusion).

Out of 453 patients admitted to the ED and administered chest CT during the study period, 159 had a confirmed diagnosis of COVID-19 pneumonia, according to WHO guidance.[4] In 28 of these confirmed cases (mean age, 64 ± 15 years; male/female, 18/10), the patients initially tested negative by RT-PCR (study group). SARS-CoV-2 infection was confirmed in these patients by repeated NO/OP swab test (nineteen cases) and bronchoalveolar lavage test (nine cases) over a 6-day duration (range, 3–8 days).

Unilateral lung involvement was detected in 20 out of the 28 cases. Radiologic abnormalities had peripheral distribution in 27 cases (96%) and involved two or more lobes in four cases (14%). Unilateral GGOs with or without consolidations or crazy paving were significantly more common among patients in the study group compared with those who initially tested positive (19/28 vs. 6/131; $p < 0.0001$) (Table 1) (Fig.1). Fibrous stripes on the basal regions were present in seven patients. Finally, mediastinal lymph node

Table 1 CT features of patients with initially negative or positive NP/OP swab test. (GGO = ground-glass opacity; NP = nasopharyngeal; OP = oropharyngeal).

CT feature	Pts with initially negative NP/OP swab test (n = 28)	Pts with initially postive NP/OP swab test (n = 131)	p-Value
GGO			
- Unilateral	19	6	<0.0001
- Bilateral	8	110	<0.0001
Consolidation			
- Unilateral	15	3	<0.0001
- Bilateral	3	89	<0.0001
Crazy paving			
- Unilateral	4	0	0.0008
- Bilateral	4	65	0.0008
Fibrous stripes			
- Unilateral	3	0	0.005
- Bilateral	3	40	0.0353

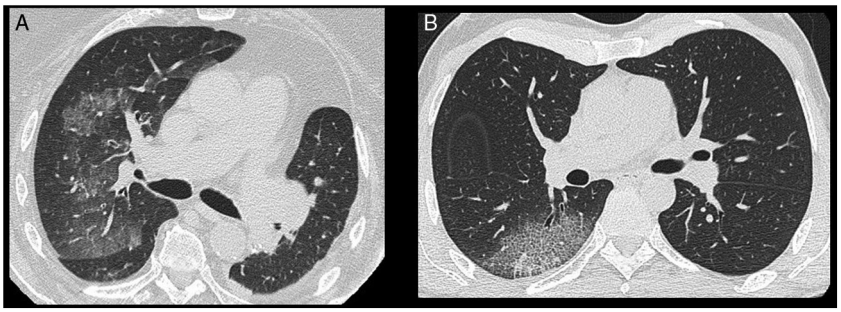

Figure 1 CT scan of a 74-year-old woman showing unilateral ground-glass opacities in the right upper lobe (A), and a 47-year-old man showing unilateral crazy paving in the right lower lobe (B). Both patients had initially tested negative by NP/OP swab.

enlargement and pleural effusion were detected in six and two cases, respectively.

Our study describes chest CT scan findings in a group of patients with COVID-19 pneumonia who initially tested negative by NP/OP swab tests. To date, only a small case series, consisting of five patients, by Xie et al.[5] has investigated the relationship between negative RT-PCR tests and chest CT scans and concluded that GGOs were the most typical finding in this context. The data presented here suggest that unilateral GGOs with or without consolidation are the most frequent abnormalities in this patient population.

We hypothesize that predominant unilateral lung involvement could be due to a relatively low viral load. Similarly, Zhao et al. examined the relationship between CT findings and the clinical courses of patients with COVID-19 pneumonia and concluded that viral load may influence the extent of lung involvement.[6] A relatively low viral load has also been suggested to be a possible cause of false-negative NP/OP swab tests in symptomatic patients with pulmonary lesions suspected of COVID-19 pneumonia.[7] On this basis, we argue that our study group patients could represent a 'low-dose phenotype', characterised by negative NP/OP swab tests and unilateral lung lesions.

Quantitative determination of viral load could have confirmed our hypothesis, but this test is not available in our hospital.

Because false-negative NP/OP swab tests have important implications for timely COVID-19 diagnosis, early treatment, and the risk of spreading the disease, we recommend that clinicians continue to monitor for COVID-19 when patients present with unilateral GGOs and have initially tested negative by NP/OP swab tests. A combination of tests is urgently needed to minimize the risks of false-negative results.

Declarations of interest

None.

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Reversibility of venous dilatation and parenchymal changes density in Sars-Cov-2 pneumonia: toward the definition of a peculiar pattern

Dear Editor,

In SARS-CoV-2 infection the mild-to-moderate phase of the disease shows type II pneumocytes hyperplasia without hyaline membranes, inflammatory interalveolar infiltrates.[1-4] Vascular changes like hyperplasia/dilatation of alveolar capillaries, new angiogenesis, endothelialitis, thrombotic microangiopathy have been also reported.[3] From a radiologic point of view, Lang et al.[5] using the dual-energy CT scan technology, described peculiar vascular enlargement and mosaic attenuation as a pattern of disordered vasoregulation characterized by a pronounced vascular dilatation (in 85% of the patients) in the affected regions, beside the typical aspects of ground glass attenuation and consolidations. These features were labeled as ''hyperemic halo'' pattern.[5] Here we describe CT findings of five patients affected by COVD-19 in the early phase of the disease emphasizing the vascular and alveolar changes modified by the gravity.

Five subjects with a diagnosis of COVID-19 based on nasal swab test underwent CT scan in supine and later in the same session the prone position. CT protocol consisted of two consecutive acquisitions respectively in supine and prone position, the latter during administration of contrast medium, with a protocol able to opacify pulmonary both arteries and pulmonary veins.

Clinical and laboratory profiles are summarized in Table 1.

In all the five cases, pulmonary veins were patent. Other radiological features for each patient were as follows:

Case 1: 78 years-old male. In the supine position, focal pure ground glass opacities were present in both upper lobes, and some peripheral part-solid ground glass areas with a coexisting crazy paving attenuation in both costophrenic angles. Furthermore, the peripheral branches of the pulmonary veins of the lower lobes appeared enlarged. In the prone position a significant decrease in diameter of veins and a kind of parenchymal ground glass attenuation in both lower lobes. Moreover, a rapid reduction of the density was observed in the ''former crazy paving component'' that changed into pure ground glass attenuation (Fig.1).

Case 2: 64-year-old male. Subsegmental pulmonary arteries defects were present in the right lower lobe. Pulmonary veins showed a relative reduction in caliber in the prone positioning.

Case 3: 52 year old female. Bilateral central and peripheral ground glass attenuation and vessel enlargement. In the right upper lobe and in the left lower lobe the consolidative aspect present in supine position reduced significantly in the prone. Moreover, veins decreased in caliber (Fig.2).

Case 4: 57 years old female. Bilateral, extensive areas of ground glass attenuation with central and peripheral distribution, some peripheral consolidation in upper and lower lobes and bilateral venous enlargement. In the prone position a significant reduction in caliber of the enlarged veins is associated with relative increase in density of the pulmonary infiltrates in the anterior segments of both upper lobes.

Case 5: 58 years old female. Part-solid ground glass attenuation in supine position with band-like opacities in left lower lobe. Vessel enlargement was present in both lower lobes, mainly on the left. With the prone positioning the ground glass attenuation redistributed in the medullary portion of the lung, with a concomitant reduction in density attenuation. Caliber of the veins reduced (1.2 vs 2.8 mm).

Table 1 Clinical and laboratory features.

Clinical features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	79	64	52	57	58
Gender	Male	Male	Female	Female	Female
Smoking Habitus	Former smoker	Former smoker	Non-smoker	Nonsmoker	Former smoker
Comorbidity	Hypertension Psoriasis Diverticulosis Anemia	Multiple sclerosis			Asthma Hypertension
Contact epidemiology	Hospital	Family member	Family member	Return from abroad	Family member
BMI	24	20	21	30	32
Symptoms	Fever	Fever	Fever Cough Epigastric pain Dyarrea	Fever Headache Dyspnea	Fever Dyspnea
Days of symptoms (n)	5	4	7	7	7
Saturation in room air	96%	97%	97%	86%	96%
Treatment		Interferon*		Azithromycin**	
C reactive protein (mg/L)	79	16.1	47.7	139.2	17.5
LDH (U/L)	305	254	238	487	159
D-Dimer (μg/mL)	1903	499	663	2245	1369
Ferritin (ng/mL)	138	1677			
IL-6 (pg/mL)	29.8	34.4			
Platelets (n/mm3)	63.000	154.000	275.000	228.000	356.000
Lymphocytes (109 /L)	600	1780	1310	1640	1550

The relevant observations of this series are: the enlarged vessels are pulmonary veins; the diameter of these enlarged vessels and the density of ground glass and/or crazy paving areas pouring in them decrease when they are no longer in the dependent zones.

These findings were detected in patients with an early and mild-to moderate form of disease supporting the hypothesis that a large part of the ground glass attenuation/crazy paving pattern could be due to the vascular changes taking place in the alveolar septa instead of accumulation of proteinaceous edema and hyaline membranes in the alveolar spaces.[3]

The ''bandlike'' opacities described in Covid-19 pneumonia are reversible in the prone position, suggesting again the presence of lung parenchymal vascular gravity-dependent changes.[5]

Furthermore, dilatation of the lumen of the pulmonary veins reversed by pronation could be related to dysregulation of their muscular tone induced by substances produced in the areas with ground glass/crazy paving opacification and released in the blood flow.[6,7]

The significant increase of oxygen saturation after pronation observed in patients with early stage of COVID-19 interstitial pneumonia might not actually reflect the recruitment of previously atelectatic alveoli, as observed in cases in which interalveolar edema, hyaline membranes and loss of alveolar stability are the histopathologic background, but rather the reduction of the ''dead space'' and shunt effect related to pulmonary capillary and venous blood redistribution induced mainly by gravity changes.[7]

In conclusion in this series we suggest that intra-alveolar capillary changes could be the main anatomic background of ground glass/crazy paving opacification, and hypothesize a link between veins enlargement, ground glass/crazy paving opacification and the pathophysiology profile observed in the early phase of the disease. We labelled all these features ''venoplegic/hyperemic pattern''.

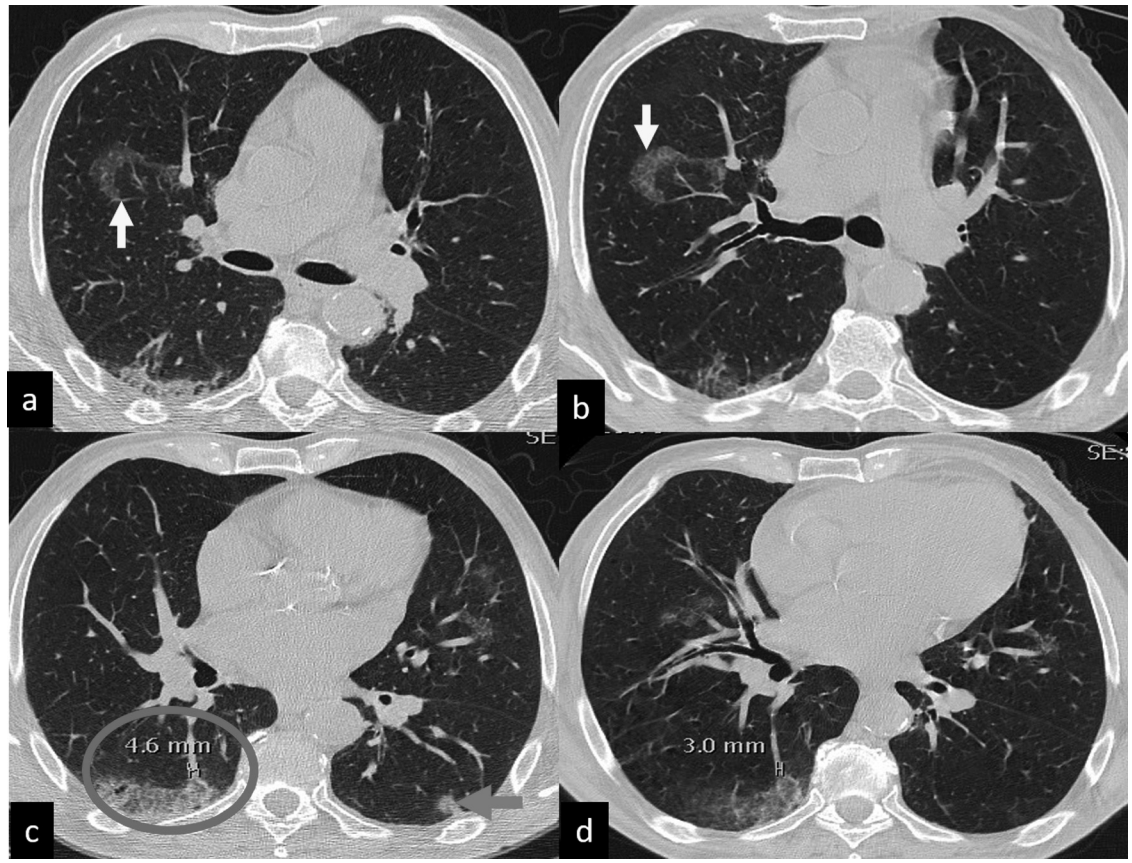

Figure 1 CT scan in supine (a,c) and prone (b,d) position. Some rounded areas of pure ground glass attenuation are present in the right upper lobe (a, upward yellow arrow), middle lobe and lingula. The GG attenuation in right upper lobe, in prone becomes crazy paving and is associated with occurring of an inside vessel enlargement (b, downward yellow arrow).
In the right lower lobe a part-solid ground glass attenuation with a coexisting minimal crazy paving pattern, is present beneath the pleura (c; red ellipse) in the apical and postero-basal segments.
Some vessel enlargement is present in both lower lobes. In the right lower lobe, the enlargement is both outside and inside the GG attenuation and involves branches of the pulmonary veins (caliber of 4.6 mm). Finally, in the left lower lobe, a nodular consolidation is present, adjacent to the pleura (pink arrow), with a drastic reduction in density with the prone positioning.

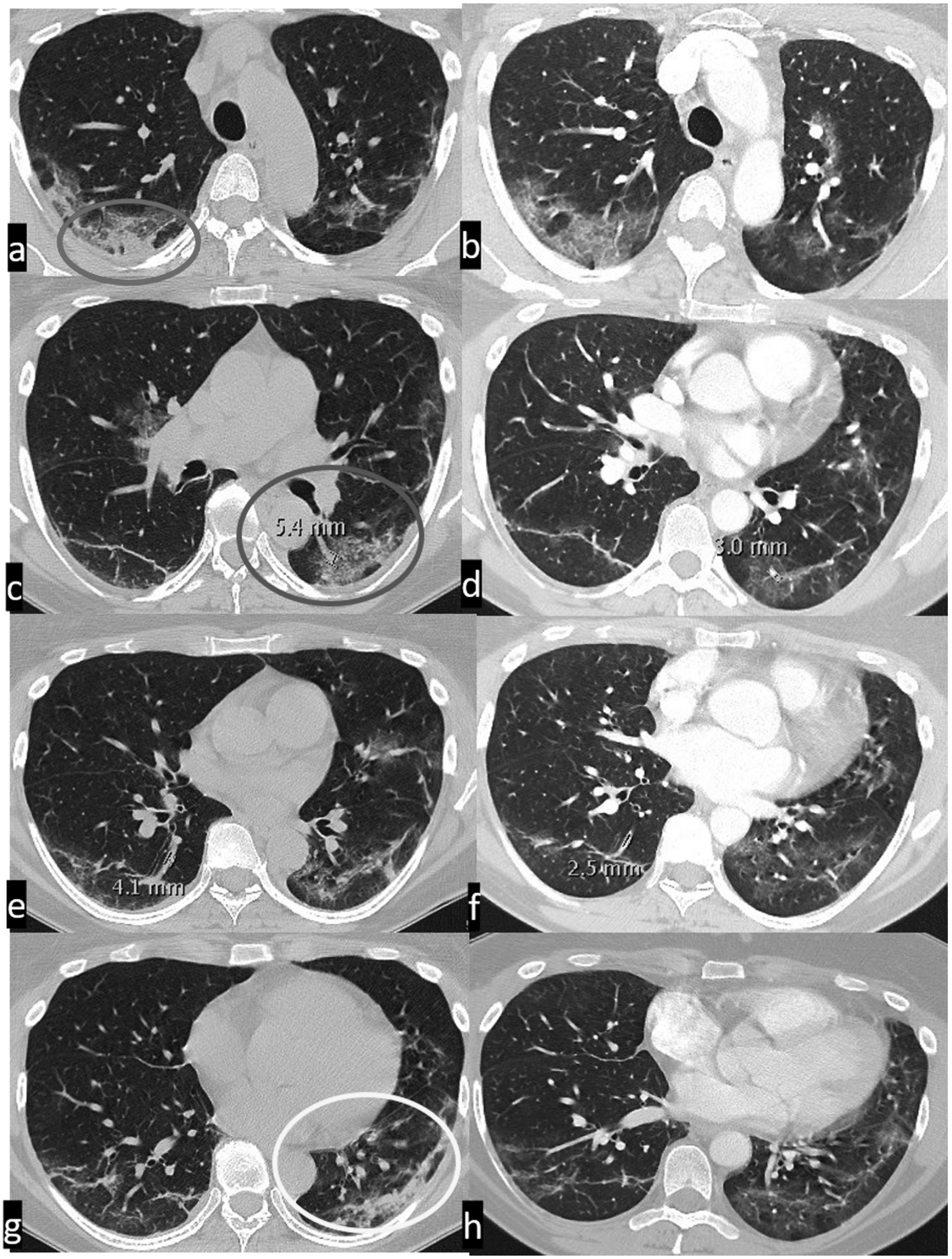

Figure 2 CT scan in supine (a, c, e, g) and prone (b, d, f, h) position. Bilateral peripheral ground glass attenuation, with solid component in the right postero-basal segment (red ellipse) and left postero-basal segment of the left lower lobe (yellow ellipse). The density of the attenuation decreases significantly with prone positioning.
Vessel enlargement, consisting in venous dilatation, is present in both lower lobes, with a significant reduction in caliber with prone positioning (in the left lower lobe: 3 mm vs 5,4 mm).

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.2020.10.010.

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Cystic fibrosis and amyotrophic lateral sclerosis, an unexpected association

Dear Editor:

Cystic fibrosis (CF) is a multisystemic disease with clinical heterogeneity, and progressive lung disease remains the major cause of morbidity and mortality.[1] Some CF patients can be diagnosed later in life. Studies have suggested that patients with a delayed diagnosis survive better, reflecting the prevalence of mutations with a less severe phenotype.[2] Some rarer mutations have been associated with mild CF and delayed diagnosis; one such example is the p.Val232Asp mutation.[3]

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that frequently spreads to involve most muscles leading to severe disability.[4,5] Progressive weakness of respiratory muscles leads typically to respiratory failure, and lung function tests are valuable in predicting its course. The decline in pulmonary function closely correlates with death for patients not managed with respiratory aids (non-invasive ventilatory support – NVS, and cough assistance techniques).[6]

A twenty-two years old male, with a history of allergic asthma and rhinitis since childhood, with no current follow-up. No smoking or relevant family history. He presented with weakness of upper right limb, and muscle cramps, for four months. In association, he referred to worsening of cough and sputum. The neurologic examination revealed atrophy of the right forearm and arm, hyperreflexia and weakness of the upper limbs. Besides the presence of fever, the physical examination was normal. The patient was admitted to the Neurology department for clinical evaluation. Laboratory studies showed a slight elevation of infection markers. Arterial blood gases test were normal. Brain/vertebral magnetic resonance imaging and electromyography (EMG) were normal. Chest computed tomography scan showed cylindrical bronchiectasis with wall thickening, with a tree-in-bud micronodular pattern (Fig. 1, panel A–C). Due to recurrent respiratory infections since childhood, with cough and chronic bronchorrhea and, isolation of methicillin-susceptible *Staphylococcus aureus* in bronchial secretions, CF was suspected. The sweat test was 91 mmol/L, and the genetic study identified p.Val232Asp and p.Phe508del mutations. Both neurological and respiratory symptoms improved with antibiotic therapy, so the patient was discharged. He began follow-up and treatment at the CF outpatient clinic, and radiological improvement was noticeable (Fig. 1 – panel D). No other organ involvement was observed. Spirometry revealed moderate obstructive ventilatory pattern (FVC: 2690 mL/62.9%; FEV1: 2440 mL/65.9%). For the following three months, he experienced worsening of the neurological deficits, with severe weakness of the four limbs (upper right limb with muscle atrophy, Fig. 1 – panel E–F), with an abnormal gait. Repetition of EMG showed neurogenic injury and active denervation, and with the clinical background were indicative of a definitive ALS diagnosis. At this point, he was experiencing a decline in respiratory muscle function, with a VC of 2100 mL, decreasing 15% in the supine position, a peak cough flow of 270 L/min and elevation of partial carbon dioxide pressure (47.8 mmHg). Home mechanical ventilation was initiated with NVS (assisted/controlled

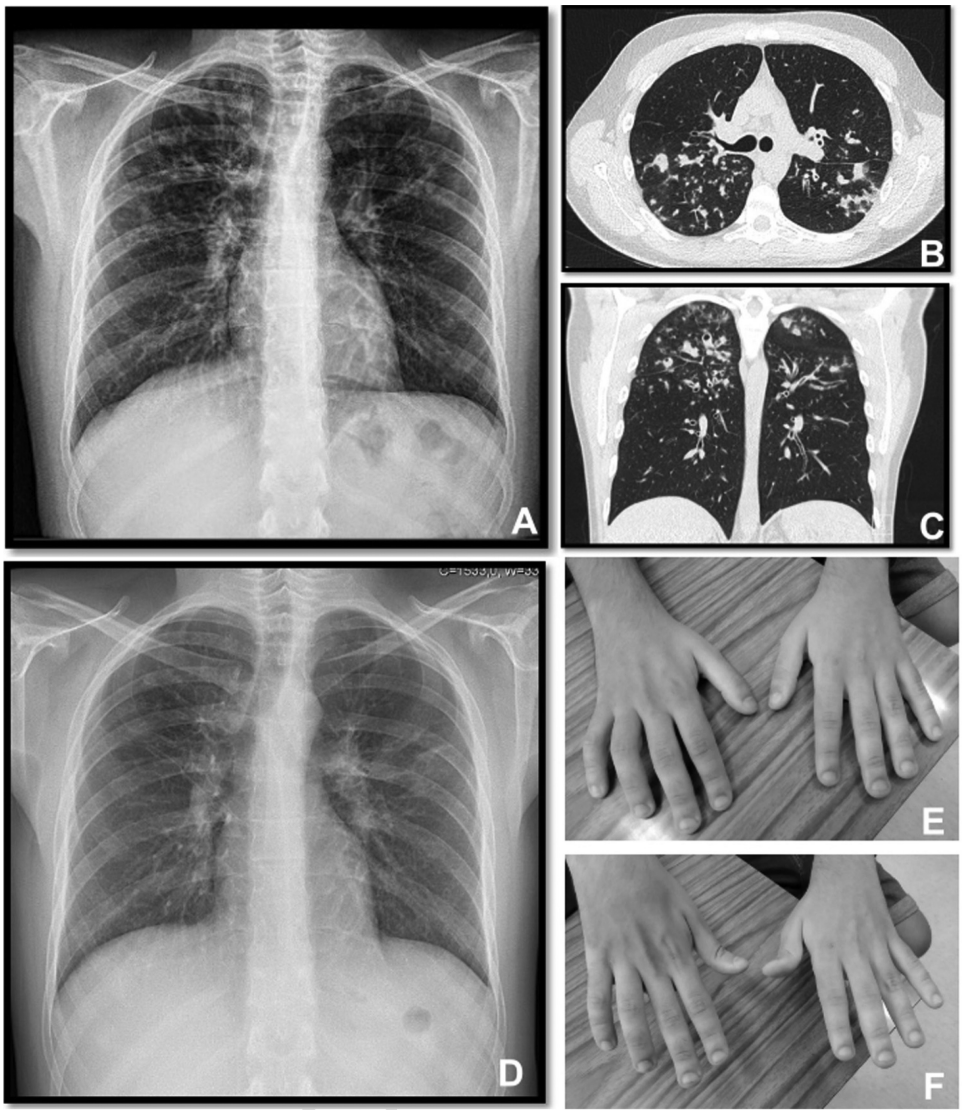

Figure 1 Panel A, B and C: Chest x-ray and thoracic computed tomography showed cylindrical bronchiectasis with wall thickening associated with a tree-in-bud micronodular pattern; Panel D: Chest x-ray with radiological improvement, after CF therapy was initiated; Panel E-F: severe weakness of upper limbs (worse in the upper right limb with muscle atrophy).

mode, with oronasal mask) during sleep, and cough assistance techniques were optimized. Although he had not reported orthopnea or other sleep related symptoms, after beginning NVS he reported better sleep quality without orthopnea and a global improvement during the day; symptoms that he previously undervalued. Palliative care team was also involved.

The authors present a challenging clinical case. On the one hand, we intend to show an example of a late diagnosis of CF and a young-onset of ALS. Given the diversity and versatility of CF presentation, the diagnosis may go unnoticed for years, therefore it is essential to maintain high suspicion regarding the association of certain clinical characteristics. Moreover, this case exemplifies a young-onset of ALS; while it has a progressive course, young patient's survival is frequently longer and the percentage of bulbar onset is lower in the young-adult type. Also, this patient had no family history of ALS. On the other hand, the simultaneous diagnosis of CF and ALS presents several challenges in follow-up and treatment. Airway clearance techniques, a key feature in treating CF, will be compromised due to the inevitable respiratory muscle weakness and ineffective cough associated with ALS with progressive increase of ventilatory dependence. Patients with strictly non-bulbar presentation (as in this case) retain effective speech and swallowing although their VCs can decrease to <100 mL, and all breathing tolerance can be lost and substituted by effective continuous NVS. This case also unveils the psychological issues arising when treating a young patient with two progressive and incurable diseases. The personal impact of the functional decline, the increasing assistance over time and lifestyle changes resulting from such a complicated situation will be hard to manage, highlighting the importance of a multidisciplinary team.

To the best of our knowledge this is the second case reported with CF and ALS.[7] Previously reported was a case of a 30-year-old female, diagnosed with CF 16 years earlier. Genotyping revealed a complex heterozygote of p.Gly542

and p.Pro67Leu mutations. The authors suspected that TDP-43 dysfunction could be linked to both pathologies, but the patient did not display TDP-43 mediated aberrant splicing of the CFTR gene. Alternative reasons were also considered.

In the last few years, the treatment of CF has experienced a period of evolution, with survival estimated around 40 years-old.[1] Survival in ALS is slightly longer in young patients, and improved due to the use of NVS; despite this, the average survival after the diagnosis is up to 2–4 years.[6] Therefore, the authors realize that concurrent CF and ALS might have poor prognosis.

Conflicts of interest

The authors have no conflicts of interest to declare.

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The influence of the non-invasive ventilation mask interface on the upper airway of patients with amyotrophic lateral sclerosis

Dear Editor,

Hypoventilatory respiratory failure is the most common cause of death and respiratory morbidity in patients with amyotrophic lateral sclerosis (ALS).[1] Non-invasive ventilation (NIV) prolongs survival and improves quality of life; however, its benefits depend on the optimization of both ventilation and adherence.[1,2] Upper motor neuron involvement and impairment of bulbar function are associated with upper airway (UA) spasticity and sometimes preclude NIV support in ALS patients.[2]

NIV's acceptance and adherence can be influenced by the site of disease onset, NIV settings and comfort, presence of asynchrony, aggressiveness of disease, ALS phenotype, psychological defense to clinical status,[3] and types of mask interface.[1,4] However, this subject remains debatable and is inconclusive, requiring further exploration and strategies, as marked by Vitacca et al.[3]

Telemonitoring could be one of the strategies to obtain greater adherence, offering information on the presence of leaks, continuous monitoring of breathing, continuous pulse oximetry, and even capnography monitoring, according to Angelucci et al.[5] In addition, physiological changes such as hypoventilation, hypoxemia, hypercapnia, and sleep disorders can be monitored.[5] Home care ventilators can have a built-in monitoring system. It enablesn earlier effective intervention and is a promising solution both from the technical and economic points of view, as it improves the quality of the care provided.[5]

ALS patients may exhibit weaknesses of the tongue and pharyngeal muscles, promoting UA obstruction, especially when positive inspiratory pressure (PIP) is applied.[2,4,6] During insufflation, especially in bulbar ALS patients, adduction of supraglottic laryngeal structures can occur. This compromises airflow and, when posterior displacement of the base of the tongue is associated, increases hypopharynx obstruction.[2] Pharyngeal collapse caused by abrupt inspiratory-expiratory pressure reduction are other potential mechanism of NIV's influence on the upper airway.[2,4,6] These changes can influence ventilatory parameters because positive pressures may compromise the laryngeal inlet during insufflation due to a retroflex movement of epiglottis[2], narrowing the glottis, decreasing the tidal volume delivered[6], and affecting adherence to the NIV.[3]

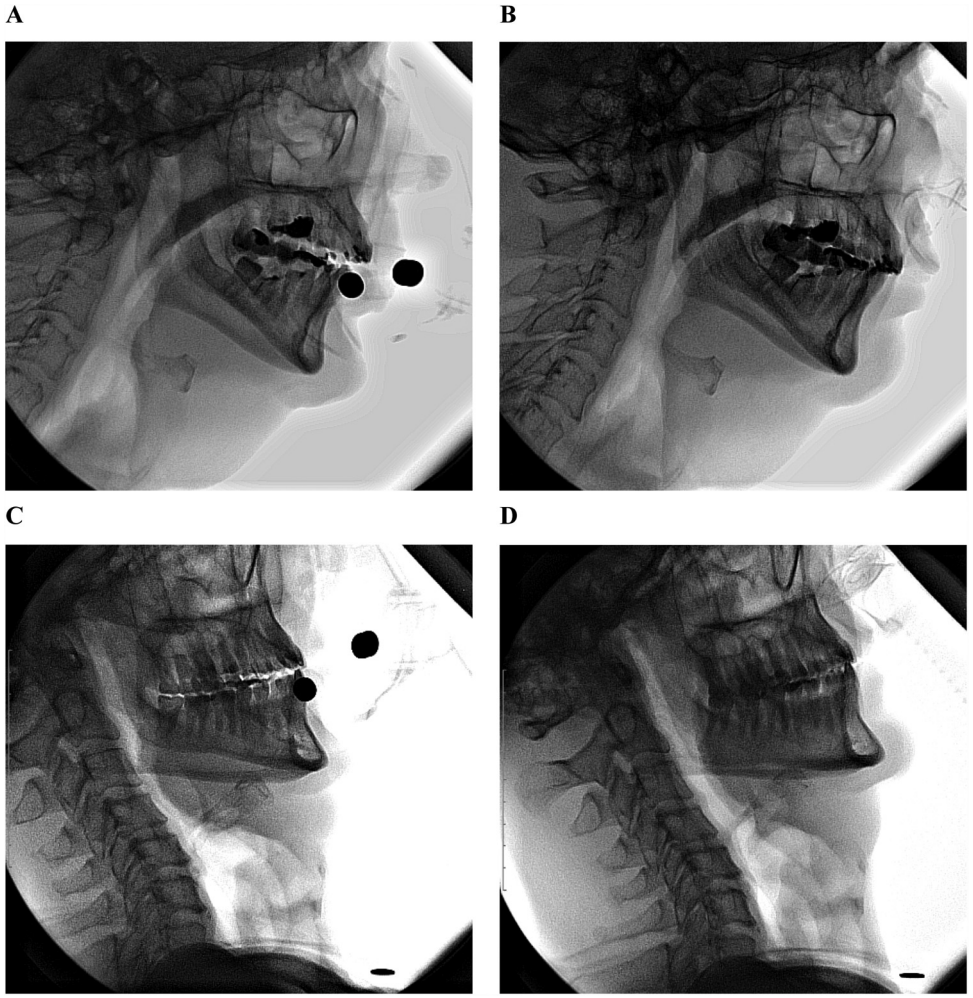

Figure 1 Clinical data, ventilation details and pharyngeal area measurements. Patient 1 is a 64-year old male, diagnosed with ALS 1.5 years ago, ALSFRS-R of 32 points, Fuctional vital capacity of 69%, ventilated with a ResMed Stellar 150 (ET mode; IPAP 12 cmH_2O; EPAP 4 cmH_2O; Inspiratory time 0.7-1.2s; Respiratory frequency: 16 bpm; Cycle: medium; Rise time: 250 msec; Fall time: 100 msec). Using an oronasal mask RedMed AirFit F20 he presented a pharyngeal area (squared C2-C4, as proposed by Stokely et al.) of 8.91 cm^2 (**A**) and with an intranasal mask ResMed AirFit P10 of 8.74 cm^2 (**B**). Patient 2 is a 48-year old male, diagnosed with ALS 8 years ago, ALSFRS-R of 6 points, Functional vital capacity of 12%, ventilated with a ResMed Stellar 150 (ET mode; IPAP 17 cmH_2O; EPAP 6 cmH_2O; Inspiratory time: 0.8-1.5s; Respiratory frequency: 16 bpm; Cycle: medium; Rise time: 300 msec; Fall time: 200 msec). Using an oronasal mask ResMed AirFit F20 he presented a pharyngeal area (squared C2-C4) of 2.29 cm^2 (**C**) and with an intranasal mask ResMed AirFit P10 of 6.21 cm^2 (**D**).

Oronasal masks may be preferred because of better oral leak control, but potential disadvantages include claustrophobia, aspiration risk, increased dead space ventilation, and relevant compromises of eating and speaking.[4] Other potential mechanisms related to the oronasal mask that can happen even in patients with elevated EPAPs (>12 cmH_2O) are the collapse of the soft palate, backward movement of the epiglottis, or tongue base obstruction, with a consequent reduction in the retroglossal space, as reported in a review by Conde et al.[2] Nasal masks are usually preferred for convenience, but bear the risk of insufficient ventilation if mouth leaks occur. These are considered advantageous for positive airway pressure therapy due to better tolerability and sleep quality, lower pressure needs, and increased adherence.[4]

Videoendoscopy[2] and videofluoroscopy[7] are used to assess UA spaces and anatomo-functional changes. UA videoendoscopy during ventilation titration,[2] while implying some degree of invasiveness, may be useful in detecting non-predictable problems and in guiding therapeutic decisions, such as replacement of the mask interface, extending the use of NIV, correcting the observed collapse, and selecting the best time and patients to perform a tracheostomy. There are no standardized videoendoscopic evaluation protocols for assessing UA spaces during NIV use in patients with ALS, but these strategies could extend NIV support to another level, as pointed out by Conde et al.[2] There are no reports in the literature on the use of videofluoroscopy to assess UA during NIV use.

Vrijsen et al.[6] reported a case of a patient with ALS who showed intermittent posterior displacement of the tongue by PIP when using an oronasal mask, inducing obstructive events in the UA and resulting in sleep fragmentation and decreased efficiency of NIV. These findings can possibly be generalized in the ALS clinical setting.[4,6]

To illustrate this, we present two cases of ALS patients using NIV while awake, monitored through videofluoroscopy (Video S1). The aim is to demonstrate the qualitative differences in the UA when using NIV with two different mask interfaces. Clinical data, ventilation details, and pharyngeal area measurements (squared C2–C4), as proposed by Stokely et al.,[7] are shown in Fig. 1.

During the use of the oronasal mask, the patient with 1.5 years of disease presented a slight increase in the UA spaces, while the patient with an 8-year history presented an important reduction in the pharyngeal area. This finding is probably related to bulbar weakness, which is part of the natural ALS evolution. This raises the need to test different interfaces according to the severity of the disease to investigate adherence and improvement of ventilatory parameters.

Disparities can be seen with regard to UA area and position of the mandible, tongue, soft palate, and hyoid bone, considering that ALS is a clinically heterogeneous disease. Non-invasive methods to assess UA during NIV use, such as videofluoroscopy, should be performed in patients with low adherence to explore additional causal factors. Future studies must be conducted to quantitatively assess these differences, especially with respect to ALS severity.

Conflicts of interest

The authors have no conflicts of interest to declare.

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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.2020.12.002.

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Pulmonary hyalinizing granuloma: Atypical presentation☆

Dear Editor,

In 1977, Engleman et al. described pulmonary hyalinizing granuloma (PHG) as a separate entity.[1] This disease is rare and is radiologically characterized by multiple and often bilateral nodules with no preferential localization.[1,2] Its etiology and pathogenesis remain unclear, and a definitive diagnosis is provided by histopathological study of the lesions describing hyalinized lamellar collagen bundles surrounded by plasma cells, lymphocytes, and histiocytes. This disease usually evolves with a benign course with nodules slowly increasing in size over years. Specific treatment is

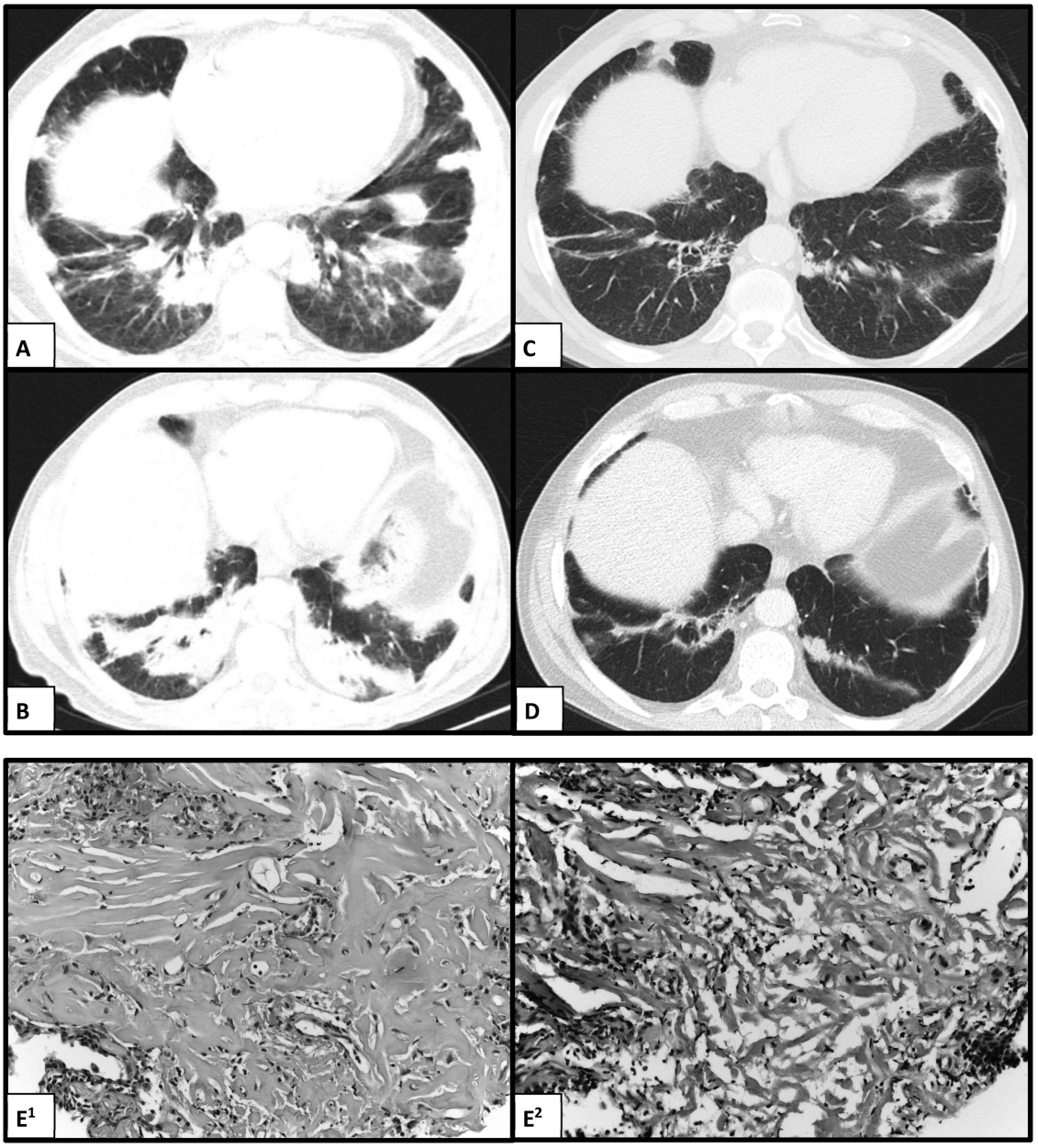

Figure 1 Chest CT scan showing bilateral peripheral consolidation areas in the lower lobes before (A and B) and after (C and D) complete chemotherapy scheme. (E^1) Histology showing hyalinized lamellar collagen tissue surrounded by lymphoplasmacytic infiltrates (hematoxylin and eosin, ×200); and (E^2) negative Congo red stain (CR, ×200).

☆ The authors present a clinical case of a rare disease with atypical radiological presentation, and an uncommon association between Pulmonary Hyalinizing Granuloma and a lymphoproliferative disorder.

not usually required, although corticosteroids have demonstrated some efficacy.[1–3]

The etiology of PHG is not well established, and no relation to occupational exposure has been identified. Due to the frequent association with infectious, autoimmune, and tumoral diseases, an abnormal immune reaction has been proposed to explain the development of PHG.[1,3,4] In the case in the present report, we describe an uncommon association between PHG and a lymphoproliferative disorder. We found only four similar reports of associations with multicentric Castleman disease[5,6]; diffuse lymphocytic lymphoma of the abdomen[7]; and pulmonary small lymphocytic lymphoma[8]. The ages of these patients ranged between 43 and 50 years, and the patients were predominantly male (3 males/1 female). All patients presented with multiple and bilateral pulmonary nodules, and diagnosis was made through video-assisted thoracoscopic lung biopsy in three cases and by post-mortem examination in one case. Chemotherapy schemes targeted at lymphoproliferative disease which included corticosteroid were initiated in three cases. In two of these cases, there was a reduction in the lung nodule dimensions.

We report a case of a 69-year-old man, former smoker (70 pack-years), with occupational exposure to dust and fumes from metallurgical casting and contact with birds, who presented to the emergency department with a 6-month history of progressive dyspnea. He reported mild fever, anorexia, and weight loss (10 kg over the prior 3 months). A physical examination revealed inspiratory crackles in the lower lungs. Chest computed tomography (CT) scan showed bilateral peripheral consolidation areas, mainly in the lower lobes but also involving the middle lobe and lingula (Fig. 1 — A and B); the CT also revealed hepatosplenomegaly. Laboratory data demonstrated normocytic and normochromic anemia, and elevated levels of C-reactive protein and erythrocyte sedimentation rate. An autoimmunity study was negative. No endobronchial lesions were detected in the bronchoscopy. In the bronchoalveolar lavage, the total and differential cell counts revealed lymphocytic (47%) and neutrophilic (7.4%) alveolitis, which was negative for microorganisms and malignant cells. An initial pulmonary function test revealed moderate restrictive ventilatory alteration with a forced expiratory volume in one second (FEV1) 2.06 L (72.8% of the predicted value), forced vital capacity (FVC) 2.42 L (65.6%), preserved FEV1/FVC ratio, a total lung capacity (TLC) 4.51 L (68.5%), and carbon monoxide transfer factor (TLCO) 52%. A CT-guided transthoracic core biopsy was subsequently performed, and hyalinized lamellar collagen tissue surrounded by lymphoplasmacytic infiltrates was reported on histological examination (Fig. 1E[1]). No evidence of neoplastic cells was found, and acid-fast, fungal, and Congo red stains were all negative (Fig. 1E[2]). These findings were consistent with a diagnosis of PHG. The patient was started on oral corticosteroid therapy (deflazacort in an equivalent dose of 0.5 mg/kg/day of prednisolone, within a weaning scheme) and demonstrated partial clinical and functional but not radiological improvement.

Throughout the investigation, an indolent non-Hodgkin's lymphoma (NHL) was incidentally diagnosed, supported by a bone marrow biopsy. The clinical case was, therefore, discussed in a multidisciplinary team, and with PHG hypothesized as a paraneoplastic manifestation of hematological disease, a decision to start NHL treatment was made. After completing eight cycles of chemotherapy (rituximab, cyclophosphamide, vincristine, and prednisolone), the patient had significant clinical, functional, and radiological improvement (Fig. 1 — B and D). At the time this report was written, the patient was asymptomatic and functional with FEV1 2.88 L (106.5%), FVC 3.66 L (103.1%), TLC 5.83 L (89.7%), and TLCO 68%. No residual disease was found on further bone marrow tests.

In summary, PHG is a rare entity with nonspecific symptoms and slow progression. Although isolated or multiple nodular lesions are the most frequent findings, PHG can occaisonally appear as lung parenchymal infiltration or consolidation with irregular or indistinct borders, such as in this case.[3] In patients showing a rapid course and significant functional impairment, corticosteroid treatment may be attempted, despite the unclear efficacy of this approach. Due to the frequent association with underlying diseases, a careful investigation should be performed for therapeutic and prognostic implications.

Ethical disclosures

There are no personal details of patient in any part of the paper and in any supplementary materials (including illustrations).

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Conflicts of interests

The authors have no conflicts of interest to declare.

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Miliary tuberculosis in a rheumatoid arthritis patient receiving long-term tumor necrosis factor monoclonal antibody therapy

Dear Editor,

A 51-year-old woman had a diagnosis of seropositive rheumatoid arthritis (RA) with polyarthritis involving bilateral elbow, small joints of hand and knee areas on March 12, 2004. Owing to refractory therapeutic responses with a DAS28 score of 6.16 under methotrexate 15 mg/week, hydroxychloroquine 400 mg/day and prednisolone 10 mg/day, she started to receive regular biweekly 40 mg subcutaneous injection of adalimumab, a tumor necrosis factor (TNF) monoclonal antibody (mAb) since June 17, 2011. She had no history of lung diseases with a clear chest X-ray (Fig. 1A). There was a negative QuantiFERON test before initiating anti-TNF therapy. She had reduced disease activity after treatment without further prescription of hydroxychloroquine and prednisolone. Owing to productive cough with intermittent fever and weight loss for 3 weeks, the use of TNF mAb was discontinued on February 20, 2018, 80 months after initiating such a treatment. However, she did not receive follow-up QuantiFERON test during her long-term anti-TNF therapy. Chest images including X-ray (Fig. 1B) and computed tomography (Fig. 1C) showed bilateral diffuse miliary lesions characterized by innumerable micronodular opacities. She had no exposure to fine mineral or chemical dust, and her malignancy survey and human immunodeficiency virus examination were negative results. Sputum cultures were positive for *Mycobacterium tuberculosis*. There was no recent household tuberculosis (TB) contact history. She received anti-TB medications with daily dosages of rifampicin 480 mg, isoniazid 320 mg, pyrazinamide 1000 mg and ethambutol 800 mg for 9 months from April 12, 2018 (drug-susceptibility testing in TB with resistance to streptomycin and sensitive to others). After antibiotic therapy, there were no more respiratory or constitutional symptoms, negative sputum culture results and resolved pulmonary miliary nodules (Fig. 1 D). For her arthritis flare-up after discontinuing TNF mAb injection, rituximab, a B-cell depleting mAb, under a regimen of 1 g × two fortnightly infusions every 6 months was initiated on February 7, 2020 with improved disease activity (DAS 28 score 5.34 to 2.70) after 4 infusions at the end of 2020.

Miliary TB, a rare fatal presentation of mycobacterial infection, can occur in the presence of impaired host immunity under the prescription of immunosuppressive agents.[1,2] TNF blocker administration has been recognized as a risk for TB reactivation in various autoimmune-mediated inflammatory disorders,[3] especially when anti-TNF treatment is combined with the use of immunosuppressive agents like methotrexate.[4] Greater incidences are found during the first year of treatment than afterwards, while there are higher occurrences with mAb than with recombinant soluble receptor fusion protein therapy. Despite an additional risk of having been born in an area of endemic TB,[5] the reported case raises a potential infection hazard under the long-term TNF mAb treatment.

In conclusion, we reported miliary TB in a RA patient receiving long-period TNF blocker therapy. In addition to the initial QuantiFERON survey, periodic latent TB testing should be carried out in patients receiving the long-term immunosuppressive agents like TNF monoclonal antibodies.

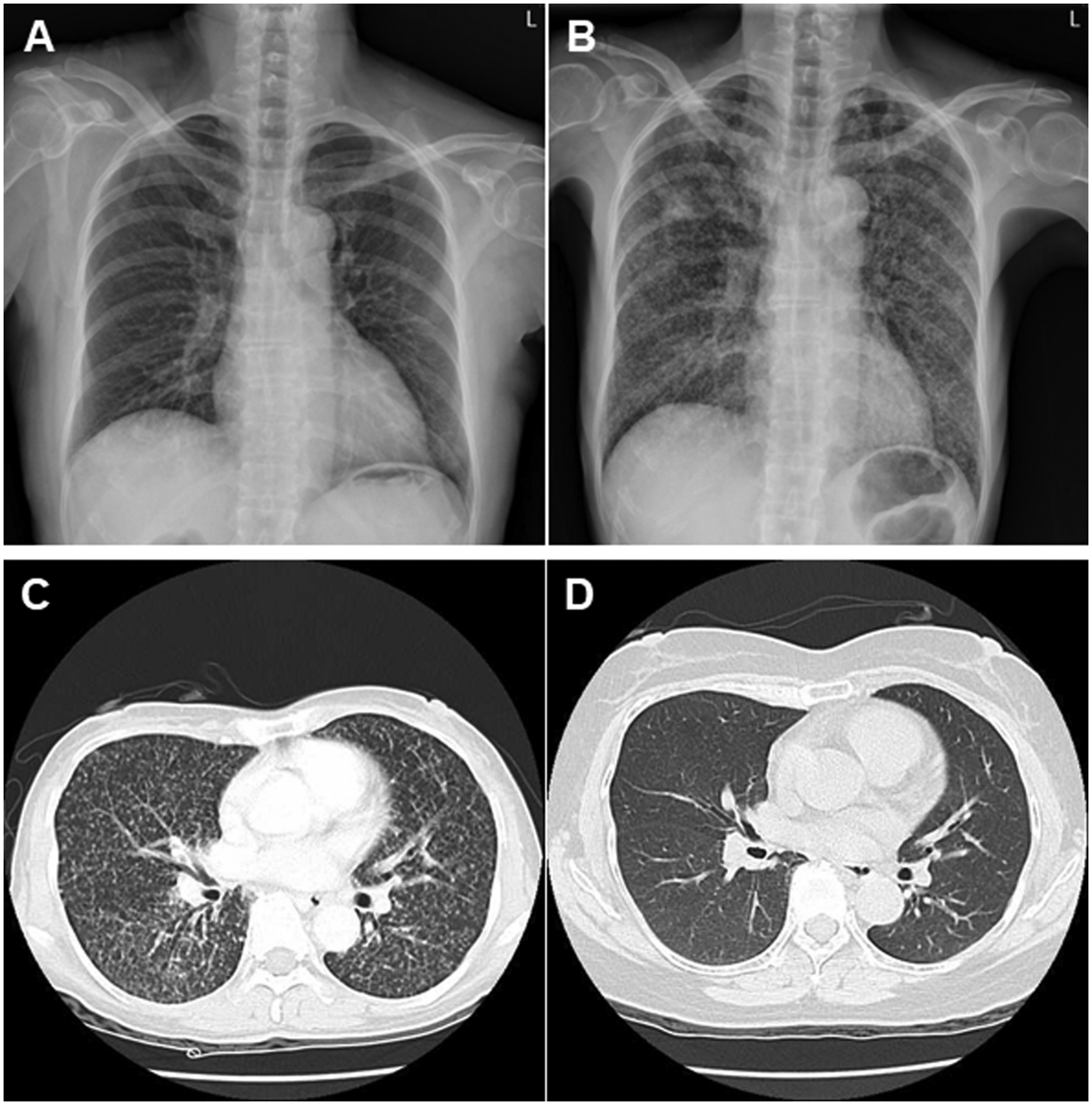

Figure 1 Clinical images of miliary TB in a RA patient receiving TNF mAb therapy. (A). A clear chest X-ray without any lung lesions before starting TNF mAb therapy. (B). Bilateral diffuse military lesions on chest X-ray after TNF mAb therapy. (C). Bilateral innumerable micronodular opacities on chest computed tomography after TNF mAb therapy. (D). Resolved bilateral military nodules on chest computed tomography after anti-TB treatment.

Author contributions

Study conception and design: Chrong-Reen Wang.

Data analysis and acquisition: Chrong-Reen Wang, Wei-Chieh Lin, Yi-Shan Tsai.

Drafting of the manuscript: Chrong-Reen Wang.

All authors had access to the data and played a role in writing this manuscript.

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Conflict of interest

The authors have no conflicts of interest to declare.

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This study was approved by the Institutional Review Board (B-ER-105-108) with informed consent from the patient.

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International predictive equations of maximum respiratory mouth pressures: Are they suitable for the Portuguese adult population?

Dear Editor,

Predictive equations of maximum inspiratory (Pimax) and expiratory (Pemax) pressures are important for detecting respiratory muscle weakness. A recent systematic review identified 42 Pimax and 34 Pemax equations as available for healthy adults, but to date no single equation has been recommended.[1] This is problematic as it is known that the presence or absence of respiratory muscle weakness is critically dependent on the equation selected.[1] Predictive equations should be population-specific and none of the identified equations have been developed in Portugal.[2] Portuguese people present specific characteristics, for example they tend to be shorter than people of most other European countries,[3] which may affect how these equations are applied. In the current absence of an equation developed for Portugal, healthcare professionals need short-term guidance on which equations are more appropriate to use. Thus, we explored the suitability of the available predictive equations in a sample of healthy Portuguese adults.

A cross-sectional study, approved by the Ethics Committee of the University of Aveiro (8/2015), was conducted with healthy Portuguese adults recruited from the community. All participants signed an informed consent. Sociodemographic, anthropometric and clinical data were collected to characterise the sample. Respiratory muscle testing followed the European Respiratory Society guidelines[1] (MicroRPM, Carefusion, Basingstoke, UK). Descriptive statistics, Wilcoxon signed-rank tests, Bland-Altman plots and Spearman correlation coefficients were used to characterise the sample, test differences between real and predicted values and ascertain the absolute reliability and concurrent validity, respectively. The lower limit of normality (LLN) was computed as: mean $-$ 1.645 $\times$ standard deviation.[4]

A total of 229 Caucasian individuals (n = 141, 61.6% men) were included. Participants' characteristics are detailed in Table 1.

Thirty-six Pimax and 29 Pemax equations were tested (Fig. 1). Nine equations could not be tested either because some variables were not collected (e.g., waist circumference and vital capacity) or due to lack of information provided by authors (e.g., constant of the equation).

The Pimax predicted values were significantly different from the real values obtained ($p < 0.05$), except for the equations for men developed by Enright et al. (1995),[5] Hautmann et al. (2000)[6] and Sachs et al. (2009),[7] and for women developed by Neder et al. (1999).[8] Values obtained with these equations were amongst the ones with higher correlations (r_s = 0.32–0.47) and lower bias (0.19–4.06) with the actual data (Fig. 1 and supplementary material – Appendix A).

Twelve equations underestimated the real values and 4 equations overestimated the real values for men. The same pattern was found for women, with 15 equations underestimating and 3 equations overestimating the real values.

Regarding Pemax, all equations showed significant differences between real and predicted values ($p < 0.001$), with most equations (n = 10) underestimating the real values for both genders (Fig. 1).

LLN of Pimax resulted in a cut-off of 43.7 cmH_2O for women and 50 cmH_2O for men. The predicted values from all equations were above the LLN, hence not detecting inspiratory muscle weakness according to the LLN.

This study showed that all equations performed poorly, with none of the equations being suitable for detecting people below the LLN.

Nevertheless, of all equations for Pimax, 4 showed no significant differences between predicted and real values: 3 for men[5–7] and 1 for women.[8] Regarding men, the best agreement was found for the equation developed by Sachs et al.[7] This might be explained by the similar equipment and protocol used (e.g., handling of subjects). In fact, almost half of the equations were developed with a lack of compliance with the guidelines,[2] which might explain the disagreement with the real values in this study. Additionally, intrinsic fac-

Table 1 Characteristics of the participants ($n = 229$).

	Total ($n = 229$)	Women ($n = 88$)	Men ($n = 141$)
Age, years (range)	66.7 ± 9.7 (43–90)	65.3 ± 10.4 (46–90)	67.6 ± 9.2 (43–89)
Smoking status, n (%)			
Never	173 (75.2)	85 (96.6)	88 (61.4)
Former	52 (23.1)	3 (3.4)	49 (35.8)
Current	4 (1.7)	0(0)	4 (2.8)
Smoking, pack-years, median [interquartile range]	16 [5.0–35.0]	0.9 [0.6–1.2]	20 [6.7–35.8]
CCI, median [interquartile range]	2 [2–3]	3 [2–3]	2 [1–3]
0, *n* (%)	6 (2.7%)	3 (3.4%)	3 (2.3%)
1–2, *n* (%)	114 (51.8%)	40 (46%)	74 (55.6%)
3–4, *n* (%)	94 (42.7%)	41 (47.1%)	53 (39.8%)
≥5, *n* (%)	6 (2.7%)	3 (3.4%)	3 (2.3%)
BMI, kg/m²	27.8 ± 4.4	28.1 ± 5.3	27.7 ± 3.7
FEV_1, % predicted	101.8 ± 20.5	109.7 ± 23.3	96.8 ± 16.7
Pimax, cmH_2O	88.5 ± 26.1	79.4 ± 21.7	94.7 ± 27.2
Pemax, cmH_2O	126.9 ± 36.6	104.9 ± 25.5	140.8 ± 35.7

Data are presented as mean ± SD, unless otherwise stated. BMI: body mass index; CCI: Charlson comorbidity index; FEV_1: forced expiratory volume in one second; Pimax: maximum inspiratory pressure; Pemax: maximum expiratory pressure.

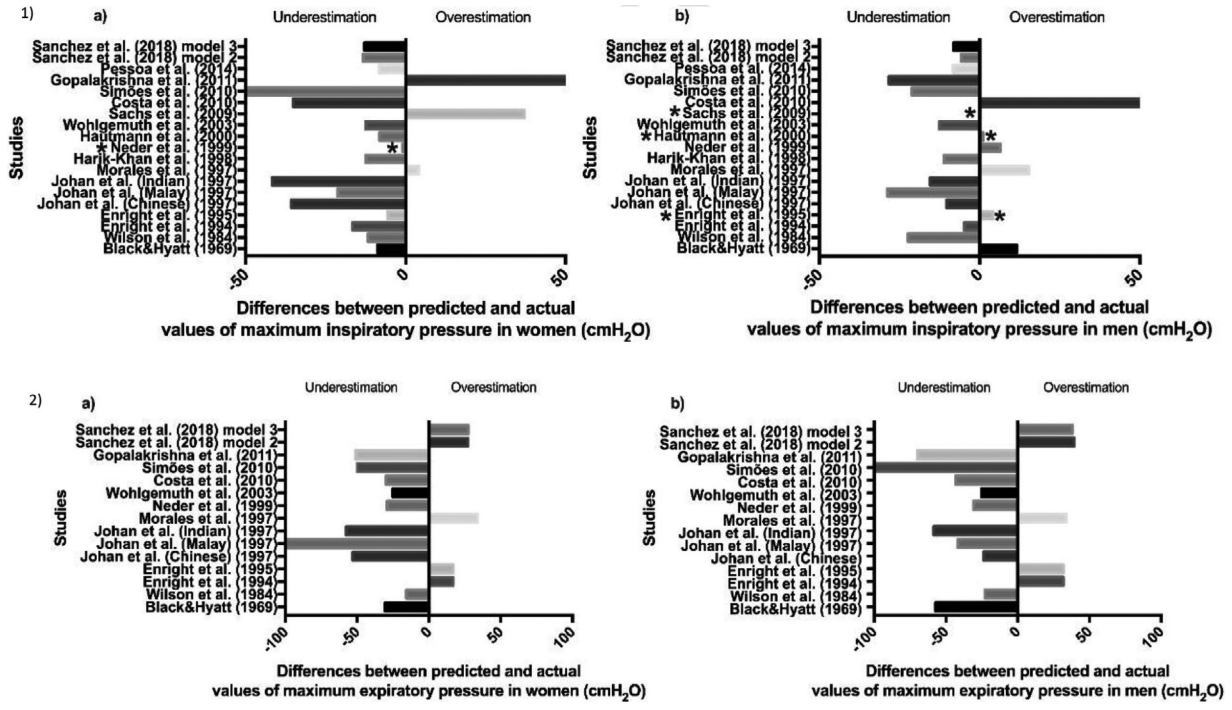

Figure 1 Estimation differences across studies between predicted and actual values of (1) — (a) maximum inspiratory pressure in women; (b) maximum inspiratory pressure in men; (2) — (a) maximum expiratory pressure in women; (b) maximum expiratory pressure in men. *$p > 0.05$.

tors such as age, gender and ethnicity disparities across the reported studies and this one may have also contributed to the equations' lack of suitability.

None of the equations were able to detect people below the LLN, which is of most importance to identify people with respiratory muscle weakness.[9] The LLN established for Pimax in this study, 43.7 cmH_2O for women and 50 cmH_2O for men, can now be used in clinical practice and are similar to the cut-offs previously proposed.[9]

A recent study showed that Black and Hyatt, Bruschi et al. and Neder et al. equations were the most accurate to detect muscle weakness,[10] and these equations were amongst the ones included in the recent guideline.[1] However, in our study, only the equation from Neder et al. showed good

reliability and validity, highlighting the importance of choosing carefully when using predictive equations and reference values from distinct populations.

As no Pemax equation was suitable for this population and expiratory muscle weakness is also important to detect,[1] no recommendation can be made at this point and future studies should develop new equations.

This study has some limitations that need to be acknowledged. Due to our unbalanced sample (i.e., inequalities in gender and in the distribution of age decades), it was not possible to develop equations for Pimax or Pemax. Although studies of predictive equations have been published with small sample sizes and no power calculation,[11] a balanced and powered sample is imperative for developing reliable and appropriate regression models and reference values.[12] Some necessary variables were not collected, which hindered the analysis of 14 equations but those are the variables which are the most difficult to implement across distinct settings (e.g., vital capacity, through plethysmography), leading to a limited use in daily clinical practice. Moreover, the absence of healthy individuals below 40 years old impaired the generalisation of conclusions for younger adults. Testing the available equations or the development of new ones in a younger sample of healthy people is therefore recommended.

No equation was found to be suitable for the Portuguese population, thus future studies should attempt to develop new Pimax and Pemax equations and reference values with powered and balanced samples. In the absence of specific equations, the ones developed by Sachs et al. and Neder et al. are the most appropriate to be used. Our study can be replicated in countries where no specific predictive equations are available to improve accuracy of respiratory muscle weakness interpretation.

Conflict of interest

The authors declare no conflicts of interest.

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This work has been presented as a Poster Discussion in the European Respiratory Society International Congress 2019.

Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version available at http://dx.doi.org/10.1016/j.pulmoe.2020.07.005.

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Urinary symptoms are very frequent in people with chronic respiratory disease attending pulmonary rehabilitation

To the Editor,

Chronic respiratory diseases (CRD) progressively lead to physical inactivity and worsening dyspnoea,[1] and cause disability and mortality.[2] Strong evidence shows that pulmonary rehabilitation (PR) improves dyspnoea, fatigue, emotional status, exercise capacity and reduces exacerbations.[3,4] However, one in two people with CRD referred for PR never attend, and up to one third do not complete the program.[5] Others who complete the program have few clinical benefits.[6] We recently discussed how urinary symptoms (US), which are frequent in CRD,[7] might be a major barrier to participation, completion and response to PR.[8] However, our discourse was speculative because no data are available about the relationship between US and PR. A first step to address this question would be to determine its frequency and to characterize the type of symptoms in people with CRD attending PR. Hence, we report the results of a study aimed to assess the frequency and types of US, and their relationship with baseline demographic and cardiorespiratory characteristics, in people with CRD attending PR.

A retrospective chart review of people attending PR between December 2019 and March 2020 was conducted in ADIR Association, Rouen University Hospital, France. Inclusion criteria were adults with CRD (any type) and referral to PR. Ethical approval was granted (E2020-71) and informed consent was not required.

US were assessed during the first PR session using the Urinary Symptom Profile (USP) questionnaire[9] which evaluates stress US, urge US and dysuria. No thresholds have been established to define the presence of symptoms, therefore we considered a score above the upper bound of the 95% CI of the mean score for asymptomatic people[9] to indicate US. Thus: stress incontinence = score above 1/9, urge incontinence = score above 4/9 and dysuria = score above 1/9.

Continuous data were expressed as means (standard deviation) or medians (25^{th}–75th percentile) and qualitative data as counts and percentages, and their corresponding 95% CI were calculated. The overall rate of US was calculated as the occurrence of at least one type of US. US were also compared between obstructive and non-obstructive CRD using a Fisher test. The relationship between US and demographic or cardiorespiratory characteristics was analysed using a binomial logistic relationship. A p-value <0.05 was considered significant. GraphPad Prism 5.03 and R 3.6.1. software were used.

Thirty people with CRD (43% female, median age 61 years (range 53–67), mean body mass index 26.2 kg/m^2 (SD 4.9)) were included. Eighteen (60%) had obstructive CRD, 5 (17%) had lung cancer, 5 (17%) had interstitial lung disease and 2 (7%) had other restrictive CRD. Five (17%) were long term oxygen therapy users. Twelve participants (40%, 95% CI 25–58) experienced at least one type of US; urge US was the most frequent (Fig. 1A). There was no difference in the proportion of participants who experienced at least

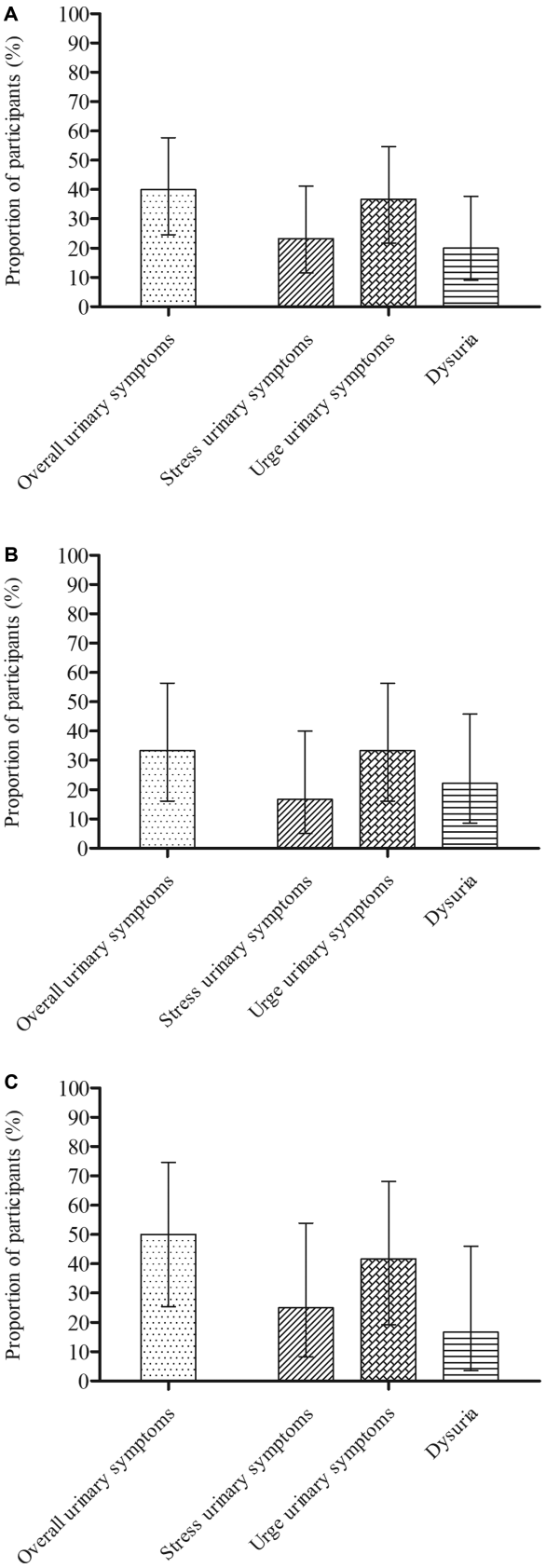

Figure 1 Overall and specific rates of urinary symptoms in (A) the whole cohort, (B) participants with obstructive chronic respiratory diseases and (C) participants with non-obstructive chronic respiratory diseases.
Data are shown as proportions with 95% confidence intervals.

one type of US between obstructive and non-obstructive CRD ($p = 0.26$) (Fig. 1B and C). US was not significantly related to demographic or cardiorespiratory characteristics.

The results of this study revealed that US are very frequent in people attending PR. Furthermore, the true rate may be higher since US were assessed on the first day of PR and previous physical inactivity may have masked some symptoms.[8] Indeed, PR involves regular and sustained physical exercise, therefore it may both reveal and worsen US, leading participants to reduce their participation or even drop out.[8] Since the physiological effects of PR depend on training intensity, lack of adherence considerably reduces the benefits.[8,10] In addition, US can worsen the quality of life of people with CRD.[11] These results therefore highlight a concerning issue that must be considered in both research and clinical practice.

Importantly, the occurrence of US was similar between participants with obstructive and non-obstructive CRD. It was beyond the scope of this study to evaluate the causes of US, but several risk factors may be common between obstructive and non-obstructive CRD (particularly for tobacco-induced lung cancer). Impaired diaphragm and expiratory muscle biomechanics alter both the stability of the lumbopelvic muscle system and intra-abdominal pressure regulation[12] and thus may be a cause of US in people with restrictive CRD or interstitial lung disease.

This study has several limitations. Firstly, the sample size was small and the design was retrospective. The lack of a relationship between US and demographic and cardiorespiratory characteristics may therefore be due to a lack of power. The presence of US was based on threshold scores for the USP that have not been specifically determined[9] and may therefore be somewhat inaccurate.

Despite these limitations, the high frequency of US in people with all types of CRD attending PR is concerning. Large, prospective studies are now warranted to evaluate the impact of US on PR adherence and outcomes. Clinicians should screen PR participants for US and provide appropriate treatment to facilitate adherence.

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Ethical approval and consent to participate

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Acute respiratory distress due to a bronchogenic cyst submitted to percutaneous drainage followed by thoracoscopic resection

Dear Editor,

A clinical case of severe respiratory distress due to a mediastinal bronchogenic cyst (BC) that was managed exclusively by a minimally invasive approach is here presented.

Case report

A 2-year-old boy was referred to the pediatric intensive care unit in acute respiratory distress. He was febrile and presented tachypnea, dyspnea, stridor, global chest retraction and hypoxia. Over the previous 25 days, he had been admitted twice due to cough, wheeze and mild respiratory distress with poor response to medical treatment. Thoracic computed tomography scan revealed a well-circumscribed, bilobed cyst ($48 \times 46 \times 30$ mm) in the superior and posterior mediastinum, causing displacement of the supra-aortic vessels, and compressing the esophagus and the trachea; there was a cervical extension, contiguous to the left thyroid lobe and common carotid artery (Fig. 1A, B).

Due to the severe respiratory distress, in an attempt to stabilize the patient condition and improve ventilation, a decision was made to perform percutaneous cyst drainage.

Under ultrasound and fluoroscopic guidance, an 8 Fr pigtail catheter was inserted into the cyst with aspiration of 40 cc of fluid, which resulted in near complete collapse of the cyst and immediate clinical improvement (Fig. 1C). Elective thoracoscopic excision of the mass was then planned.

With the patient in modified right lateral decubitus, three 5 mm trocars were inserted. The cyst was identified posterior to the left subclavian artery (Fig. 2A–C); because of the intimate relation with the esophageal wall, an intraoperative upper endoscopy was performed to assist the dissection. The cystic mass was then removed *en bloc*, the resulting muscle defect of esophageal wall being closed with interrupted absorbable sutures; a thoracic tube was left in place through one port.

The postoperative course was uneventful. After removal of the thoracic tube, the child was discharged home on postoperative day 1. Histological examination revealed a uniloculated cyst lined by respiratory type epithelium with underlying fascicles of smooth muscle, respiratory-type mucous glands and cartilage, consistent with a bronchogenic cyst.

At 2-year follow-up, the child is doing well with no digestive or respiratory symptoms; the scars are almost imperceptible.

Comment

Foregut cystic malformations are rare congenital entities. Bronchogenic cysts (BC) in the mediastinum form early in fetal development from abnormal buds of tracheobronchial tree. Most of them are asymptomatic in the early stages, thus they are rare in infancy and often recognized in young adults. In fact, most diagnoses occur when the BC become infected or grow large enough to compress adjacent organs.[1,2]

The treatment of asymptomatic BC is not consensual. In adults, conservative management under close long-term follow-up is an option.[3] In children, both symptomatic and asymptomatic cysts should be surgically excised because of risk of enlargement/compression (due to secreting mucosa

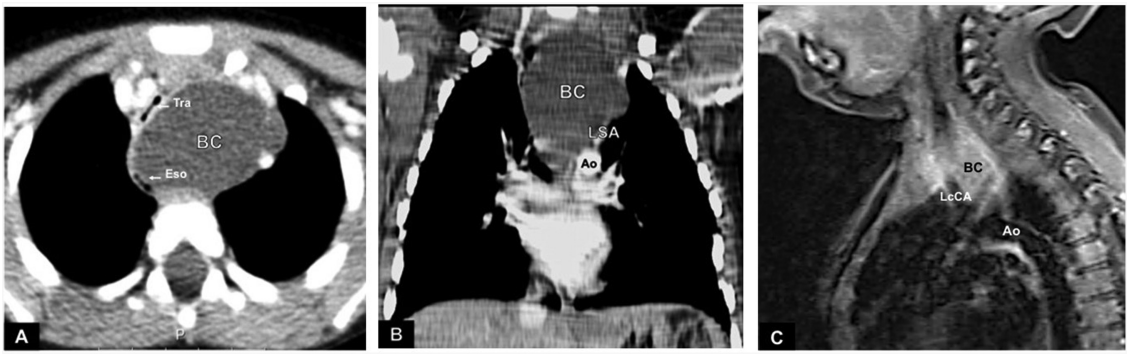

Figure 1 (A, B) Computed tomography scan before drainage; (C) magnetic resonance imaging after drainage.
Ao—aortic arch; BC—bronchogenic cyst; Eso—esophagus; LcCA—left common carotid artery; LSA—left subclavian artery; Tra—trachea.

or infection), erosion/perforation, bleeding, and malignant degeneration. As these lesions do not regress, it is probably more appropriate to resect asymptomatic BC not only in children but also in the young and in the healthy adult in order to prevent life threatening complications such as the present case illustrates.[2,3]

Drainage of symptomatic BC is a minimally invasive procedure when performed by percutaneous access under ultrasound guidance or by endobronchial ultrasound-guided fine needle aspiration (EBUS-FNA).[1,4–6] The latter has been used mainly for diagnostic purpose, but several experts have applied it successfully to BC drainage[1,6]; unfortunately, there is no bronchoscopy with EBUS-FNA available for young children. Drainage can be used in patients who are non-surgical candidates, but it is a less than optimal definitive treatment because the risk of infection or cyst recurrence remains. In addition to the rapid resolution of respiratory distress, the drainage should be viewed as a first step to facilitate the subsequent cyst excision due to the reduction of size and inflammation.[5]

Surgical excision of mediastinal BC is demanding because of vicinity and possible adhesions to surrounding vital organs, with potentially life threatening complications.[5,7] In addition, some patients do not tolerate thoracoscopy well, thus thoracotomy is the procedure usually performed.[5] Video-assisted thoracoscopic surgery (VATS) has been increasingly used to excise BC and is the preferred ''minimally invasive technique'' for most thoracic surgeons.[1,5] However, a purely thoracoscopic procedure (not VATS) is even less invasive, with a more rapid recovery and better cosmesis. As the present case illustrates, it is viable despite the tight space available, particularly for suturing, a more pronounced issue in young children. So, if the patient can tolerate a ''purely'' thoracoscopic procedure, it should be endeavored.

In summary, this unique report demonstrates the feasibility of strict minimally invasive techniques to decompress and to excise a BC, which were crucial for the excellent outcome.

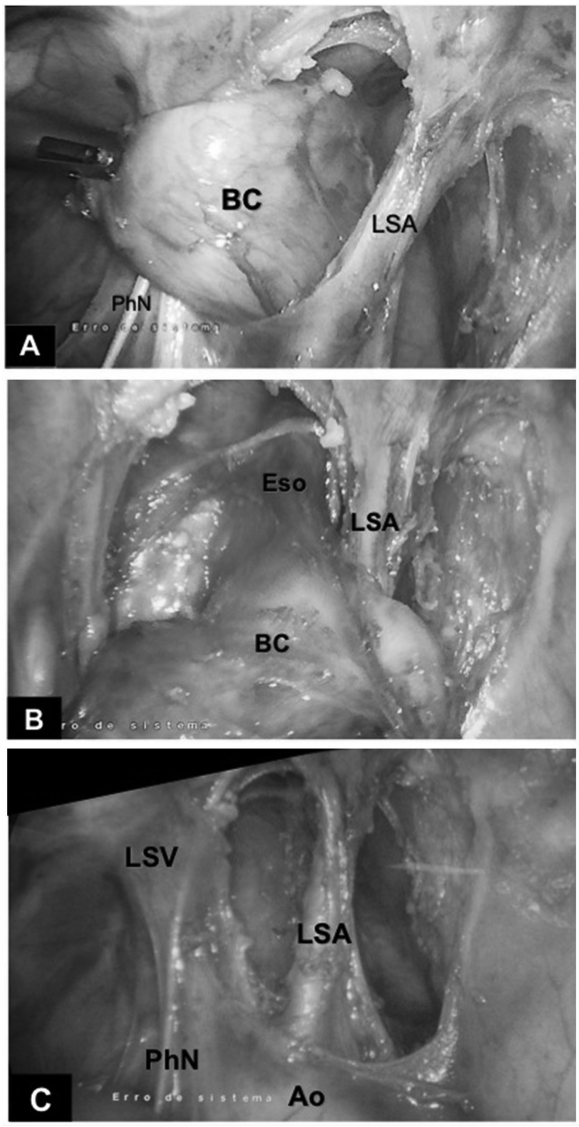

Figure 2 (A–C): Intraoperative view.
Ao—aortic arch; BC—bronchogenic cyst; Eso—esophagus; LSA—left subclavian artery; LSV—left subclavian vein; PhN—phrenic nerve.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Assessment of compliance with the smoking ban in children's playgrounds in Portugal: a case study

The smoking behavior of friends, peers and family members is an important predictor of tobacco use by adolescents.[1] Concomitantly, it is widely acknowledged that tobacco consumption by parents is a risk factor for childrenś later smoking behavior. In Portugal, Law no. 63/2017 entered into force on January 1st 2018 and extended the smoking ban to outdoor locations attended by children (e.g., children's playgrounds).[2] This law is relevant not only to protect children from secondhand smoke exposure, but also to decrease tobacco normalization. This study aimed to describe tobacco-related variables (e.g., persons smoking, smell of tobacco smoke, cigarette butts) in children's playgrounds before and after the implementation of this new Law, considering the socioeconomic status (SES) of the neighborhood surrounding the playground.

An observational study was developed in children's playgrounds in the municipality of Braga (Portugal), between May and June 2017 (before the law entered into force), followed by two follow-ups carried out in the same months in 2018 and 2019 (after the law entered into force). This study followed the methodology of the TackSHS Project Consortium, whose aims included the assessment of SHS exposure in children's playgrounds in European countries.[3,4] A convenience sample of 20 playgrounds was assembled. Playgrounds were selected according to the neighborhoods' SES: 9 were located in the most deprived urban areas (low SES) and 11 located in the most affluent ones (high SES). Neighborhood SES was established based on a deprivation index for Portugal.[5] The number of playgrounds observed varied in each year due to temporary closures for maintenance. Playgrounds were observed in similar weather conditions and each playground was observed for a period of 30 min. The inclusion criterion was that a minimum of five people, including children, were inside the playground at the beginning of the observation, regardless of the time or day of the week. Most playgrounds were observed during weekends (41 out of 57) and in the afternoon (51 out of 57). On average each playground had a total of 9.77 (SD = 5.60) people inside, of which 5.55 (SD = 4.73) were children.

The researchers recorded the data on a grid developed based on the variables collected on the TackSHS project[4]: existence of persons smoking (cigarettes and e-cigarettes/heated tobacco products) inside and around the playground (<1 meter); presence of the smell of tobacco smoke; presence of non-smoking signs; and existence of cigarette butts on the floor inside and outside the playground.

The associations between tobacco-related variables and the year of the observations or the neighborhoods' SES were calculated using a Chi-squared test for the categorial variables (Fisher's Exact test when the expected count in cells was lower than five). The median differences were compared through a Kruskall–Wallis or Mann–Whitney Test, as appropriate. All analyses were performed with the IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 26.0, Armonk, NY, USA.

The main results are presented in Table 1. There was a statistically significant decrease in the number of playgrounds with cigarette butts outside, reducing from 20 in 2017 to 15 in 2018 ($p = 0.028$). However, in 2019 this number increased to 19 playgrounds. In 2017, almost all the play-

Table 1 Tobacco-related variables in children's playgrounds in the municipality of Braga, Portugal, by year.

Variables	2017 N = 20[a]	2018 N = 18[a]	2019 N = 19[a]	*p*-value*
		n (%)		
Smell of smoke	3 (15.0)	1 (5.6)	1 (5.6)	0.603[c]
Smoking sign	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Smoking inside	2 (10.0)	0 (0.0)	1 (5.3)	0.643[c]
Smoking outside[b]	3 (15.0)	0 (0.0)	2 (10.0)	0.310[c]
e-cigarette/heated tobacco users	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Butts inside	19 (95.0)	17 (94.4)	15 (78.9)	0.298[c]
Butts outside[b]	20 (100.0)	15 (83.3)	19 (100.0)	**0.028**[c]
	Median (P25-P75)			
Butts inside, *number*	14.00 (4.00–20.00)	5.00 (3.00–12.75)	5.00 (1.00–9.00)	0.083[d]
Butts outside, *number*	20.00 (12.50–20.00)	20.00 (6.50-20.00)	20.00 (12.00–20.00)	0.701[d]

Note: SD, standard deviation; n.a., not applicable.
[a] The number of playgrounds observed varied in each year due to temporary closure for works of some of them.
[b] Just around the playground area at a maximum distance of 1 meter.
[c] Fisher's Exact Test.
[d] Kruskal–Wallis Test.
* $p < 0.05$.

Table 2 Tobacco-related variables in children's playgrounds in the municipality of Braga, Portugal, according to SES.

	N	Smell of smoke *n* (%)	Smoking inside	Smoking outside	Butts inside	Butts outside	Number butts inside *Median* (P25-P75)	Number butts outside
SES								
High	32	4 (12.5)	1 (3.1)	1 (7.0)	28 (87.5)	29 (90.6)	5.00 (5.00—10.50)	20.00 (9.75—20.00)
Low	25	1 (4.0)	2 (8.0)	0	23 (92.0)	25 (100.0)	11.00 (3.50—19.50)	20.00(16.50—20.00)
p-value		0.372[a]	0.576[a]	0.123[a]	0.686[a]	0.248[a]	0.067[b]	0.177[b]

Note: SES, socioeconomic status.
[a] Fisher's Exact Test.
[b] Mann–Whitney Test.

grounds had cigarette butts inside (19/20). Although not statistically significant, this number reduced to 15/20 playgrounds in 2019, and the median number of butts inside the playground reduced from 14.00 (P25-P75: 4.00—20.00) to 5.00 (P25-P75: 1.00—9.00). None of the playgrounds presented non-smoking signs and e-cigarette users were never observed.

No statistically significant differences were found in the tobacco-related variables according to the playgroundsńeighbourhood SES (Table 2). Notwithstanding, the presence and the number of cigarette butts within the playgrounds were higher in deprived neighbourhoods.

This was the first study developed in Portugal collecting tobacco-related variables in children's playgrounds and analyzing its change over a two-year period during the enforcement of a new smoking ban law. This study showed that there is evidence of smoking in playgrounds in the municipality of Braga, which indicates that children continue to be exposed to smoking behavior and secondhand smoking in these places. Although some reduction was found in the number of butts outside the playgrounds, this study revealed a generalized non-compliance with the smoking ban, shown in the number of butts found both inside and outside the playgrounds, as well as in the total absence of signs informing about the smoking prohibition.

The low number of cases in our sample may have hindered the statistical power needed to find statistically significant results, being relevant the development of studies with larger samples and in different regions of the country.

In summary, better enforcement of the new law is required. Town Halls should take the necessary actions to promote health education in communities and protect children from the exposure to smoking behavior.

Authors' contributions

The study was designed by J. Precioso, M.J. López, X. Continente and E. Fernandez. Data was collected by C. Samorinha and V.H. Oliveira. J. Precioso and C. Samorinha designed and carried out statistical analysis and wrote the first draft of the letter. All authors gave a substantial contribution to the interpretation of data, critical discussion and revision of the manuscript, and approved its final version.

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Protection of human and animal subjects

The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data

The authors declare that the procedures followed were in accordance with the regulations established by the Commission for Clinical and Ethical Research and in accordance with the Helsinki Declaration of the World Medical Association.

Right to privacy and informed consent

No individual data was retrieved from participants.

Conflict of interest

The authors declare they have no conflicts of interest.

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Screening of inhalation technique and treatment adherence in asthma, COPD and ACO patients

Inhaled medication is essential for the treatment of chronic lung disease.[1–3] Inhaler misuse is quite common, and it reduces medication effectiveness.[4] This problem leads to poor clinical outcomes.

The aim of this study was to assess the inhalation technique of patients with asthma, chronic obstructive pulmonary disease (COPD) and asthma/COPD overlap (ACO), and to evaluate the impact of constant technique learning in every appointment.

A quasi-experimental study was conducted in the outpatient Pulmonary clinic of Faro Hospital, from September 2017 to September 2018. Patients with asthma, COPD and ACO, who were already on inhaled therapy, were included along the first six months of the study. A questionnaire was designed to evaluate patients' demographic and clinical data, pulmonary function and inhalation technique (using pre-defined checklists). These questionnaires were filled in at three stages: at baseline, one month later and after six months. When errors were detected the correct technique was explained verbally by a physician following each assessment and a visual explanation also given.

Ninety-seven patients were included: 41.2% had asthma, 41.2% COPD and 17.5% had ACO. Table 1 describes patients'

Table 1 Baseline sociodemographic and clinical characteristics of the participants.

Variable	All (n = 97)	Asthma (n = 40)	COPD (n = 40)	ACO (n = 17)	p value
Age (years)	61.2 ± 14.3	53.5 ± 16.2[#1]	69.1 ± 8.6[#1]	60.7 ± 10.0	[#1]<0.001
≥65 years old	44 (45.4%)	11 (27.5%)	27 (67.5%)	6 (35.3%)	0.001
Male	52 (53.6%)	8 (20%)	35 (87.5%)	9 (52.9%)	0.001
Body Mass Index (kg/m^2)	28.6 ± 6.8	30.9 ± 7.8[#1]	26.6 ± 5.4[#1]	27.9 ± 6.3	[#1]0.019
Level of education					
None	4 (4.1%)	1 (2.5%)	2 (5%)	1 (5.9%)	
Low (primary school)	45 (46.4%)	16 (40%)	25 (62.5%)	4 (23.5%)	0.038
Middle (high school)	41(42.3%)	18 (45%)	11 (27.5%)	12 (70.6%)	
High (bachelor or higher)	7 (7.2%)	5 (12.5%)	2 (5%)	0 (0%)	
Smoking status					
Non-smokers	22 (22.7%)	20 (50%)	0 (0%)	2 (11.8%)	
Current smokers	36 (37.1%)	7 (17.5%)	18 (45%)	11 (64.7%)	<0.001
Ex-smokers	39 (40.2%)	13 (32.5%)	22 (55%)	4 (23.5%)	
Pack years	38.7 ± 25.7	13.4 ± 9.1[#1 #2]	52.1 ± 25.8[#1]	36.6 ± 9.2 [#2]	[#1]<0.001 [#2]0.001
Lung function test					
FEV_1 % predicted	69.3 ± 25.5	89.5 ± 19.4[#1#2]	54 ± 19.7[#1]	61.7 ± 20.0[#2]	[#1#2]<0.001
FVC % predicted	98.5 ± 21.4	108.7 ± 20.9	90.1 ± 20.2	96.6 ± 16.8	
FEV_1/FVC ratio	56.4 ± 15.3	68.3 ± 10.5	47.0 ± 12.0	52.2 ± 14.1	<0.001
mMRC					
0	24 (24.7%)	16 (40%)	4 (10%)	4 (23.5%)	
1	28 (28.9%)	14 (35%)	8 (20%)	6 (35.3%)	
2	34 (35.1%)	9 (22.5%)	20 (50%)	5 (29.4%)	
3	10 (10.3%)	1 (2.5%)	7 (17.5%)	2 (11.8%)	
4	1 (1%)	0 (0%)	1 (2.5%)	0 (0%)	
mMRC ≥2	45 (46.4%)	10 (25%)	28 (70%)	7 (41.2%)	<0.001
COPD Assessment Test					
Total score			17.0 ± 7.7		
Low impact (≤10)			8 (20%)		
Medium impact (11-20)			18 (45%)		
High impact (21-30)			14 (35%)		
Very high impact (31-40)			0 (0%)		
Asthma Control Test					
Total score		19.4 ± 5.0		19.3 ± 5.1	
Poorly controlled (5-15)		10 (25%)		6 (35.3%)	
Not well-controlled (16-19)		3 (7.5%)		1 (5.9%)	
Well controlled (20-25)		27 (67.5%)		10 (58.8%)	
GOLD grade (n = 59)					
1			4 (10%)	4 (23.5%)	
2			22 (55%)	9 (52.9%)	
3			11 (27.5%)	3 (17.6%)	
4			3 (7.5%)	1 (5.9%)	
GOLD group (n = 59)					
A			5 (12.5%)	8 (47.1%)	
B			20 (50%)	4 (23.5%)	
C			1 (2.5%)	2 (11.8%)	
D			14 (35%)	3 (17.6%)	
GINA step of treatment (n = 59)					
1		1 (2.5%)		0 (0%)	
2		0 (0%)		0 (0%)	
3		12 (30%)		3 (17.6%)	
4		21 (52.5%)		11 (64.7%)	
5		6 (15%)		3 (17.6%)	
Total follow-up time (years)	4.0 ± 4.3	3.7 ± 4.7	4.5 ± 4.3	3.3 ± 3.2	ns

Table 1 (*Continued*)

Variable	All (n = 97)	Asthma (n = 40)	COPD (n = 40)	ACO (n = 17)	p value
Number of inhalers					
1	59	31	21	7	
2	30	7	13	10	
3	6	2	4	0	
4	2	0	2	0	
Patients with ≥2 different devices	38 (39.2%)	9 (22.5%)	19 (47.5%)	10 (58.8%)	0.028
Type of inhaler device					
DPI	109	38	52	19	
MDI	28	12	11	5	
SMI	8	1	4	3	
Number of moderate to severe exacerbations in the past 12 months	2.4 ± 5.5	2.0 ± 3.2	1.3 ± 2.0	3.5 ± 11.3	ns
Number of exacerbations with hospitalization in the past 12 months	0.3 ± 0.6	0.2 ± 0.4	0.4 ± 0.6	0.3 ± 1.0	ns
Number of ER visits in the past 12 months	1.0 ± 4.1	0.6 ± 1.0	0.9 ± 1.5	2.4 ± 9.4	ns
Number of antibiotic treatments in the past 12 months	0.6 ± 1.0	0.6 ± 1.1	0.7 ± 0.9	0.3 ± 0.7	ns
Number of OCS treatments in the past 12 months	0.6 ± 1.0	0.6 ± 1.2	0.5 ± 0.8	0.5 ± 1.2	ns
Number of errors	1.8 ± 2.2	1.3 ± 1.4[#1]	2.5 ± 2.7[#1]	1.7 ± 2.1	[#1]0.048

Data presented in number (%) and average ± standard deviation. [#1] Comparing asthma and COPD; [#2] Comparing asthma and ACO; COPD: chronic obstructive pulmonary disease; ACO: asthma COPD overlap; ns: non-significant; FEV_1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; mMRC: modified Medical Research Council scale; GOLD: Global Initiative for Chronic Obstructive Lung Disease; GINA: Global Iniciative for Asthma; DPI: dry powder inhalers; MDI: metered-dose inhalers; SMI: soft-mist inhalers; ER: emergency room; OCS: oral corticosteroids.

characteristics at baseline. In total, 444 observations of inhalation technique were documented: 305 dry powder inhalers (DPI), 112 metered-dose inhalers (MDI with or without spacer) and 27 soft-mist inhalers (SMI).

At baseline, 69% of the patients made at least one error related to the inhaler technique. Errors were more prevalent among: ≥65 years old patients (2.5 ± 2.8 vs 1.3 ± 1.4 errors, p = 0.021); <1 year of a total follow-up time by Pulmonology (2.9 ± 1.6 vs 1.6 ± 2.2 errors, p = 0.002); mMRC scale ≥2 (2.5 ± 2.6 vs 1.3 ± 1.6 errors, p = 0.002); ≥1 severe exacerbations in the previous year (2.8 ± 2.8 vs 1.3 ± 1.6, p = 0.001); patients with low and middle education levels (53.7% and 40.3%, respectively, p = 0.033) and in those using ≥1 inhaler device (84.6% had errors, p = 0.007). At the outset of the study 56.7% of the patients who did not have proper inhalation techniques were more symptomatic, with a mMRC scale ≥2 (p = 0.002). COPD patients had statistically more errors than the asthmatic population. Of the patients who had moderate to severe exacerbations during the year before entering the study, 90.5% misused the inhaler (p < 0.001).

Analysing per device (Table 2), the most common errors were device-independent: not exhaling before and not breath-holding after the inhalation. The most frequent device-dependent errors were activation errors in DPI and SMI, and omitting to shake the MDI device. From the first to the last evaluation there was a significant reduction in the number of errors, especially in DPI. Fig. 1 shows the number of errors made by each patient per device type, in every evaluation. In general, there was a reduction in the number of patients who had three or more errors, and an increase in those who had no errors over the three interviews.

Binary logistic regression indicates an odds ratio (OR) of 6.9 (95% CI 1.8–25.6, p = 0.004) for multiple-inhalers users and an OR of 12.9 (95% CI 2.2–75.6, p = 0.005) for those who make more errors. This implies a 6.9 and 12.9, respectively, increased risk of severe to moderate exacerbation in these patients, when controlling for gender, diagnosis, education level, treatment adherence, years of follow-up, symptoms and FEV1%.

This was a real-life study that demonstrated the issues related to inhaled treatment of the chronic obstructive lung diseases population: COPD patients, most of whom with a lower education status and a higher symptoms burden, showed a worse technique[1]; incorrect inhalation technique seems to increase with age, probably due to lung function decline and reduced hand strength and ability[1,3,5]; patients with at least one error had more exacerbations in the year before entering the study. These findings are consistent with studies previously published.[1,2,4,6,7]

Comparing the second and third evaluations, we recognize the differences between a shorter period to re-check inhalation technique (one month) against a longer one (six months). Though there was an overall improvement in both evaluations compared to the baseline, we emphasise that after a shorter period the technique and symptomatic

Table 2 Description of the evolution trough the three evaluations.

	1st evaluation (n = 97)	Difference 1st and 2nd p value	2nd evaluation (n = 90)	Difference 2nd and 3rd p value	3rd evaluation (n = 90)	Difference 1st and 3rd p value
Number of errors	1.9 ± 2.3	ns	1.8 ± 2.0	0.002	1.0 ± 1.6	<0.001
Total number of devices						
DPI	145		163		136	ns
- Number of devices	109		99		97	
- Device dependent errors	10 (0.1 ± 0.4)	ns	12 (0.1 ± 0.4)	ns	8 (0.1 ± 0.3)	
- Device independent errors	112 (1.3 ± 1.5)	0.023	77 (0.9 ± 1.1)	<0.001	42 (0.5 ± 0.8)	0.007
- Total number of errors	122 (1.4 ± 1.6)	0.018	89 (1.1 ± 1.3)	0.010	50 (0.6 ± 1.0)	<0.001
MDI						
- Number of devices	28		56		28	
- Device dependent errors	15 (0.5 ± 0.6)	ns	28 (0.5 ± 0.5)	ns	15 (0.6 ± 0.7)	ns
- Device independent errors	28 (1.0 ± 1.1)	ns	44 (0.8 ± 1.0)	ns	16 (0.6 ± 0.9)	ns
- Total number of errors	43 (1.5 ± 1.4)	ns	72 (1.3 ± 1.1)	ns	31 (1.2 ± 1.3)	ns
SMI						
- Number of devices	8		8		11	
- Device dependent errors	2 (0.3 ± 0.5)	-	0	-	2 (0.3 ± 0.7)	ns
- Device independent errors	10 (1.3 ± 0.7)	ns	8 (1.1 ± 1.1)	ns	6 (0.6 ± 1.5)	ns
- Total number of errors	12 (1.5 ± 0.8)	ns	8 (1.1 ± 1.0)	ns	8 (0.7 ± 2.1)	ns
Patients with ≥2 inhalers	38 (39.2%)		57 (63.3%)		40 (44.4%)	
Hospitalizations	0.3 ± 0.6	<0.001	0.04 ± 0.3	ns	0.08 ± 0.3	0.001
ER visits	1.0 ± 4.1	<0.001	0.3 ± 1.3	0.008	0.5 ± 1.3	ns
Severe exacerbations	1.3 ± 4.6	<0.001	0.3 ± 1.5	0.002	0.6 ± 1.5	0.009
Antibiotic treatments	0.6 ± 1.0	<0.001	0.2 ± 0.4	0.010	0.4 ± 0.7	ns
OCS treatments	0.6 ± 1.0	<0.001	0.1 ± 0.3	<0.001	0.3 ± 0.5	0.006
Asthma						
- Severe exacerbations	0.8 ± 1.4	0.012	0.1 ± 0.3	ns	0.3 ± 0.7	ns
- Hospitalizations	0.2 ± 0.4	0.034	0 ± 0	ns	0 ± 0	0.020
- ER visits	0.6 ± 1.0	0.018	0.1 ± 0.3	ns	0.3 ± 0.7	ns
- Antibiotic treatment	0.6 ± 1.1	0.030	0.2 ± 0.5	ns	0.3 ± 0.7	0.050
- OCS treatment	0.6 ± 1.2	0.003	0.1 ± 0.2	0.015	0.2 ± 0.4	ns
- FEV_1% predicted	78.8 ± 15.8		-		81.0 ± 21.0	ns
- Number of errors in general	1.3 ± 1.4	ns	2.1 ± 2.2	0.003	0.7 ± 1.1	0.050
- Errors in DPI	1.0 ± 1.0	ns	1.1 ± 1.3	0.009	0.4 ± 0.7	0.002
- Errors in MDI	1.1 ± 1.1	ns	1.0 ± 0.9	ns	1.1 ± 1.7	ns
- Errors in SMI	-		-		-	
COPD						
- Severe exacerbations	1.3 ± 2.0	0.002	0.3 ± 0.9	ns	0.6 ± 1.2	0.025
- Hospitalizations	0.4 ± 0.6	0.008	0.1 ± 0.4	ns	0.1 ± 0.4	ns
- ER visits	0.9 ± 1.5	0.002	0.2 ± 0.6	0.046	0.5 ± 1.0	ns
- Antibiotic treatment	0.7 ± 0.9	0.004	0.2 ± 0.4	0.033	0.4 ± 0.6	ns
- OCS treatment	0.5 ± 0.8	0.001	0.1 ± 0.3	0.005	0.3 ± 0.6	ns
- FEV_1% predicted	54.0 ± 19.7		-		56.5 ± 29.6	ns
- Number of errors in general	2.5 ± 2.7	0.011	1.7 ± 1.9	ns	1.2 ± 1.6	0.003
- Errors in DPI	1.9 ± 2.0	0.001	1.0 ± 1.3	ns	0.8 ± 1.3	0.001
- Errors in MDI	1.9 ± 1.4	0.016	1.1 ± 0.8	ns	1.4 ± 1.0	ns
- Errors in SMI	1.5 ± 0.6	ns	1.3 ± 0.5	ns	0.2 ± 0.4	ns
ACO						
- Severe exacerbations	1.3 ± 4.5	<0.001	0.3 ± 1.5	0.002	0.6 ± 1.5	0.009
- Hospitalizations	0.3 ± 1.0	ns	0.1 ± 0.2	ns	0.1 ± 0.5	ns
- ER visits	2.4 ± 9.4	ns	0.7 ± 2.9	ns	0.9 ± 2.5	ns
- Antibiotic treatment	0.3 ± 0.7	ns	0.1 ± 0.2	0.020	0.5 ± 0.7	ns
- OCS treatment	0.5 ± 1.2	ns	0.1 ± 0.5	ns	0.3 ± 0.6	ns
- FEV_1% predicted	51.1 ± 15.5		-		53.6 ± 16.4	ns
- Number of errors in general	1.6 ± 1.9	ns	2.0 ± 1.8	ns	1.3 ± 2.3	ns
- Errors in DPI	0.9 ± 1.1	ns	1.1 ± 1.1	ns	0.6 ± 1.1	ns
- Errors in MDI	1.8 ± 1.8	ns	1.2 ± 1.2	ns	1.0 ± 1.0	ns
- Errors in SMI	1.7 ± 1.2	ns	1.3 ± 1.5	ns	2.3 ± 4.0	ns

Data presented in number (%) and average ± standard deviation. ns: non-significant; DPI: dry powder inhalers; MDI: metered-dose inhalers; SMI: soft-mist inhalers; ER: emergency room; OCS: oral corticosteroids; FEV_1: Forced Expiratory Volume in the first second; COPD: chronic obstructive pulmonary disease; ACO: asthma COPD overlap.

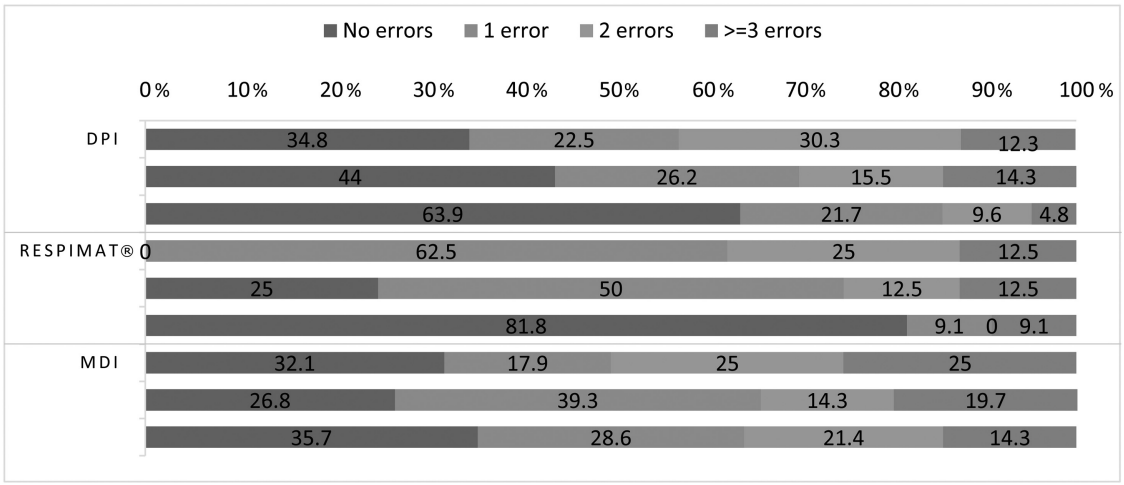

Figure 1 Description of the number of errors per patient and per device type in each evaluation.
Each column represents the number (%) of errors per device type in every evaluation, from the first to the third, respectively from the top to the bottom. DPI: dry powder inhalers; MDI: metered-dose inhalers. DPI: first evaluation n = 109, second evaluation n = 99, third evaluation n = 97; Respimat®: first evaluation n = 8, second evaluation n = 8, third evaluation n = 11; MDI: first evaluation n = 28, second evaluation n = 56, third evaluation n = 28.

improvement, with fewer exacerbations, was higher. These values increased slightly after five months. Therefore, this study reinforces the importance of providing regular educational training, especially within shorter periods of time, to enhance inhaler technique, ensure medication effectiveness, improve clinical management, and avoid unnecessary drug dose increments or drug modifications.[1,2,4,6,7] Furthermore, this decline in exacerbations will lead to an impact in health care costs.[1,5]

To the best of our knowledge, there is only one Portuguese study that analysed COPD and asthma,[5] which analysed a much smaller sample in two different periods. Our study included more variables and an additional evaluation, which strengthens our analysis. It shows that the positive effect of the educational intervention wanes over time stressing the need for periodic training reinforcement. Inhalation technique should, therefore, be reviewed at every appointment.

Authors contribution

Marta Nobre Pereira and Vanda Areias conceived the idea and design of the study. All the authors filled in questionnaires. Marta Nobre Pereira collected the data and wrote the manuscript. Vanda Areias revised it critically for important intellectual content. All the authors read and approved the final version.

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Conflicts of interest

The authors declare no conflict of interest.

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IMAGES

Show me your skin and I will tell you who you are

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M. tuberculosis infection remains a highly relevant topic worldwide and it is estimated that approximately 25% of the population is infected, with 95% of cases occurring in developing countries[1].

The manifestations of tuberculosis can be divided into pulmonary and extrapulmonary, the latter occurring in approximately 15% of cases[2]. Skin involvement in tuberculosis is rare, and represents less than 2% of extrapulmonary manifestations[3].

The main agent responsible for the skin lesions is *Mycobacterium tuberculosis*, but they can also be caused by *M. bovis* or the BCG vaccine[4]. They can manifest as inflammatory papules, verrucous plaques, chronic ulcers or suppurative nodes, as in the case presented[3]. This variety results from the mechanism of entry of *M. tuberculosis* into the skin (autoinoculation, exogenous inoculation or hematogenous route) [5], the patient's immune status, sensitization of the host to the agent [3], factors inherent to the host such as age, sex and race, and environmental factors such as climate and geographic location [4].

Skin lesions are essentially divided into *true cutaneous TB*, a direct result of infection, and *tuberculids*, indicating hypersensitivity to *M. tuberculosis* antigens[3]. Sarcoidosis, abscesses, and nontuberculous infections are common differential diagnoses[3]. The diagnosis can be challenging, culture and histological study must be performed, histopathology can show nonspecific inflammation, without the formation of granulomas[5]. The definitive diagnosis is confirmed by a positive culture for *M. tuberculosis*[3].

The authors present the case report of a 75-year-old independent man who visited his Assistant Physician due to a 6-month history, approximately, of multiple, recurrent, suppurating skin lesions in the right and left supraclavicular regions and upper thoracic regions.

On physical examination, the lesions had painless, granulomatous ulcer with a fibrinous base and the patient had another abscess next to the sternocleidomastoid muscle. He also showed signs of collateral circulation (Fig. 1).

This was immunocompetent patient with no relevant medical history and no usual chronic medication. Laboratory results showed a slight increase in inflammatory markers (PCR 5.81 mg/dl) with negative procalcitonin and serum tumor markers. Computed tomography of the neck and chest showed several abscesses, namely in the right and posterior lateral cervical region and in the right supraclavicular cavity (Fig. 2), there was no pulmonary involvement. The patient underwent a video bronchial fibroscopy that showed no endobronchial lesions; the microbiology and cytology of the aspirate and bronchoalveolar lavage were negative.

The abscess in the right supraclavicular cavity was aspirated. The cytology revealed a necrotic area with an associated inflammatory process and the culture in Loewenstein-Zensen medium was positive for *Mycobacterium tuberculosis*. The patient was sent to the Pneumology Diagnosis Center (CDP) and began treatment with the four initial antitubercular drugs (isoniazid 300 mg/day, rifampin 600 mg/day, pyrazinamide 1500 mg/day and ethambutol 1200 mg/day).

The treatment is similar to that of systemic tuberculosis, with tuberculostatic drugs[3], and biopsies or surgical debridement may sometimes be necessary[5]. With the exception of disseminated miliary cutaneous forms, skin lesions respond well to treatment and have a good prognosis [5].

IMAGES: Show me your skin and I will tell you who you are

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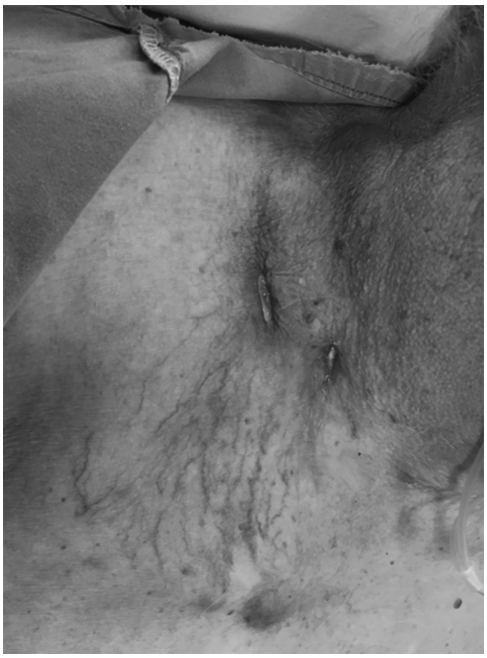

Fig. 1 Patient's skin lesions.

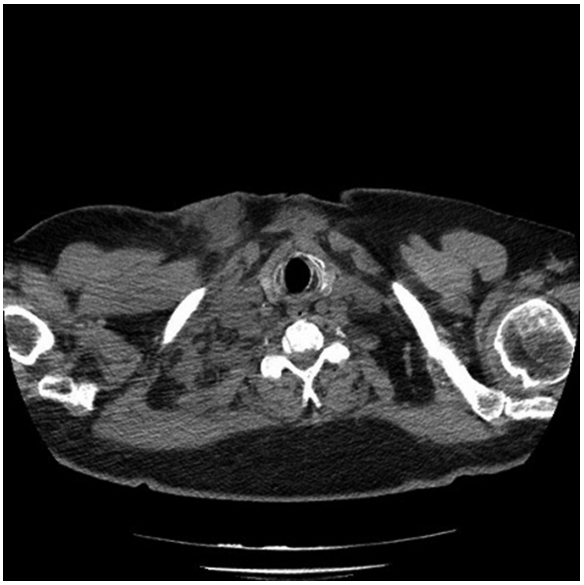

Fig. 2 Patient's CT scan.

With this case, the authors intend to show a rare form of a condition that still has a very negative impact on World Public Health, reinforcing the need to maintain strong clinical suspicion [3,5] so as not to delay the start of effective therapy.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2021.03.010.

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