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EDITORIAL

COVID-19: Once upon a time in Portugal
A brief atlas of ongoing pandemic Portuguese research

Once upon a time...

... a novel coronavirus was described in China. The new year 2020 had just arrived full of hope and promise. Portugal was preparing to defend its European Football Champion title. And China was far far away.

Suddenly, something changed. The virus had a name, as did the disease it caused. The cases were spreading fast and arrived in Europe. Now, the threat was real. Portugal was panicking with suspected cases and the scientific community was warning of a lack of preparedness.

And it arrived indeed on March 2nd.

Then what?

Epidemiologists began to develop mathematical models to predict the epidemic, describing different scenarios.[1] The predicted peak in the number of cases in Portugal could be as high as 2.5 million.[1]

As the days went by, journalists and television commentators were becoming ''experts'' in epidemiology. Recommendations from health authorities were extensively publicized in the media.

Anticipating the worst-case scenario and keeping an eye on other European countries, the state of emergency was officially declared in Portugal on March 18th. And, in the name of public health, individual freedom was suspended.

Contingency plans were adopted across the National Health Service and the rule was clear: only emergencies allowed![2]

The number of cases began to rise. And the testing capacity was struggling to meet the high demand. Investigators advised that scaling up testing could be cost-saving, since early isolation would lead to prevention of new infections and fewer hospitalizations.[3]

Scientific knowledge was evolving...

... but a lot of uncertainties remained... COVID-19 had too many faces[4] and asymptomatic carriers were an unsolved mystery.[4]

Clinical evidence kept growing, and recommendations for intensive care approach to COVID-19 patients were published.[5] Safety of health-care professionals was a major concern, especially regarding aerosol-generating procedures. Non-invasive ventilation and high-flow nasal cannula oxygen therapy were a controversial subject. A literature search found a window of opportunity for those strategies in some non-severe patients.[6]

About all the potential COVID-19 therapies, was there something missing? Potential benefits from a drug widely used in asthmatic patients – Montelukast – were proposed and are being submitted to investigation in a clinical trial.

What's coming next?

Coming to a point where the curve of new infection cases is progressively declining (Fig. 1), it is time to look forward.

The persistence of the virus in the community increases the risk of new mutations. Until now, 436 genomes were analyzed in Portugal.[7] 350 mutations were already identified, with a mean number of mutations by genome of 8. These results are compatible with the mutation rate predicted for SARS-CoV-2 – about 2 mutations/genome/month.

A lot of concerns arise, but with the arrival of spring and summer in the Northern hemisphere, encouraging data are coming in as well.

While waiting for a vaccine, it is important to talk about herd immunity. It's currently believed that herd immunity to SARS-CoV-2 infection requires 60–70% of immune individuals. However, individual variation in biological susceptibility and exposure (heterogeneity of populations) needs to be

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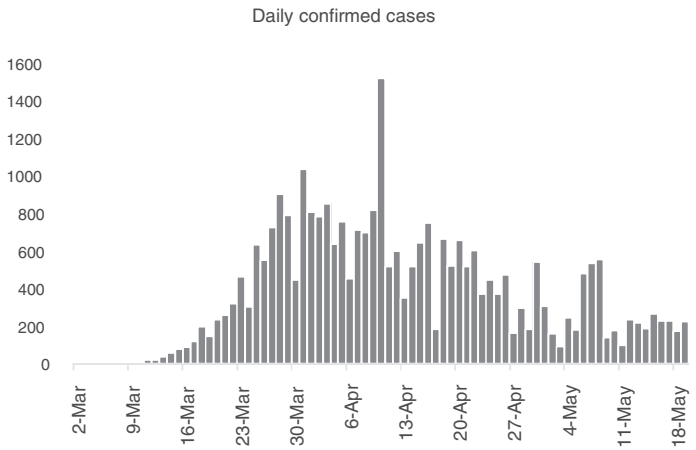

Fig. 1 Daily confirmed cases of SARS-CoV-2 infection in Portugal (from 2nd March until 19th May).

considered, as it accelerates the acquisition of immunity in populations – this can reduce the herd immunity threshold to 10–20%.[8]

COVID-19 has dominated our minds over the previous months. But what was left behind?

Many health activities were neglected and an excess mortality was described, 3–5 fold higher than can be explained by the official COVID-19 deaths.[9] And this is probably just the tip of the iceberg.

This story ends with the words of a pulmonologist: *we must learn how to evolve in the wake of these new Coronaviruses, the nCoVs, to make a sustained and responsible change in our behaviour and attitudes. New citizens, new mankind: 2020-nMan*.[10]

After it all ends, let's just hope to live happily ever after.

For this storytelling, a literature search on Portuguese publications on COVID-19 was performed. Up to May 19th, 43 articles were retrieved, 11 of them not peer-reviewed and distributed by preprint server – medRxiv. Among the studies already published, 11 were in Portuguese journals and 21 in international journals. The mean impact factor was 3.044.

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EDITORIAL

Pulmonology (is) on the air

''We are what we think. All that we are arises with our thoughts. With our thoughts we make our world''. Buddha

The coronavirus disease 2019 (COVID-19), caused by a betacoronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents a new global challenge.

As I write this Editorial, there are almost 3 million people infected with SARS-Cov-2 worldwide and more than 200,000 people have died.

This pandemic scenario, of a dimension not experienced for over a century, has globally determined extreme measures that can mitigate, as far as possible, the most serious consequences for public health.

Just one week after the first cases occurred in Portugal and when there were still no deaths registered, the Portuguese Medical Schools decided, on March 9, to suspend all classroom teaching activities, implementing distance-learning measures, which was the lever for the first universities to take the decision, on March 11, to suspend classes and other face-to-face activities.

Before that, on February 25, the Faculty of Medicine of the University of Coimbra (FMUC) had already suspended any teaching which involved direct contact with patients, due to the circulation of students from areas that in Italy were starting a cordon scenario.

In fact, in an unprecedented mobilization, involving teachers, students and administrative staff, all Portuguese Medical Schools set up, in record time, distance learning models, using the latest technology at their disposal. This also proved to be an excellent opportunity to explore new pedagogical methodologies in Medical Education in Portugal, highlighting the proactive role of the Academy and the University in a modern country.

Teaching pulmonology in this period of lock down has been quite a challenge.

How can face-to-face teaching be effectively replaced, specifically with regard to contact with the patient?

In recent years, the use of Biomedical Simulation and Virtual Clinical Cases has been progressively implemented in the teaching-learning of FMUC as a very useful tool in the development of the clinical reasoning of our students.

Using the Body Interact platform, students, through their personal computers or other portable devices, can remain active and apply their clinical reasoning skills, safely and faithfully to the clinical reality. This platform also includes integrated and automated feedback tools, which provide students with information about their individual performance in the different phases of the management of each clinical case, thus promoting the processes of self-assessment and learning regulation.

During this period of distance learning, a new series of Virtual Clinical Cases have been made available in FMUC, adding to the experience acquired in previous years, new Pulmonology cases of different levels of complexity and performance, such as Community acquired pneumonia (basic level), Asthma and COPD (intermediate level), COPD and pneumonia (advanced level).

On March 19, FMUC, with national and international collaboration, made available virtual clinical cases of patients infected with the new coronavirus, simulating patients who answer questions, who have had changes in auscultation and the other aspects of observation, allowing diagnostic tests, preventive measures against further spread, promoting appropriate isolation and reporting to health authorities and even improving and curing patients when they have the right treatment.

These virtual cases of SARS-CoV-2 infection, available at https://covid19.bodyinteract.com, are a good example of the scope and timeliness of these methodologies.

A further challenge is to develop the remote assessment process, a task that the Medical Schools have also set up in an exemplary and diversified manner in a short period of time.

It is true that the means and technology have evolved in an overwhelming way. We live in the era of artificial intelligence and robotics, but the medical act remains immutable; the voice and hand of the doctor and health professionals have a power that is irreplaceable.

It is a fact that the best a medical student can and should take out of their university experience is essentially knowing how to be with a patient.

Because the doctor–patient relationship, a candidate for humanity's intangible cultural heritage, is the most deci-

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sive timeless element of Medicine, it is expected that the teacher should impart not only what he knows but above all what he does and the student must not only grasp this knowledge but more importantly learn how to apply it.

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COMMENT

COVID-19 and asthma: To have or not to have T2 inflammation makes a difference?

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KEYWORDS
Allergy;
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SARS-CoV-2;
T2 inflammation

During this pandemic, there has been some data discrepancy about whether patients with asthma have a lower risk of becoming infected or seriously ill from coronavirus disease 2019 (COVID-19)[1] but there is no information about the real impact of SARS-CoronaVirus-2 (SARS-CoV-2) on asthma control. Recent reports from the United States of America suggest that asthma is more common in children and adults with mild to severe COVID-19 than was previously reported in Asia and in Europe, but the prevalence is no higher than that described in the same population.[2]

SARS-CoV-2 binds mainly to angiotensin converting enzyme 2 (ACE2) receptors in host cells which are abundant in the lungs, heart, blood vessels and intestine and, after more than a decade of research, there are still no specific treatments or effective vaccines for coronavirus.[3]

COVID-19 mainly presents with respiratory symptoms, from mild to severe and a significant percentage of patients develop acute respiratory disease syndrome (ARDS); these severe symptoms are associated with a true cytokine storm, in particular IL-6, and death can occur.[4]

Old age and underlying morbidities, such as cardiovascular diseases (in particular hypertension), metabolic disorders (obesity and diabetes), and respiratory system diseases were identified as significant risk factors for COVID-19 morbidity and mortality.[5]

Even though respiratory viruses are one of the most common triggers for asthma exacerbations, not all of these viruses affect patients equally. In asthma exacerbations the human rhinovirus was identified as the main individual contributor and coronavirus does not seem to frequently induce asthma exacerbations.[6] In a literature review concerning virus detection during asthma exacerbations, Zheng et al. confirmed that exacerbations were mainly associated with rhinovirus infection.[7]

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In previous SARS outbreaks, patients with asthma, in particular children, appeared to be less susceptible to the coronavirus: the rate of asthma exacerbations described is low and prognosis good.[1,8] In contrast, during influenza epidemics, asthma is involved in more severe cases, some needing mechanical ventilation, including patients of paediatric age.[9] The exact reasons for this remain unknown, but it has been confirmed during the current coronavirus pandemic with children having a better prognosis, although as likely as adults are to get infected with SARS-CoV-2.[10] Different ACE2 expression or maturation, innate immunity memory and a constitutional high lymphocyte count in children may be part of the explanation.[10]

From the recent COVID-19 literature, no information can be extrapolated about asthma phenotypes, specifically about whether asthma was allergic or not. In a recent study that included paediatric and adult patients with asthma from three different cohorts, it was found that ACE2 expression was lowest in those with high levels of allergic sensitization, but non-atopic asthma was not associated with this reduced expression.[11] Given that ACE2 serves as the receptor for SARS-CoV-2, these data suggest that this expression may be a potential contributor, among several other factors, to reduced COVID-19 severity in patients with T2 inflammation,[11] namely in patients with allergic asthma but also with other allergic diseases, such allergic rhinitis, which are more prevalent in all age groups.

Additionally, considering that the virus cell entry also depends on S protein priming by host cell proteases, including transmembrane protease serine 2 (TMPRSS2), there is some early evidence coming from the Severe Asthma Research Programme-3 (SARP), that inhaled corticosteroid therapy is also associated with reduction in ACE2 and TMPRSS2 gene expression from sputum.[12] Although gene expression for ACE2 and TMPRSS2 did not differ in healthy people and in asthmatics, the author's report that males, African Americans, and patients with diabetes mellitus have increased expression of ACE2 and TMPRSS2 in their sputum cells that can be associated with a poor prognosis when infected with the SARS-CoV-2.[12]

Dong et al.,[13] described eleven selected cases of patients with COVID-19, children and adults, demonstrating the profile complexity and different clinical presentations, from asymptomatic cases to patients with mild to severe symptoms. Patients with common allergic diseases, such as rhinitis or atopic dermatitis, did not develop distinct symptoms and severe clinical courses, suggesting a role of type 2 immune regulation in COVID-19 pathogenesis.

During this outbreak it is more likely for a person with asthma to have an exacerbation caused by other triggers, including allergens or other virus exposures. New data are emerging daily, rapidly updating our understanding of this novel coronavirus, but it is crucial that patients with asthma and other allergic diseases maintain their controller medication, from inhaled steroids to biologics,[14–16] including allergen immunotherapy.[17] Self-dose adjustments or stopping medication may lead to higher risk of asthma exacerbations, increased OCS use and higher probability of recourse to emergency room and hospitalization which themselves represent risk factors for coronavirus exposure and spread.

Asthma may worsen the disease course of COVID-19, should infection occur, namely if rescue OCS are prescribed,[18] as was suggested in previous coronavirus outbreaks when systemic steroids were associated with a higher viral load.[19,20] Clinicians must be aware and recognize the differences between hypoxic respiratory failure and bronchospasm on physical examination to carefully judge the need for a course of OCS.[14]

Compliance with ethics

This study involves a comment on the literature and did not involve any studies with human or animal subjects performed by the authors.

Authorship

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ORIGINAL ARTICLE

Hospitalization direct cost of adults with community-acquired pneumonia in Portugal from 2000 to 2009

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Pneumonia;
Hospitalization;
Health economics;
Cost analysis

Abstract
Introduction: Hospitalizations due to community-acquired pneumonia (CAP) in mainland Portugal from 2000 to 2009 accounted for 3.7% of all hospital admissions in population with 18 or more years of age. There is no direct-cost data regarding these admissions.
Methods: In this observational descriptive study all adult hospitalizations associated with CAP diagnosis were retrospectively analyzed for the period between 2000 and 2009. Patients under 18 years old, those with pneumonia as secondary diagnosis, patients with tuberculous or obstructive pneumonia, and immunocompromised patients were excluded from the study. The direct cost of hospitalization was calculated according to the diagnosis-related groups (DRG), established for the respective year of hospitalization.
Results: There were 294,026 hospital admissions with an average annual direct cost of 80 million Euros, which almost doubled between 2000 and 2009. The average direct hospitalization costs per admission, including wards and Intensive Care Units (ICU), amounted to €2,707, with an increasing trend. The average hospitalization cost was €2,515 for admissions resulting in live discharge, and €3,457 for the deceased.
Conclusion: The average direct cost of adult hospitalizations associated with CAP amounted to €2,707 in mainland Portugal from 2000 to 2009, showing an increase of 37.5% in hospitalization

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cost of living and deceased patients. The economic impact of CAP-related hospital admissions justifies the need for better implementation of preventive measures.

Introduction

Community-acquired pneumonia (CAP) is a major public health problem, and a significant cause of mortality and morbidity.[1,2] The incidence of CAP in adults varies between countries, and is estimated to reach up to 12 cases per 1000 individuals per year.[1] In mainland Portugal, the annual incidence of hospital admissions for CAP was 3.61 per 1000 adult inhabitants from 2000 to 2009, and 13.4 per 1000 inhabitants in the population over 65 years of age.[3]

Treatment of patients with CAP at any level of medical care is associated with significant direct and indirect costs, which are further pronounced at the hospital level. Hospitalization costs for CAP are estimated to represent the largest part of the annual direct costs, which are between 8.4 and 10 billion Dollars in the United States (US),[4] and 10.1 billion Euros in Europe.[5] In the US, approximately 40% of CAP episodes require hospitalization with an average 5.6 days of hospital stay, incurring a direct cost of US$18,000 per episode.[2]

Few studies are available on the economic impact of pneumonia. Some European studies show a considerable difference between the cost of patients treated in an outpatient setting and a hospital setting. In a study published in 2004 in Spain between 1993 and 1995 with 292 patients, the average direct cost of outpatient treatment per patient was €196 versus an average direct cost of €1,553 in hospitalized patients.[6] In Italy, a study with 120 patients between 1999 and 2000, the average cost of medical care per patient, including a follow-up period of 6 months, amounted to €1,586.[7] These two studies did not include patients admitted to the ICU. In Germany, a multicenter study performed in the first semester of 2003 with 580 patients and 13.8% of patient admitted to ICU, the average direct cost of hospitalization was US$1,333 with a maximum value of US$9,488 and the major determinants of cost were length of hospital stay and ICU admission.[8]

In Portugal, there are no studies on the economic impact of hospital admissions of adults with CAP. The existence of a centralized database in the Portuguese Health System Central Administration (Administração Central do Sistema de Saúde – ACSS) containing clinical and administrative information on hospital admissions within the Portuguese National Health Service (Serviço Nacional de Saúde – SNS) allow a better characterization of the economic impact of CAP, and in particular, the direct cost of hospital admissions.

The aim of this study was to characterize the direct cost of hospital admissions for CAP in mainland Portugal, including the average direct cost per day, per hospitalization, and by outcome (living or deceased). Based on the average cost per day, an estimate was made on the time required to reach 1 million Euros of expenditure.

Materials and methods

The ACSS, an entity under the Portuguese Ministry of Health, contains the administrative and clinical data of all hospital admissions within the Portuguese National Health Service, which covers almost the entire population resident in mainland Portugal, i.e., approximately 10 million inhabitants. Clinical information, including diagnoses and procedures, is coded by a medical team specifically trained in coding using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).[9]

In this observational descriptive study, a retrospective analysis of the ACSS data was carried out, covering a period of 10 years between 2000 and 2009. Inclusion criteria were hospital admissions of adults with a main diagnosis of pneumonia (ICD-9-CM 480-486 and 487.0). Those excluded were patients under 18 years old, hospitalizations with pneumonia as secondary diagnosis, tuberculous pneumonia and obstructive pneumonia (e.g., associated with pulmonary neoplasia), patients with HIV infection (ICD-9: 042-044 and/or DRG 488, 489 or 490), patients immunocompromised due to antineoplastic or immunosuppressive therapy (E933.1), and transplant patients (V42). Data from ward and ICU admissions were treated jointly since the database did not allow for separate analysis. Patient data was kept anonymous throughout the study.

According to the official Portuguese ordinance regarding diagnosis-related groups (DRG), the direct cost of hospitalization was calculated in accordance with the amount established for the respective year of hospitalization.[10] The total direct cost of hospital admissions between 2000 and 2009 was analyzed to calculate the average cost by year, by day and according the discharge outcome (living or deceased) using a Microsoft Excel® spreadsheet (Microsoft Corp., Redmond, WA, USA).

Results

In mainland Portugal, 7,849,266 hospital admissions were recorded between 2000 and 2009 among individuals aged 18 years or more. Of these, 294,027 (3.7%) were diagnosed as CAP according to the inclusion criteria of the study. 164,655 (56%) patients admitted were male and 129,372 (44%) were female. The median age was 77 years, corresponding to a mean (SD) of 73.1 (16.0) years, with a steady increase (5%) of the mean age over the 10 years (Table 1). The annual average incidence of hospitalization was 3.61 per 1000 adult population, and an increase in incidence from 1.02 to 13.40 per 1000 inhabitants was observed in the age range of <65 and ≥65 years. Overall, there was an increase of 64.7% in the number of hospital admissions.

Table 1 Direct costs of hospitalization for CAP between 2000 and 2009 in mainland Portugal, by hospital admission, daily and annual expenses (source ACSS).

Year	No. of hospitalizations	Average age	Average duration of hospital stay (days)	Average ventilated patients (%)	Expenses (€)		
					Average cost/ hospitalization	Average cost/day	Annual expenditure
2000	23,679	70.1	10.8	3.1	2,460	159,581	58,247,386
2001	22,442	71.3	11.1	3.5	2,603	160,096	58,435,329
2002	26,092	71.6	11.0	3.8	2,657	189,959	69,335,196
2003	27,978	72.1	10.8	3.7	2,937	225,164	82,185,015
2004	26,582	73.3	11.4	3.4	2,948	214,745	78,382,055
2005	31,302	73.8	11.2	3.4	2,869	246,073	89,816,706
2006	29,131	73.8	11.6	3.4	2,665	211,951	77,362,123
2007	33,726	74.2	11.5	3.4	2,637	243,695	88,948,820
2008	34,083	75.0	11.6	3.2	2,659	248,372	90,655,981
2009	39,011	73.6	11.5	3.1	2,628	280,864	102,515,526
Total	294,026	73.1	11.3	3.4	2,707	218,050	795,884,142

The average duration of hospital stay was 11.3 days, and the percentage of mechanically ventilated patients was 3.4%. These figures remained constant throughout the period analyzed (Table 1).

Global direct cost amounted to approximately €800 million, corresponding to an annual average of €80 million, and a daily average of €218,050 (Table 1). Each hospitalization had an average direct cost of €2,707. Over the 10 years analyzed, the average cost of hospitalization increased by 6.8%, from €2,460 in 2000 to €2,628 in 2009. The annual expenditure almost doubled due to the increase in the number of hospitalizations, from €58,247,386 to €102,515,526 respectively, which corresponds to an increase of 76.0%.

The intra-hospital mortality rate was 20.4% (59,925 patients) with deaths in all age groups. Analyzed by discharge outcome, the average hospitalization cost resulting in live discharge was €2,515, and for the deceased it amounted to €3,457, marking a difference of 37.5%.

Considering the inpatient treatment of CAP and using an estimated average daily cost of 218,050 Euros, it took only 4.6 days to reach 1 million Euros of expenditure.

Discussion

A total of 294,027 hospital admissions for CAP were assessed, which corresponded to 3.7% of total hospitalizations. The total direct cost of hospitalization for CAP amounted to approximately 800 million Euros, corresponding to an annual average of 80 million Euros, a daily average of €218,050, and an average direct cost of €2,707 per hospitalization, regardless of the inpatient setting (ward or ICU).

Over the studied period, there was an increase of 64.7% in the number of hospital admissions, and of 5.0% in the mean age of hospitalized patients. Meanwhile, no significant increase was observed in the duration of hospital stay and the percentage of patients that underwent invasive mechanical ventilation, which could be an indirect indicator of severity. This increase in the number of hospitalizations may explain the 76.0% raise in direct annual cost over the same period from €58,247,386 in 2000 to €102,515,526 in 2009. Given that the rate of hospital admissions for CAP in patients aged ≥65 is five times higher than that of patients <65 years of age, this rising trend in costs over the years is considered to be equally correlated with age. However, other factors must be taken into account, namely the different annual distribution of admissions GDH's and the increase cost of GDH's over the time period analyzed.

In the data analyzed, the average daily cost of hospitalization with live discharge was €2,515, and the cost for the deceased was €3,457, showing an increase of 37.5%. In the literature review, we did not find any data on direct cost according to the outcome of hospitalization, which precludes a comparison with our figures. It is assumed that the cost for deceased patients is higher due to a greater consumption of resources, and most likely, the need for admission to the ICU. The period analyzed (2000–2009), the number of patient (294,026), the inclusion of ICU patients, and the different methodology in our study may have contributed to an average direct cost higher than the reported amounts of €1,553 in Spain,[6] €1,586 in Italy[7] and US$1,333 in Germany.[8]

The data examined allows us to quantify the direct costs of hospitalization for CAP in mainland Portugal (10 million inhabitants), which add up to one million Euros every 4 days and 14 h (4.6 days).

It should be noted this study covers a period during which adult conjugated pneumococcal vaccine was not yet available and the national influenza vaccination coverage rate ranged from 14.2 to 17.5%.[11] The present study showed preventive measures are another factor to take into account. These should include intervention in lifestyle risk factors as well as influenza and pneumococcal vaccination.[12]

This study has several limitations. This is a descriptive retrospective administrative data-based study with coded clinical information that only allows direct hospitalization costs to be determined. As such, it is not possible to assess the severity of the pneumonia cases, nor to identify the inpatient setting, that is, admission to a ward or the ICU. The good hospital coverage in Portugal, ease of access, and fear of dying at home may justify the inclusion of patients with

end-of-life pneumonia. This population will understandably increase average length of stay as well as cost, particularity in the older age groups. Similarly, some cases of nosocomial pneumonia have been included. Despite these limitations, the methodology used is valid, and has been applied in multiple studies carried out in various countries.[3,13–16]

In conclusion, the high economic impact of hospital admissions for CAP, coupled with an aging population and an increase in co-morbidities, decisively highlights the importance of better implementation of preventive measures.

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Conflicts of interest

All the authors have nothing to disclose.

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REVIEW

Construct validity and reliability of the Brazilian version of the Falls Efficacy Scale in patients with COPD

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Abstract
Introduction and objective: The Brazilian version of Falls Efficacy Scale (FES-BR) used to assess the fear of falling, has not yet been validated in patients with Chronic Obstructive Pulmonary Disease (COPD). The aim of the present study was to investigate the construct validity and reliability of the (FES-BR) in patients with COPD.
Methods: A cross-sectional study involving subjects with COPD, aged between 48 and 83 years. Data were collected by two independent and blind assessors. Construct validity was assessed using the Spearman's rank correlation coefficient between FES-BR and Berg Balance Scale, Downton fall risk index, Timed Up and Go Test (TUG), hand-grip strength (HGS), Five Times Sit to Stand Test (FTSST) and 6-Minute Walk Test (6MWT). Reliability was measured by the Cronbach's alpha coefficient, Intraclass Correlation Coefficient (ICC), and Bland-Altman plot.
Results: The study included 60 subjects aged 68.3 ± 9.9 years and FEV1 56.0 ± 19.3. The correlations were significantly strong between FES-BR and the Berg Balance Scale ($r = -0.66$), TUG ($r = 0.64$), HGS ($r = 0.61$) and FTSST ($r = 0.62$); and moderate between FES-BR and the Downton fall risk index ($r = 0.38$) and the 6MWT ($r = -0.48$). All correlations had $p < 0.001$. Intra-rater [ICC = 0.94, (95% CI = 0.91–0.96)] and inter-rater [0.97, (95% CI = 0.97–0.98)] reliability were considered excellent.
Conclusions: The Brazilian version of FES was valid and reliable in assess fear of falling in subjects with COPD.

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Introduction

Falls are a real risk of multifactorial origin and have been presented as one of the main causes of changes in lifestyle and performance of activities of daily living. According to the World Health Organization 2007,[1] approximately 30% of the elderly fall at least once a year. This is also happens to patients with Chronic Obstructive Pulmonary Disease (COPD), recent studies report incidence of between 25% and 46% of falls within this group.[2,3,4]

Fear of falling, currently defined as low self-efficacy to prevent falls, has been considered not only a consequence but also a determinant of falls,[5] since loss of confidence in performing activities of daily living leads to less independence and, consequently, a sedentary lifestyle. This sedentary behavior entails altered balance, reduction of social interaction and depression, which end up generating more fear.[6]

In this context, the use of instruments that assess fear of falling is relevant, as it may guide prevention and treatment strategies.[7] Several instruments are used to assess the risk of falls in COPD[8,9,10]; however, as far as the authors know, only two scales assess fear of falling. The simplest one to apply in clinical practice is Falls Efficacy Scale International (FES-I).[11,12] Its translated and adapted version for the Brazilian Portuguese language presents excellent psychometric properties to assess fear of falling in the elderly, but its validity and reliability in patients with COPD has not yet been verified.

Therefore, the objective of this study was to verify the construct validity and reliability of the Brazilian version of the Falls Efficacy Scale (FES-BR) in subjects with COPD.

Methods

This was a cross-sectional observational study, carried out from May to August 2018, involving patients in follow-up in the Pulmonary Function Service at the Hospital de Clinicas, Federal University of Paraná (HC/UFPR), in Curitiba, state of Paraná. After approval by the Institutional Ethics Committee (CAAE: 48393915.5.3001.010, Opinion No 1.552.888/2016), patients who met the inclusion criteria were selected to receive telephone contact during which they were invited to participate in the study and to schedule the assessments. They were all informed about the nature and objectives of the study and signed their informed consent.

The study included subjects of both genders, who had COPD diagnosed according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[13] and were clinically stable (no exacerbation of the disease in the previous month), regardless of the staging of the disease. Subjects who had neuromuscular and/or neurodegenerative diseases; arthrodesis and/or prostheses in the lower limbs; severe cardiac arrhythmias or any dysfunction that could hinder their performance in the proposed tests; and subjects who presented any cognitive impairment according to the score by the Mini-Mental State Examination (MMSE)[14] were excluded from the test.

Pulmonary function was assessed using a spirometer (Spirobank G, MIR, Italy), following the guidelines of the American Thoracic Society/European Respiratory Society,[15] using reference values for the Brazilian population.[16] Dyspnea was assessed by the Medical Research Council scale.[17]

Falls Efficacy Scale, used to assess fear of falling, raises questions about how concerned subjects are about the possibility of falling when performing 16 activities, with scores ranging from 1–4. The total score ranges from 16 (not concerned) to 64 points (extremely concerned), with the score of $\geq$23 representing high fear of falling.[18] Falls Efficacy Scale has already been translated and validated for the Brazilian Portuguese language (FES - BR).[11]

The validity of the FES-I BR construct was tested to determine its relation with others scales that evaluate the balance (Berg Balance Scale)[19] and risk of falling (Downton fall risk index),[20] as well as the functional tests. These instruments were used because of the absence of another Portuguese-translated specific instrument for the evaluation of fear of falling, and since functional incapacity is know to be associated with falls.

Balance was assessed by the Berg Balance Scale,[19] with scores varying from 0 to 56. High scores indicate better balance. The perception of risk of falls was assessed by the Downton fall risk index,[20] which addresses issues such as: known previous falls (yes or no), medications (tranquilizers/sedatives, diuretics, antihypertensives, antiparkinsonian drugs and antidepressants, other medications), sensory deficits (none, visual impairment, hearing impairment, limb impairment), mental state (oriented, cognitively impaired) and gait (normal: safe without walking aids; safe with walking aids; unsafe: with or without walking aids; and unable). Scores of 3 or more indicate a high risk of falls.

The functional tests followed a standard order, with the application of a familiarization test for each one and a rest period of 5 min after each of them. The following functional tests were performed: (1) Timed Up and Go (TUG),[21] in which the participant is instructed to stand up from a sitting position, walk 3 m at his normal walking speed and return to the sitting position; (2) Hand-grip strength[22] (HGS) assessed using an hydraulic dynamometer (JAMAR Hydraulic Hand Dynamometer - Model PC-5030J1, Fred Sammons, I, 23nc., Burr Ridge, IL: USA), following the protocol recommended by the American Association of Hand Therapists, in which the individual should be seated in a chair, with shoulders in a neutral position, with one hand resting on the thigh while the elbow of the assessed limb is kept in 90° of flexion, and the forearm is in neutral position. The dynamometer footprint was individually adjusted for all subjects according to the size of their hands so that the rod closest to the dynamometer body was positioned in the middle phalanges of the index, middle and annular fingers. The test was performed in three attempts for each side, in rotation, starting with the hand the individual considered stronger. The recovery period between measurements was of approximately 30 s. Only the best mark of the three attempts for each hand was used; (3) the Five Times Sit to Stand Test[23] that evaluates the lower limbs strength and has a strong correlation with risk of falls, performed in a chair with a 46 cm height and without support for the arms, in which the participants were instructed to remain with their arms crossed over their chest with hands on opposite shoulder. Then, after the initial command, they should sit and stand up 5 times

as fast as they were able to. The time was recorded in seconds by means of a digital timer (WTO38 DLK SPORTS); and (4) 6-minute walk test (6MWT),[24] which evaluates exercise capacity through the longest of two walks performed during 6 min in a 30-m corridor.

The reproducibility process of FES-BR followed methodological criteria established in the literature[25,26] being performed by two independent assessors (assessor 1 and assessor 2), who had received prior and standardized training. They performed the assessments blindly and independently. In an attempt to avoid bias, the score sheets were separated and the assessors did not communicate with each other. In the first assessment, assessor 1 collected data about the characterization of the sample, assessed pulmonary function, and applied the functional tests and scales. After 30 min, assessor 2 reapplied FES-I BR.[11] During the application of the scale, the assessor would read the questions and mark the answer indicated by the subject. After 7 days, having preserved the same place and time, FES-I BR was applied again by assessor 1. In addition, the duration of the application was recorded in the two interviews.

Statistical analysis

The sample size followed the methodology proposed by Terwee[25] that recommends a sample of at least 50 subjects to assess the validity and reliability of an instrument. For data analysis, the Statistical Package for the Social Sciences (SPSS) software (version 22) was used. The normality and homogeneity of the data were evaluated by the Shapiro–Wilk test and the results are presented in mean and standard deviation or frequency, depending on the type of variable and on the data distribution. The test-retest reproducibility was evaluated by the intraclass correlation coefficient (ICC) and its 95% confidence interval. ICC values between 0.61 and 0.80 and 0.81 and 1.00, respectively, were considered to indicate good and high reliability. The internal consistency of the scale was also verified by Cronbach's alpha coefficient, which evaluates the magnitude by which the items of an instrument are correlated, where values of $\alpha > 0.70$ indicate high consistency. The correlation between the test and the retest was also evaluated using the graphical representation of Bland-Altman plot (Medcalc Statistics Software, version 18), in which it was expected that all values of the intra and inter-rater differences would be arranged in parallel around the horizontal axis of zero and within the limits of correlation. The Spearman test was used to examine the degree of association between FES-BR and dyspnea, perceived risk of falls, and all of the above functional tests. The magnitude scale proposed by Hopkins[27] was used to interpret the correlation coefficients: <0.1, trivial; between 0.1–0.29, small; 0.30–0.49, moderate; 0.50–0.69, high; 0.70–0.90, very high; >0.90, almost perfect. Differences between groups were investigated by Mann–Whitney and Qui-Square test. The multiple linear regression analisys was performed to determine whether the independent variables with values of $p < 0.05$ in Table 3, gender, dyspnea, TUG, HGS, FTSST, 6MWT, Berg's Balance Scale and Downton fall risk index could explain the variability in fear of falling. A stepwise insertion regression approach was used to construct the multivariate models. The established level of significance was $p \leq 0.05$.

Table 1 Sample characterization.

Characteristics	n = 60
Age (years)	68.3 ± 9.9
Gender n (%)	
Female	30 (50)
Male	30 (50)
BMI (kg/m^2)	26.8 ± 5.7
Cognitive status (MMSE)	26.3 ± 4.2
FEV1 (% of predicted)	56.0 ± 19.3
FEV1/FVC	52.0 ± 15.5
GOLD (I/II/III/IV)	9/28/18/5
Dyspnea (MRC)	2.4 ± 1.6
Smokers n (%)	34 (57)
Ex-smokers n (%)	26 (43)
Medications n (%)	
Bronchodilator	60 (100)
Corticosteroids	11/(18.33)

Values are expressed as mean ± SD, absolute (n) and relative (%); BMI: Body Mass Index; MMSE: Mini-Mental State Examination; FEV1: Forced Expiratory Volume in the 1 st second; FVC: Forced Vital Capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; MRC: Medical Research Council.

Table 2 Spearman's correlations between FES-BR and physical-functional capacity, balance and risk of falls.

Variables	FES	
	r	p
Functional mobility (TUG)	0.64	<0.01
Muscle strength (HGS)	−0.61	<0.01
Power/strength of the LL (FTSST)	0.62	<0.01
Exercise capacity (6MWT)	−0.48	<0.01
Dynamic balance (BERG)	−0.66	<0.01
Risk of falls (Downton fall risk index)	0.38	<0.01

TUG: Timed up and go test; HGS: Hand-Grip Strength; LL: lower limbs; FTSST: Five Times Sit to Stand Test; 6MWT: 6-minute walk test.

Results

60 patients were included in this study. Most of them were diagnosed with moderate obstruction.[13] Demographic, anthropometric and clinical data are presented in Table 1.

Construct validity

A high association was observed between the Falls Efficacy Scale (FES-BR) and the tests that evaluated physical-functional capacity such as Timed Up and Go (TUG), Hand-grip strength (HGS), Five Times Sit to Stand Test (FTSST), and balance (Berg's Balance Scale). Moreover, moderate association was found between the FES-BR and the Downton Scale, and the 6-minute walk test (6MWT) (Table 2).

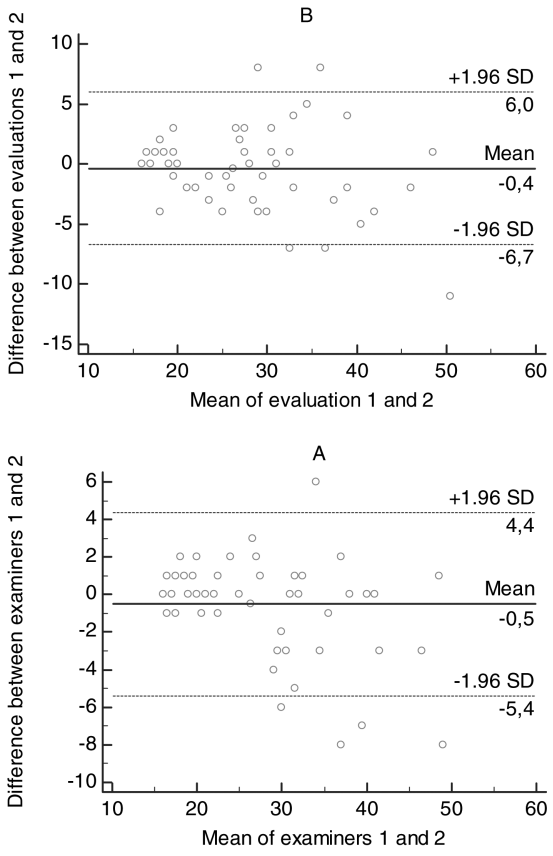

Fig. 1 Bland & Altman's graphical comparisons results in the intra [1A] inter-rater [1B].

FES-BR reliability

There was no difference between the evaluators 1 and 2 regarding the time of application of the scale (17.67 vs 17 min., $p = 0.09$). The intra-rater ICC was 0.94, (95% CI = 0.91–0.96), $p < 0.01$ and the ICC inter-rater 0.97, (95% CI = 0.97–0.98), $p < 0.01$, representing high intra and inter-rater reliability. In addition, the high value of Cronbach's alpha coefficient for the two raters (α de Cronbach = 0,90) supports these results.

Intra and inter-rater agreement is illustrated by the graphical representations of Bland-Altman plot (Fig. 1), where the existence of low bias intra [−0.4 (limit of correlation between 5.9 and −6.6)] and inter-rater [−0.5 (limit of correlation between 4.3 and −5.4] appear.

Thirty-two patients (53%) presented fear of falling (FES-BR score $\geq$23), consequently, it was possible to divide the sample into two groups: with (n = 32) and without (n = 28) fear of falling. When compared, the groups presented significant differences regarding gender, dyspnea, TUG, HGS, FTSST, 6MWT, balance (Berg's Balance Scale), fall risk index (Downton) and fear of falling (FES-BR) (Table 3).

In addition, multiple linear regression with the stepwise insertion method analisys showed that the independent variables TUG, HGS, FTSST together explained approximately 55% ($r^2 = p < 0.01$) the variability of FOF in the study population: TUG (ß = 0.465; t = 4.634; $p < 0.01$), HGS (ß = −0.303; t = −2.999; $p < 0.01$) and FTSST (ß = 0.210; t = 2.283; $p = 0.026$).

Discussion

In order to properly use an instrument, it is necessary to evaluate its psychometric properties. This evaluation is done, therefore, by analyzing the validity and reliability of the test. This study demonstrated that the Brazilian version of Falls Efficacy Scale (FES-BR) presented high construct validity and excellent reliability in patients with chronic obstructive pulmonary disease (COPD). In addition, patients classified with fear of falling have worse clinical, physical-functional, and balance profiles, besides the greater risk of falls, whereas lower functional mobility, poor peripheral muscle strength and power and strength of the lower limbs reliably predicted fear of falling.

The construct validity of the FES-BR was demonstrated by its high association with the physical-functional capacity and dynamic balance, and moderate relation with the perceived risk of falls and the exercise capacity, suggesting that the scale score also reflects the limitations presented by patients with COPD. Patients with COPD with lower physical capacity and poor dynamic balance have a considerable increase in fear of falling. Such functional tests were used because they are reliable, valid and responsive[28,29,30] in COPD. Besides, these procedures are commonly performed in most health services because they reflect the patients' physical-functional limitation. Similarly, Berg's and Downton scales were used because they involved constructs related with the individual's exposure to different situations which generate postural imbalance and fear of falling.

The relation between increased fear of falling and impairment of physical-functional capacity also been demonstrated in other studies. In Greek,[31] Turkish,[32] Persian,[33] Hungarian[34] and Arabic[35] version, FES was compared with the TUG in community-dwelling older persons and showed a high corrrelation ($0.64 < r < 0.74$, $p < 0.01$ for all). Similarly in the Portuguese version,[36] FES was highly correlated with TUG ($r = 0.50$; $p < 0.01$) and FTSST ($r = 0.54$; $p < 0.01$).

The high reliability of the FES-BR presented in this study was demonstrated by the excellent internal consistency as demonstrated by the Cronbach's alpha coefficient, which measures the existence of a correlation between the responses given by the subjects, close to 1.00, as well as by the high value of ICC intra and inter-raters, demonstrating that the scores on the scale were similar between the assessments. In addition, the high correlation demonstrated by the graphical representation of Bland-Altman plot in the test-re-test, whose variability of intra and inter-rater differences were within the 95% of concordance limits, validated the aforementioned results. Moreover, recent studies have corroborated our results.[31–33]

Therefore, our results confirm that fear of falling is a common feature among patients with COPD, affecting 53% of the subjects in this study. Patients with fear of falling presented lower functional mobility, peripheral muscle strength, power and strength of the lower limbs, greater risk of falls, walked a shorter distance in 6 min and had worse balance when compared to those without fear of falling.

Table 3 Comparison between groups classified according to fear of falling (FES-I Brazil $\geq$ 23 points).

Variables	Groups		p
	No fear of falling (n = 28)	Fear of falling (n = 32)	
Age (years)	67.6 ± 8.4	68.9 ± 11.2	0.60
Gender F/M (n)	9/19	21/11	0.02
BMI	24.6 ± 6.3	23.4 ± 10.6	0.62
FEV_1 (% of predicted)	58.9 ± 19.5	53.6 ± 19.1	0.29
FEV_1/FVC	52,2 ± 14.8	51.8 ± 16.3	0.90
GOLD I/II/III/IV (n)	4/14/6/4	5/14/12/1	0.30
Dyspnea (MRC)	1.5 ± 1.4	2.7 ± 1.3	<0.01
TUG (s)	10.5 ± 1,7	17 ± 9.3	<0.01
HGS (Kgf)	25.8 ± 8.4	16.4 ± 5.7	<0.01
FTSST (s)	13.8 ± 2.5	21.9 ± 10.7	<0.01
6MWT (m)	380 ± 98	297 ± 114	<0.01
BERG Balance Scale	53.4 ± 1.6	48 ± 9.5	<0.01
Downton fall risk index	1.86 ± 1.1	2.9 ± 1.5	<0.01
Fear of falling (FES-BR)	18.4 ± 1.9	32.6 ± 6.6	<0.01

Values are expressed as mean ± SD; Mann-Whitney and Qui-Square for differences between groups; F: female; M: male; BMI: Body Mass Index; FEV_1: forced expiratory Volume in the 1st second; FVC: Forced Vital Capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; MRC: Medical Research Council; TUG: Timed Up and Go test; HGS: Hand-Grip Strength; FTSST: Five Times Sit to Stand Test; 6MWT: 6-minute walk test; FES-BR: Falls Efficacy Scale Brazil.

Moreover, they are mostly female and clinically presented greater dyspnea during Activities of Daily Living (ADL). This relationship was already expected, since the fear of falling restricts the patient in their ADL, and, consequently, worsens their functional performance and their symptoms. This is the first study to demonstrate differences in these functional variables between COPD' patients with and without fear of falling. This result can be explained by the fact that COPD is considered a systemic disease that leads to musculoskeletal disorders[13] increasing the proportion of people with a higher fear of falling.

In addition, the regression analisys showed that lower functional mobility, poor peripheral muscle strength and power and strength of the lower limbs together explain more than half of the fear of falling variability. The influence of reduced physical function on the fear of falling is clinically relevant, as there is evidence that fear of falling is an independent predictor of future falls in older adults.[37] The results of this study strengthens the inclusion of the fear of falling assessment in a pulmonary rehabilitation program. Similar associations have also been demonstrated in other studies where increased fear of falling was particularly related to lower quadriceps muscle strength and impaired balance.[5,38]

Finally, some limitations of the study should be considered: (1) it was not possible to evaluate the FES-BR responsiveness, because even with psychometric evidence of reliability and validity, an instrument must be responsive. That is, it should detect change after an intervention; (2) the reduced sample size, since it is a unicentric study; (3) the average FEV1 of the sample was 56% predicted, indicating a sample with predominantly moderate disease, and (4) the identification of clear causal relationship between fear of falling and the physical function capacity was limited by the cross-sectional study design.

The results presented in this study indicate the need to introduce the assessment of fear of falling in the treatment of the patient with COPD. This addition can make the patient aware of the risk factors which cause falls and, consequently, provide effective measures to prevent them. Following this principle, the authors emphasize that, at the end of each evaluation, the patients that were subjects to this study received an educational booklet with guidelines related to the risk of falls and how to prevent them.

In summary, the conclusion is that the Brazilian version of FES can be used in patients with COPD as an important tool to assess the fear of falling.

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Conflict of interest

No conflicts of interest.

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ORIGINAL ARTICLE

Can PET-CT predict diagnostic success in ultrasonography-guided transthoracic fine needle aspiration biopsies in lung cancers?

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KEYWORDS
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Abstract
Objective: To examine any correlations between tumor maximum standard uptake values (SUVmax) in positron emission tomography-computed tomography (PET-CT) and homogeneous/heterogeneous tumor FDG uptake in PET-CT, and the diagnostic success of the procedure in thoracic ultrasonography (US)-guided transthoracic fine needle aspiration biopsy (TFNAB).
Methods: The files of patients who underwent thoracic US-guided TFNAB between 2013 and 2018 were examined. Patients who underwent thoracic US-guided TFNAB and were diagnosed as having primary lung cancer were considered as the US-TFNAB diagnostic group. Patients whose disease was diagnosed as primary lung cancer using a different diagnostic method (e.g. CT-guided biopsies, fiberoptic bronchoscopy) due to a lack of diagnosis despite undergoing thoracic US-guided TFNAB were allocated to the US-TFNAB non-diagnostic group. The clinical and radiologic characteristics and PET-CT parameters of the two groups were compared.
Results: A total of 104 patients were included in the study; 79 (76%) patients whose disease was diagnosed using US-guided TFNAB, and 25 (24%) patients whose primary lung cancer could not be diagnosed with US-guided TFNAB. The mean SUVmax value of the US-TFNAB diagnostic group was 19.5 ± 10.1, whereas it was 15.1 ± 8.9 in the US-TFNAB non-diagnostic group ($p = 0.016$). Whether a lesion showed homogeneous or heterogeneous FDG uptake did not effect diagnostic success ($p = 0.289$). SUVmax value was the only effective independent factor in the diagnostic success of the procedure ($p = 0.035$).
Conclusions: High SUVmax values in PET-CT in lung cancers may increase the diagnostic success of US guided-TFNAB procedures.

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Introduction

Thoracic ultrasonography (US)-guided transthoracic fine needle aspiration biopsy (TFNAB) performed on peripheral lung tumors is a diagnostic method with proven reliability and effectiveness, and has been used for a long time. Much work has been done on factors affecting the diagnostic success of US-guided TFNAB. These studies investigated the effects of factors on diagnostic success, including the size of the lesion, its internal structure, its location in thorax, the selected biopsy method such as FNAB or Tru-cut, the type of needle used, the use of color Doppler during the procedure, the type of US probe preferred for the procedure, and rapid on-site evaluation (ROSE).[1–6]

Studies have shown that US-guided TFNAB and computed tomography (CT)-guided TFNAB have similar diagnostic success in peripheral tumors of the lung. However, US-guided TFNAB has advantages over CT-guided procedures because it can be performed at the patient's bedside, it is a real-time procedure, and it does not require exposure to radiation.[7]

Positron emission tomography (PET) is a metabolic imaging technique in which isotopes emitting positrons are used. Metabolism is rapid due to the rapid cell proliferation and increased protein synthesis in malignant tumor cells. Therefore, glucose metabolism is also increased. The uptake of 18-fluoro-labeled FDG (18F-FDG), a glucose analogue, is proportional to glucose use in malignant tissues, and FDG is taken up into the cell like glucose, but not metabolized. In these tumor cells, metabolic imaging can be performed using FDG, which is held in the cell without being metabolized.[8,9] FDG uptake intensity is positively correlated with proliferative activity, cell differentiation, and the aggressiveness of tumor, and negatively correlated with prognosis.[10] It is also known that necrotic areas in tumor exhibit less FDG uptake, and are regarded as false-negative areas in PET-CT images.[11,12]

Studies have demonstrated that in biopsies of mediastinal lymph nodes in lung cancers, high standard uptake values (SUVmax) correlated with diagnostic success of biopsy procedures, and that in the case of high SUVmax values, diagnostic success increased.[13,14] When the literature was examined, no study investigating the relationship between PET-CT parameters and thoracic US-guided TFNABs performed in peripheral tumors of the lung was found. In the current study, correlations between tumor SUVmax values in PET-CT and homogeneous/heterogeneous tumor (presence of necrotic component) FDG uptake in PET-CT were investigated, and the diagnostic success of the procedure was assessed in peripheral lung tumors on which we performed thoracic US guided-TFNAB.

Material and method

Patient population and demographic findings

We used a retrospective and cross-sectional study design. We retrospectively reviewed hospital records of patients who had peripheral lesion localization in the lung parenchyma as detected using thoracic US due to its contact with visceral pleura, and had undergone thoracic US-guided TFNAB in the US unit of our Chest Diseases Clinic between January 2013 and May 2018.

Patients who underwent thoracic US-guided TFNAB and were diagnosed as having primary lung cancer were considered as the US-TFNAB diagnostic group. Patients whose disease was diagnosed as primary lung cancer using a different diagnostic method (e.g. CT-guided biopsies, fiberoptic bronchoscopy) due to a lack of diagnosis despite undergoing thoracic US-guided TFNAB were allocated to the US-TFNAB non-diagnostic group (Table 1). The demographic findings of the patients such as age, sex, and smoking history were recorded (Table 2).

Procedures

Computed tomography

A Hitachi Pratico (Pratico, Hitachi, Japan) device was used for thoracic CT scans. The CT examinations were performed in a caudal-cranial direction with a 1-mm slice thickness and full inspiration in the supine position. The window width was 1500 Hounsfield Units (HU) for the lung window and 400 HU for the mediastinal window. The window level was −700 HU for the lung window and 10 HU for the mediastinal window. The measurements were made in the axial plane; however, coronal and sagittal images were used if necessary. Intravenous contrast agents were used for all scans except for patients with acute or chronic renal insufficiency. The radiologic findings of the patients such as tumor size, localization, and tumor contour characteristics were recorded.

Thoracic ultrasonography in peripheral lung masses

In the US unit of our clinic, thoracic US is conducted by an experienced pulmonologist using a General Electric (GE) Logic 7 device (Healthcare, Waukesha, WI, USA)and a 3.5-MHz convex probe in the abdominal mode. With the patient in a sitting position (in the supine, oblique, lateral decubitus position if needed), the entire thorax is scanned, starting from the region where the lesion has been previously observed radiologically, by moving the probe across the intercostal spaces transversely and longitudinally, along the parasternal line, the medial and lateral clavicular line, the anterior — medial and posterior axillary line, lateral and medial scapular line, and the paravertebral line.[15]

Thoracic ultrasound-guided transthoracic fine needle aspiration biopsy procedure

In the USG unit of our clinic, prior to biopsy procedures, a complete blood count and biochemical tests and a coagulometric test results are examined. Informed consent forms of all patients are obtained before the procedure. Patients with a platelet count of <50,000/uL and INR > 1.3, and those who do not agree to US guided-TFNAB do not undergo the procedure. Prior to thoracic US guided-TFNAB procedures, no premedication or sedation is administered. Iodine-alcohol is used to sterilize the region where the procedure will be performed and the USG probe to guide the procedure. The biopsy procedure is performed in real time using a 22-G spinal needle attached to a 20-mL injector from the predetermined spot in which necessary measurements have been made and scanned using a power Doppler.

Table 1 Inclusion/exclusion criteria.

Criteria for inclusion in the study
- Patients with peripherally localized lung lesions, which could be detectable by thoracic US for contacting with the visceral pleura.
- Patients without contraindication to TFNAB (number of platelets>50,000/uL, INR < 1.3).
- Patients who agreed to undergo TFNAB.
- Patients whose PET-CT reports were available.
- Patients diagnosed with primary lung cancer.
- Patients whose final histopathological diagnoses were available.

Criteria for exclusion from the study
- Patients with contraindication to TFNAB (number of platelets <50,000/uL, INR > 1.3).
- Patients who did not agree to undergo TFNAB.
- Patients without any PET-CT scan.
- Patients whose PET-CT reports were not available.
- Patients with suspected metastasis to lung.
- Patients whose final histopathological diagnoses were not available.

CT: Computed tomography; PET-CT: Positron emission tomography-computed tomography; TFNAB: Transthoracic fine needle aspiration biopsy; US: Ultrasonography.

Table 2 Clinical, radiologic, radiometabolic (PET/CT) features of the patients.

	US-TFNAB diagnostic group (n = 79)	US-TFNAB non-diagnostic group (n = 25)	p value
Age (Mean ± SD)	62.6 ± 9.6	62.6 ± 10.1	0.961
Sex (F/M)	13/66	5/20	0.763
Smoking history (Yes/No)	75/4	22/3	0.355
Tobacco (Pack-year ± SD)	30.1 ± 11.4	29 ± 13	0.492
Radiologic characteristics(CT)			
Tumor size (mm) (mean ± SD)	7 ± 2.8	7 ± 2.5	0.831
Tumor localization			
Right upper lobe (n, %)	27/16.5%	14/56%	0.052
Right middle lobe (n, %)	–	1.4%	0.240
Right lower lobe (n, %)	15/19%	2/8%	0.351
Left upper lobe (n, %)	23/29.1%	5/20%	0.371
Left lower lobe (n, %)	13/16.5%	3/12%	0.756
Tumor contour properties			
Regularly contoured (n, %)	10–12.6%	4-16%	0.739
Lobular contoured (n, %)	20–25.3%	6-24%	0.895
Irregularly contoured (n, %)	49–62.1%	15-%60	0.856
Mean SUVmax ± SD in PET/CT (mean ± SD)	19.5 ± 10.1	15.1 ± 8.9	0.016
Heterogeneous FDG uptake in PET/CT (n, %)	41 (51.8%)	16 (64%)	0.289
The mean number of TFNABs per patient (mean ± SD)	1.1 ± 0.3	1.04 ± 0.2	0.345

CT: computed tomography; F: Female; FDG; fluorodeoxyglucose; M: Male; SD: standard deviation; SUVmax: maximum standard uptake; PET-CT: positron emission tomography-computed tomography; TFNAB: transthoracic fine needle aspiration biopsy; US:ultrasonography.

In all US-guided TFNAB procedures, after the hypoechoic mass lesion is detected using US, anechoic, irregular hypoechogenicities or areas observed as mixed echo-patterns in the lesion, if any, are assessed as necrotic foci. A biopsy procedure is performed by avoiding these areas.[16]

Integrated positron emission tomography/computed tomography findings

Patients with a fasting time of at least 8 h and a normal blood glucose level were included in the procedure. The PET-CT scans were as performed on a Philips Gemini TF ultra-speed integrated PET-CT imaging system (Philips Healthcare, Best, The Netherlands). SUV was calculated based on the ratio of the tissue radioactivity concentration and all administered doses at the time of injection divided by body weight. Patients whose PET-CT revealed different levels of FDG uptake in different areas of the tumor due necrotic areas mainly constituted by tumor cells that had lost their vitality were recorded as patients with heterogeneous FDG uptake (presence of necrotic component), and patients whose PET-CT revealed similar levels of FDG uptake across the entire tumor were recorded as patients with homogenous FDG uptake (absence of necrotic component).[8,17,18] The PET-CT findings of the patients were examined. From the PET-CT

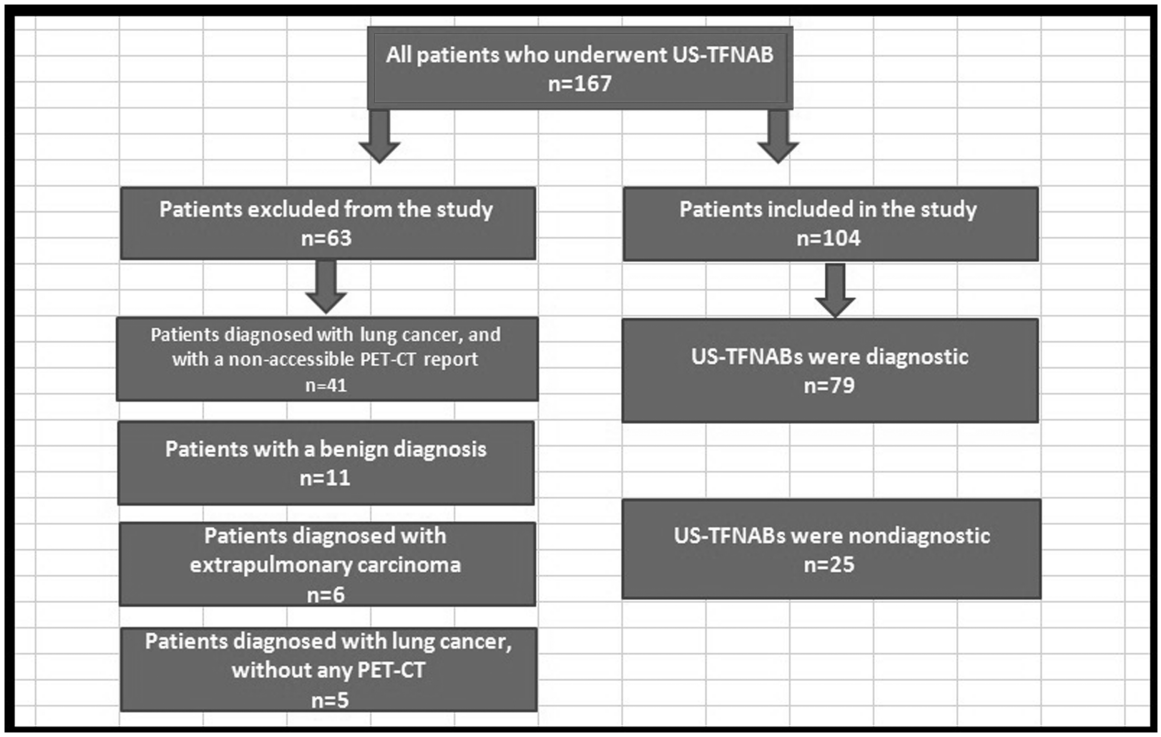

Figure 1 Flow diagram of included/excluded patients.

reports, the SUVmax value of the main mass lesion biopsied and homogeneous or heterogeneous FDG uptake features of that lesion were recorded. Patients were excluded from the study if a PET-CT report was not available or a PET-CT scan had not been performed.

Pathologic examination histopathologic results

We did not have an on-site pathologist at the time of the procedures. After the cytologic specimens were prepared using both alcohol fixation and air-drying techniques, the remaining material was separated and sent in an appropriate manner to the pathology laboratory for the preparation of a cell block. In the pathology laboratory, slides fixed in 95% alcohol are stained with the Papanicolaou stain, and air-dried slides are stained with the May-Grunwald-Giemsa stain. Three-micron-thick paraffin sections obtained from the cell blocks are stained with hematoxylin andeosin. Immunohistochemical examination is applied to cell block sections in the required specimens. Patients with a definitive diagnosis of extra pulmonary cancer metastases or benign lesions and patients without a definite histopathologic diagnosis were excluded from the study.

The size of lesions detected using CT, number of TFNABs per lesion, diagnoses of patients identified using US-guided TFNAB, final diagnoses of patients whose disease could not be diagnosed using US-guided TFNAB, and final diagnosis methods were recorded. We compared the clinical, radiologic and radiometabolic (SUVmax values and homogeneous FDG uptake of the main lesion by PET-CT/heterogeneous FDG uptake) characteristics of patients between the US-TFNAB-diagnostic and US-TFNAB non-diagnostic groups.

Statistical analysis

Statistical analysis was performed using the SPSS 17.0 (IBM Inc.,Relased 2008. SPSS Statistics for Windows Chicago, USA) and Med-Calc version 8.1.1.0, (Med-Calc Software, Ostend, Belgium) programs. In descriptive statistics, continuous variables are expressed as mean $\pm$ standard deviation, and categorical variables as percentage. The data of the groups were evaluated using the Chi-square and Mann-Whitney U test, and receiver operating characteristic (ROC) curve analysis.

Multivariate logistic regression analysis was conducted with variables likely to affect diagnosis in order to find independent variables that influenced the diagnostic success of thoracic US guided-TFNAB procedures. Logistic regression analysis was performed using the forward likelihood ratio method, and $p < 0.05$ was considered as significant.

Findings

US guided-TFNAB procedures were conducted in a total of 167 patients in our US unit during the study period. A total of 104 patients, including 86 (82.7%) males and 18 (17.3%) females who met our inclusion criteria, were included in the study (Fig. 1). The mean age of the patients was 62.6 ± 9.6 (range, 42–84) years. Ninety-seven (93.3%) patients had a smoking history, and the average smoking story was 29.8 ± 11.8 pack-years. The most common thoracic CT finding was mass in 104 (100%) cases. The mean long axis diameter of masses and nodules detected in our patients was 7 ± 2.7(min 2, max 17) cm. An analysis of anatomic localization of masses and nodules showed that the tumor

Table 3 Distribution of final histopathological diagnoses.

	US-TFNAB diagnostic group (n = 79)	US-TFNAB non-diagnostic group (n = 25)	p value
NSCLC with unidentifiable sub-type (n, %)	27–34.2%	13–52%	0.110
Squamous cell carcinoma (n, %)	30–38%	6–24%	0.201
Adenocarcinoma (n, %)	13–16.5%	4–16%	0.957
Small cell carcinoma (n, %)	6–7.6%	2–8%	0.947
LCNEC (n, %)	3–3.8%	–	0.323
Total	79	25	

LCNEC: large cell neuroendocrine carcinoma; NSCLC: non-small cell lung cancer; TFNAB: transthoracic fine needle aspiration biopsy; US: ultrasonography.

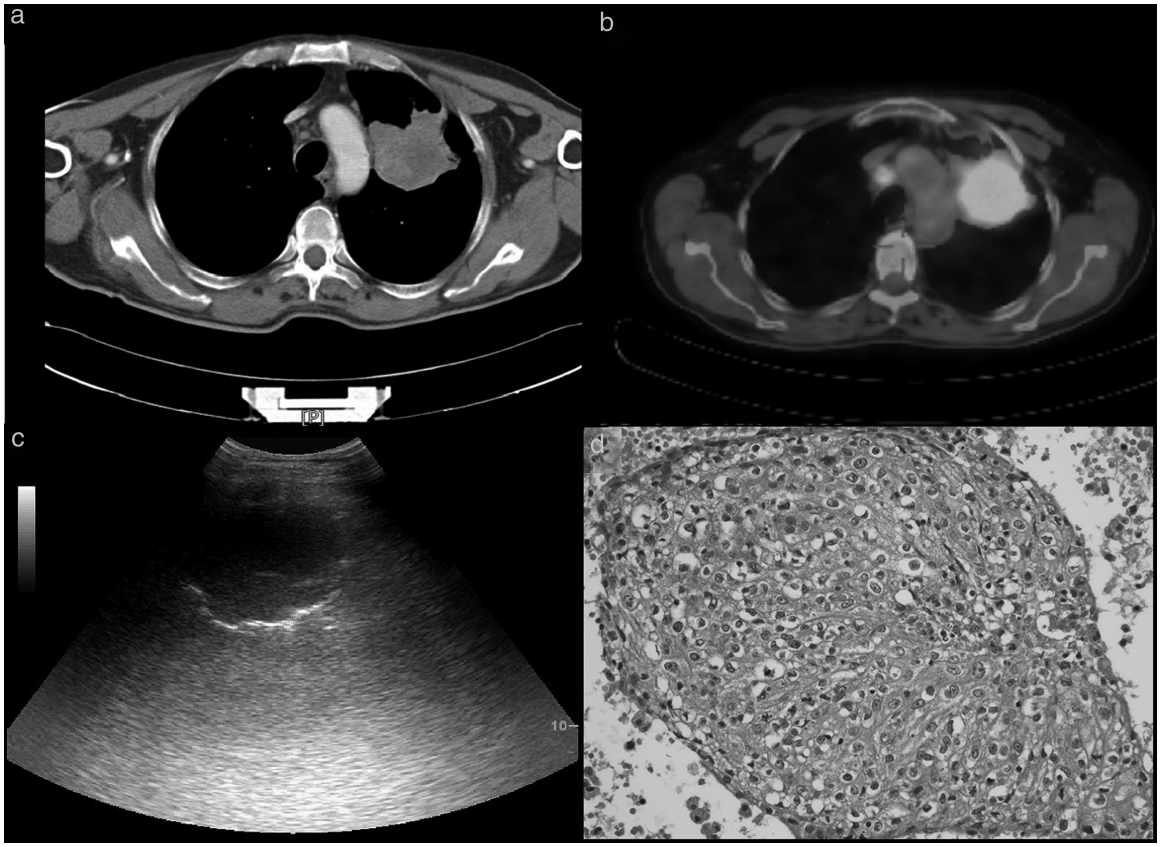

Figure 2 a) An approximately 5 × 5-cm mass in the left lung in thoracic CT. b) Homogeneous FDG uptake of the mass in PET-CT. c) Ultrasonographic image of the mass. d) Malignant tissue fragment (HEx400) whose structural and cellular details can be evaluated in the histopathologic preparation.

was most frequently localized in the right upper lobe in 41 (39.4%) patients (Table 2).

There were 79 (76%) patients in the US-TFNAB diagnostic group and 25 (24%) in the US-TFNAB non-diagnostic group. When the final diagnostic methods of these 25 patients (US-TFNAB non-diagnostic group) were examined, it was observed that 13 (52%) patients' final diagnosis was achieved using CT-guided Tru-cut biopsies, 9 (36%) with fiberoptic bronchoscopy (FOB), and 3 (12%) with thoracic US-guided Tru-cut biopsies. The distribution of the final histopathologic diagnoses of the patients is given in Table 3. The mean number of TFNABs per patient was 1.09 ± 0.28.When the PET-CT reports of the patients were examined, the mean SUVmax in PET-CT scans was 19.5 ± 10.1 in the US-TFNAB diagnostic group, whereas it was 15.1 ± 8.9 in the US-TFNAB non-diagnostic group ($p = 0.016$) (Fig. 2). When heterogeneous FDG uptake and homogeneous FDG uptake characteristics in PET-CT of biopsied mass lesions of the patients were examined, heterogeneous FDG uptake was reported in 41 (5) patients in the US-TFNAB diagnostic group and in 16 (64%) patients in the US-TFNAB non-diagnostic group (Figs. 2a–d) (Figs. 3a–d). There was no statistically significant relationship between lesions showing homogeneous or heterogeneous FDG uptake and the diagnostic success of the US guided-TFNAB procedure ($p = 0.289$) (Table 2).

The cut-off value obtained by ROC analysis made in order to determine the optimal SUVmax cut-off value in PET-CT

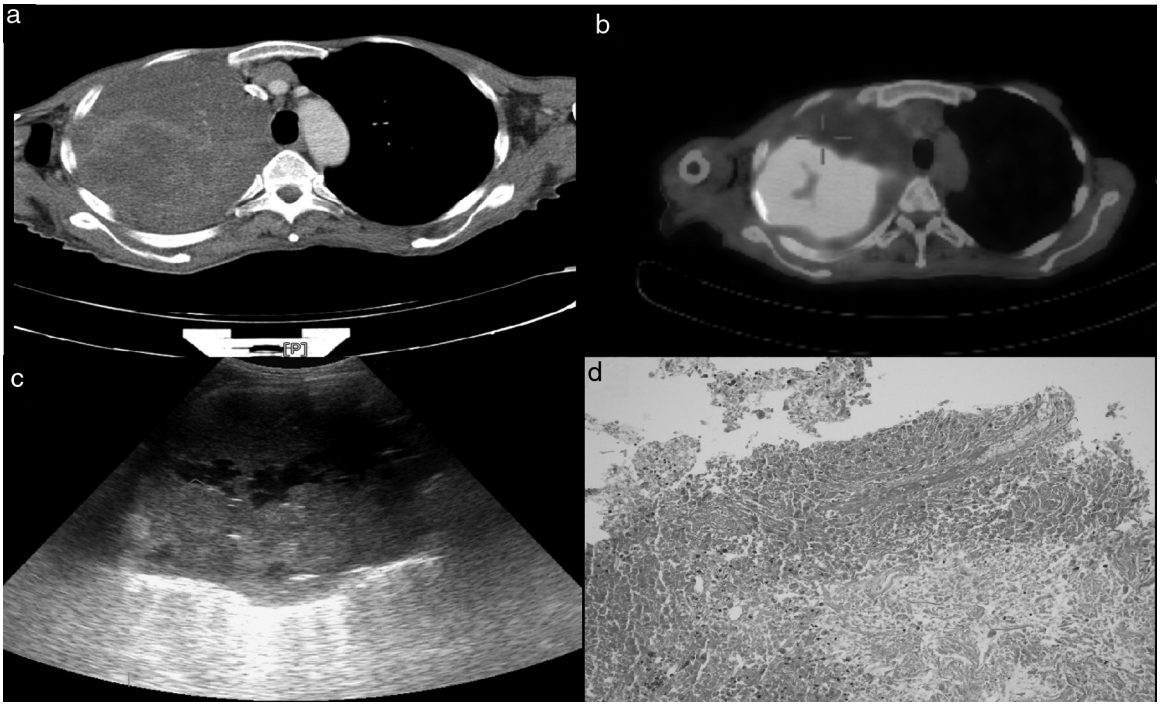

Figure 3 a) An approximately 15 × 10-cm mass in the right lung in thoracic CT. b) Heterogeneous FDG uptake with observed necrotic areas inside the mass in PET-CT. c) Anechoic necrotic foci in the ultrasonographic image of the same mass. d) Necrotic tissue specimen (HEx200) whose structural and cellular details cannot be evaluated in the histopathologic preparation.

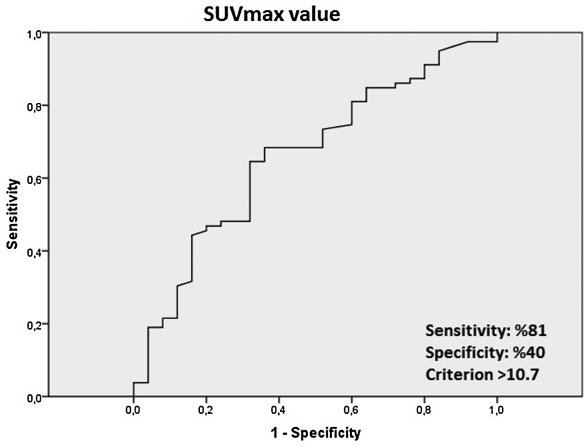

Figure 4 ROC analysis curve showing the SUVmax cut-off value of the patients.

was 10.7 (AUC: 0.661). Where SUVmax was above 10.7 in PET-CT, the sensitivity and specificity of US guided-TFNAB were calculated as 81% and 40%, respectively (Fig. 4).

When a logistic regression model was established for the variables (number of TFNABs performed, size of tumor, location of tumor, SUVmax value, presence of homogeneous/heterogeneous FDG uptake) likely to influence the diagnostic success of thoracic US guided-TFNAB, the SUVmax value was found to be the only independent factor effective in the diagnostic success of the procedure ($p = 0.035$, OR: 1.08, 95% CI: 1.0–1.1). The diagnostic success was not influenced by the number of TFNABs ($p = 347$), tumor size ($p = 0.359$), anatomic location of tumor ($p = 0.240$), or homogeneous/heterogeneous character of FGD uptake ($p = 0.095$).

Discussion

In the present study, which aimed to evaluate the impact of PET-CT findings in thoracic US-guided TFNAB on diagnostic success in primary lung cancers, US-guided TFNAB allowed us to make a diagnosis in 79 of 104 (76%) patients, whereas it failed in 25 (24%) patients. SUVmax was statistically significantly lower in patients whose disease could not be diagnosed using US-guided TFNAB. Although FDG involvement was mostly heterogeneous (64%) in mass lesions in those who could not be diagnosed, no statistically significant difference was found between the type of FDG involvement (homogeneous/heterogeneous) and diagnostic success. Furthermore, SUVmax value was the only independent factor which was effective in diagnostic success of the procedure.

Glucose affinity is increased in malignant tumor cells. The main reason for increased glucose affinity is carrier proteins such as the glucose transporter (GLUT1-GLUT3), which is increased in tumor cell membranes. Previous studies reported that tumors with extremely increased GLUT 1- GLUT 3 production, hence high FDG uptake, had poor prognosis.[19] It is known that tumors with high FDG uptake are metabolically more active.[20] The greater the glucose affinity of the tumor, the higher the FDG uptake. Aggressive tumors with high cell differentiation and proliferative activation have high FDG uptake.[10] In a study investigating the diagnostic efficiency of conventional transbronchial needle aspiration biopsies, Öztürk et al.[21] established a statistically significant correlation between SUVmax values of lymph nodes in PET-CT and diagnostic efficiency ($p < 0.05$), and concluded that the diagnostic success of the procedure increased with high SUVmax values in PET-CT. In that study, the authors performed transbronchial biopsy on 127

lymph nodes, and reported a cut-off SUVmax value of 4.8, a procedure sensitivity of 71.7%, and a specificity of 51.4%. That study is an important study because it associates high SUVmax values with the diagnostic properties of biopsies. Studies have shown a strong correlation between tumor growth and invasion and high FDG uptake.[22–24] Umeda et al.[25] published a paper on the hypothesis that there might be a relationship between SUVmax and the diagnostic efficiency of transbronchial biopsies performed with virtual bronchoscopic navigation in peripheral lung lesions.[25] In that study, 201 peripheral lung lesions were evaluated and it was concluded through multivariate analysis that high FDG uptake and positive bronchial signs were the only statistically significant determinants of diagnostic efficiency (SUVmax $\geq$2.8 OR: 3.57). Based on their results, the authors concluded that different diagnostic methods such as CT-guided biopsy or surgical biopsy, which increase diagnostic efficiency, would be more useful in lesions with low SUVmax values. In their series consisting of 140 patients who underwent transbronchial biopsies on mediastinal lymph nodes by bronchoscopy, Seijo et al.[26] investigated the effects of FDG uptake in biopsies and reported that a cut-off SUVmax value of 3 or more increased diagnostic efficiency. When a cut-off SUVmax value was 3, the sensitivity of the procedure was 98% and the specificity was 45%. In that study, of 27 patients with an SUVmax value less than 3, 26 could not be diagnosed despite a sample adequacy of 74%, adequate needle passage (3.7), and adequate lymph node size (14.4 mm). The authors concluded that FDG uptake was the only and most important variable in transbronchial biopsies of malignant mediastinal lymph nodes based on multivariate analysis.

The above-mentioned studies and many similar previous studies[13,14] demonstrated that a high SUVmax value in PET-CT affected diagnostic procedures in malignant diseases and the diagnostic characteristics of the procedures correlated with SUVmax values. Our study is in good agreement with these results. In our study, the diagnosis rate of thoracic US-guided TFNAB in patients with high SUVmax values was higher than in patients with low SUVmax values ($p = 0.016$). In multivariate regression analysis, SUVmax values were found to be the only independent factor effective in the diagnostic success of the procedure ($p = 0.035$). We associate this relationship with the fact that tumors with high FDG uptake are metabolically more active, more proliferative, and have more cell differentiation.[10,20]

The presence of various ratios of FDG uptake in various areas in PET-CT (heterogeneous FDG uptake) allows differentiation of necrotic areas, granulation tissues, and viable tumor tissues inside tumoral tissue. Clinical trials have shown that PET-CT can better assess proliferative activity in tumoral tissue and is useful in distinguishing viable tumor tissue from fibrotic tissue.[27–30] In a study by Cataluna[31] that evaluated factors affecting the diagnostic accuracy of bronchial biopsies, the degree of cell differentiation and the absence of necrosis in pathologic specimens were shown to be the most influential factors on diagnostic accuracy. They demonstrated that in the absence of necrosis in a pathology specimen, diagnostic accuracy was 5.2 times higher. Further, Greses et al.[32] found diagnostic sensitivity to be 69.6% in their series of 151 patients, and demonstrated that one of the variables that significantly affected diagnostic accuracy in biopsy procedures was the presence of necrosis in the biopsy material. They reported that the diagnostic success was 2.6-times higher when there was no necrosis in the biopsy material. In spite of a higher rate (64%) of patients whose PET-CT revealed heterogeneous uptake due to the presence of a necrotic component than in the US-TFNAB non-diagnostic group, no statistically significant difference was found between the two groups ($p = 0.289$). As is widely known, US is very sensitive in the differentiation of necrotic areas in tissues.[16] Necrotic areas with thoracic US are seen as focal heterogeneous echo-densities within a hypoechoic mass lesion[33] (Fig. 3c). We thought that mass lesions with a necrotic component in PET-CT might negatively affect diagnostic success; however, we found no statistically significant relationship. This may be associated with the low number of patients and real-time nature of US-guided TFNABs. In real-time procedures, needle movements can be tracked within the lesion. The direction of the needle can be determined by the operator. Therefore, during biopsy, necrotic regions may be identified and biopsy of those necrotic regions can be avoided.

A limitation of our study is that it was a retrospective study conducted with a limited number of patients. It reflects experiences related to this subject from a single center; therefore, the results cannot be generalized. Another limitation is that we did not evaluate the interrater differences for thoracic US procedures and SUVmax values. Furthermore, the number of patients in some sub-groups, particularly in cancers with a relatively low FDG involvement such as well differentiated adenocarcinomas, was small. It may be worth conducting controlled studies with adequate numbers of participants in cancers with a relatively lower FDG involvement such as well-differentiated adenocarcinomas and evaluating the diagnostic role of PET-CT and US-guided biopsy in cancers with a low FDG involvement.

Conclusion

With this study, we showed that high SUVmax values in PET-CT in lung cancers increased diagnostic success of US guided-TFNAB procedures, and that a lesion with a necrotic component in PET-CT was not a factor that affected the diagnostic success of TFNAB procedures. Based on the results of this study, we believe that, in patients with low SUVmax values in PET-CT — especially in cases of urgent need for diagnosis – alternative diagnostic methods for early diagnosis should be kept in mind instead of US-guided TFNAB.

Conflict of interest

Coşkun Doğan, Ali Fidan, Sevda Şener Cömert, Nesrin Kıral, Banu Salepçi, Elif Torun Parmaksız, and Benan Çağlayan and declare that they have no conflict of interest.

There are no financial or other relations that could lead to a conflict of interest

The manuscript has not been submitted to more than one journal for simultaneous consideration.

The manuscript has not been published previously, unless the new work concerns an expansion of previous work.

Ethical statements

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the local ethics committee.

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REVIEW

Conquering lung cancer: current status and prospects for the future

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KEYWORDS
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Multimodality therapy;
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Targeted therapies;
Tobacco control

Abstract Lung cancer is a major global health problem. Several strategies are required to conquer this cancer. Stricter implementations of tobacco control measures are necessary. Early detection programs should be implemented to decrease lung cancer mortality. Although chemotherapy remains a cornerstone of treatment, targeted therapies and immune checkpoint inhibitors improved treatment of metastatic cancers and are hoped to improve outcome of adjuvant and induction therapies. Novel immunotherapy approaches hold great promise. Better understanding of the molecular biology of lung cancer should lead to rational drug design.

Introduction

Lung cancer is a global health problem. Approximately 2.1 million individuals are diagnosed with lung cancer and 1.8 million die from this cancer each year.[1] Lung cancer rates continue to increase on the global level, although the rates are declining among males in some Western countries. Non-small cell lung cancer (NSCLC) makes up about 85% and small cell lung cancer (SCLC) about 15% of lung cancers. Pathological diagnosis is based on histology, immune histology and molecular analysis.[2] Lung cancers are currently staged according to the eighth edition of the TNM Classification for Lung Cancer.[3,4] Tumor stage is important for prognosis and treatment.[3,4] Overall, the five year survival rates are 15–20%. Among patients with NSCLC, these rates reach 90% for stage 1A1 but drop below 10% for stage 4. Among patients with SCLC, the rates are about 30% for limited disease and below 10% for extensive disease.

Treatment of patients with lung cancer requires multidisciplinary co-operation and is based on surgery, radiotherapy, systemic treatments (chemotherapy, targeted therapies, immune checkpoint inhibitors) and supportive care including end-of-life care. Treatment depends on tumor characteristics, tumor stage and patient-related factors. Finally, access to and re-imbursement of novel drugs are becoming an increasing challenge for many countries.

Major diagnostic and therapeutic advances have occurred during the last three decades. Here, the current status of systemic treatment and strategies for conquering lung cancer are described.

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Tobacco control

Smoking is by the far the most important risk factor for developing lung cancer. About 80% of lung cancers in Western countries are directly related to smoking. In order to decrease the incidence and mortality rates, therefore, stricter implementation of tobacco control measures is required. These measures are outlined in the WHO Tobacco Free Initiative which includes WHO Framework Convention on Tobacco Control (www.fctc.org) and MPOWER (www.who.int/tobacco/mpower/en/). The single most efficient measure to decrease smoking rates is to raise taxes on tobacco products. Other important measures include smoke-free environment, advertising bans, and better information to the public on the benefits of a smoke-free society. MPOWER means to monitor tobacco use, protect people from tobacco smoke, offer help to quit tobacco use, warn about the dangers of tobacco, enforce bans on tobacco advertising as well as promotion, and to raise taxes on tobacco products.

Early detection of lung cancer

Patients with early-stage lung cancer have better prognosis than those with more advanced disease. Therefore, early detection of lung cancer should improve cure rates and survival of patients. Screening with low-dose CT was recently shown in two large randomized trials to reduce mortality among smokers or former smokers at high risk for lung cancer.[5,6] In the National Lung Screening Trial (NLST), lung cancer mortality was reduced by 20% and overall mortality by 6.7% by low-dose CT compared to chest radiographs.[5] Three annual screenings were performed in this trial. In the NELSON trial, lung cancer mortality was reduced by 26%.[6] Based on these results and those from smaller European trials, lung cancer screening is now endorsed by several scientific societies including the European Society of Radiology and the European Respiratory Society.[7]

The implementation of early detection and screening by low-dose CT is currently ongoing in several countries and cancer centers with appropriate infrastructure, multidisciplinary expertise and quality control. A multidisciplinary expert panel should assure guidance, monitoring and quality control. The screening population should consist of current or former smokers in accordance with the inclusion criteria of the two randomized trials, although validated risk stratification approaches might play a role in the future. Persons to be screened must be informed about potential benefits and harms of screening, the risk of false-positive and false-negative results, and on the fact that screening is no guarantee for avoiding death from lung cancer. CT examinations including volumetric measurements for assessment of pulmonary nodules must be standardized. Clear definition of positive findings, establishment of algorithms for management of positive or suspicious findings, and establishment of registers for anonymous monitoring of persons are other requirements. Screening programs should also offer smoking cessation advice for active smokers. Early detection and screening programs will most likely reduce mortality rates of lung cancer in the future.

Adjuvant therapy of resected non-small cell lung cancer

Adjuvant chemotherapy with cisplatin-based regimens has been re-evaluated within phase 3 trials since 1995 when a meta-analysis indicated a trend towards improved survival for these regimens compared to observation alone.[8] Three out of five phase 3 trials demonstrated a survival benefit for cisplatin-based chemotherapy (for review see Ref.[9]). Among the positive trials, the 5-year survival rates increase by 4–15%.[10–13] The Lung Adjuvant Cisplatin Evaluation meta-analysis, which included patients from all five phase 3 trials, confirmed a survival gain at five years of 5.4% for adjuvant cisplatin-based regimens and 8.9% for cisplatin plus vinorelbine.[14,15] Therefore, adjuvant chemotherapy with a cisplatin-based doublet, preferentially cisplatin plus vinorelbine, has been established as standard for patients with completely resected tumors and pathological tumor stages 2 or 3.

Strategies to improve outcome of adjuvant therapy focused on the characterization of predictive biomarkers, targeted therapies and tumor vaccines. Predictive biomarkers and customized chemotherapy based on biomarkers remain experimental.[16–20] Bevacizumab added to adjuvant chemotherapy failed to increase survival.[21] EGFR tyrosine kinase inhibitors (TKIs) also failed to improve survival of patients unselected for EGFR mutations.[22,23] However, adjuvant therapy with gefitinib increased disease-free survival compared to chemotherapy in a Chinese study among patients with resected EGFR mutation-positive NSCLC and may be an option for these patients.[24] Further trials on adjuvant therapy with EGFR TKIs or ALK inhibitors are ongoing in patients who harbor EGFR mutations or ALK fusions in their cancers. Vaccination with the MAGE-A3 vaccine failed to improve outcome in MAGE-A3-positive patients and resected stage IB-IIIA NSCLC.[25] Immune checkpoint inhibitors hold great promise because of their efficacy in metastatic and locally advanced NSCLC and are currently evaluated within phase 3 trials in patients with completely resected NSCLC and tumor stage IB (<4 cm) – IIIA (for review see Ref.[9]). Within these trials, patients receive adjuvant chemotherapy followed by an immune checkpoint inhibitor as single agent for one year. Primary endpoints of the trials are often disease-free survival. Finally, surrogate endpoints would be of interest in order to shorten the duration of adjuvant trials. Residual disease based on circulating tumor DNA at the end of adjuvant chemotherapy could be such an endpoint and should be further studied.

Induction chemotherapy of operable NSCLC

Induction chemotherapy with a platinum-based doublet prior to surgery resulted in survival benefits similar to the ones achieved with adjuvant chemotherapy in patients with operable NSCLC.[26] Therefore, induction chemotherapy is a valid treatment option for patients with operable NSCLC, particularly for those with marginally resectable tumors. Current clinical trials evaluate tyrosine kinase inhibitors as induction therapy among patients with driver mutation-positive NSCLC. Immune checkpoint inhibitors are also

evaluated as induction therapy, either alone or in combination with chemotherapies.

Treatment of locally advanced NSCLC

Patients with locally advanced NSCLC require both local and systemic treatments and, therefore, multidisciplinary co-operation is crucial for their optimal care.[27]

Patients with completely resected tumors receive adjuvant chemotherapy. Selected patients, particularly those with marginally resectable tumors, are candidates for induction chemotherapy followed by local treatment. For the majority of patients, however, chemoradiotherapy remains standard treatment.[27,28] Concomitant chemoradiotherapy is superior over the sequential approach.[29] Consolidation therapy with durvalumab has recently been approved for patients with response or stable disease after chemoradiotherapy and PD-L1 levels $\geq$1% in their tumors. This approval was based on results of the PACIFIC trial which demonstrated improved disease-free and overall survival for consolidation therapy with durvalumab.[30] High dose conformal radiotherapy and the addition of cetuximab to chemoradiotherapy failed to improve outcome of patients.[31]

Two major therapeutic strategies to improve outcome are currently studied within clinical trials. The first strategy focuses on the integration of immune checkpoint inhibitors. These drugs are evaluated as induction therapy, either as single agent or combined with induction chemotherapy, and also in combination with radiotherapy or chemoradiotherapy. Similarly, EGFR tyrosine kinase inhibitors are evaluated as induction therapy in patients with EGFR mutation-positive NSCLC. There is great hope that these strategies will improve survival of patients with locally advanced NSCLC in the future, although there is also concern that some of these combined treatments might result in unacceptable toxicity.

Treatment of advanced NSCLC

Patients with advanced NSCLC receive palliative therapies with systemic treatments and, in case of local problems, radiotherapy or surgery. Systemic anticancer treatments are chemotherapy, targeted therapies and immune checkpoint inhibitors. The type of systemic therapy depends on tumor histology, presence or absence of driver mutations in tumors, performance status of patients and other factors. Supportive care including end-of-life care also plays a major role in patients with advanced NSCLC.

Advanced driver mutation-negative NSCLC

Patients with advanced NSCLC have received first-line chemotherapy, maintenance chemotherapy and second-line therapy for many years.[32–34] Immune checkpoint inhibitors have recently become part of the standard treatment for patients with advanced driver mutation-negative NSCLC.[35] They were initially approved as single agents for patients who had been pretreated with chemotherapy. Then immune checkpoint inhibitors became established in the first-line setting, either as single agents or in combination with chemotherapy. Current treatment options for patients with non-squamous and squamous NSCLC are shown in Tables 1 and 2.

First-line chemotherapy and chemoimmunotherapy

Platinum-based doublets have been standard first-line chemotherapy for patients with advanced NSCLC for many years.[32,33] These doublets include one of the following third-generation cytotoxic drugs: vinorelbine, gemcitabine, pemetrexed, paclitaxel, nab-paclitaxel and docetaxel. First-line platinum-based chemotherapy relieves cancer-related symptoms and increases median survival by 1.5 months and the 1-year survival rate by 9%.[36]

Cisplatin-based doublets are slightly superior to carboplatin regimens[37] and are preferred for patients with good performance status. Carboplatin-based doublets are preferred in elderly patients, patients with impaired organ (kidney, heart) functions or whenever ease of administration is of particular importance. First-line chemotherapy is combined with bevacizumab in selected patients with non-squamous NSCLC.[38] Chemotherapy combined with cetuximab or necitumumab improved survival in patients with NSCLC and squamous cell NSCLC, respectively.[39,40] Patients with high EGFR expression or EGFR FISH-positivity of tumors particularly benefited from the addition of EGFR antibodies to chemotherapy.[41–43] Elderly patients and patients with reduced performance status are treated with single agents or well tolerated doublets.[44]

The establishment of immune checkpoint inhibitors has recently changed the therapeutic landscape in patients with advanced NSCLC.[35] Immune checkpoint inhibitors were studied in the first-line setting as single agents and in combination with chemotherapy. Pembrolizumab or atezolizumab improved overall survival compared to platinum-based doublets among patients with PD-L1 expression in $\geq$50% of tumor cells.[45,46] First-line chemotherapy combined with either pembrolizumab or atezolizumab improved progression-free survival and, in some studies, also overall survival compared to chemotherapy alone.[47–52] Although the benefit from immune checkpoint inhibitors appeared to increase with increasing PD-L1 expression of tumor cells, patients with PD-L1 expression in <1% of tumor cells also derived clinically meaningful improvements from the addition of immune checkpoint inhibitor to platinum-based doublets.[53] Based on these results, chemoimmunotherapy replaced chemotherapy as standard first-line therapy in patients with advanced driver mutation-negative NSCLC.[35] Patients with good performance status now receive a platinum-based doublet plus an immune checkpoint inhibitor regardless of PD-L1 levels of tumors (Tables 1–2). Strategies to improve clinical outcome of patients focus on novel drugs which may further enhance the immune response towards tumors. These drugs are studied as single agents or in combination with current standard treatments.

Maintenance therapy and treatment at the time of disease progression

Maintenance therapy with pemetrexed is established as a valid treatment option for selected patients with non-squamous cell NSCLC. Bevacizumab, necitumumab and immune checkpoint inhibitors are usually continued as

Table 1 Treatment of advanced driver-negative non-squamous NSCLC.

	First-line	Second-line	Third-line
All	Platin + pemetrexed + pembrolizumab	Docetaxel ± nintedanib, Docetaxel ± ramucirumab	Gemcitabine, vinorelbine, erlotinib, anlotinib
	Carbo + paclitaxel + bevacizumab + atezolizumab	Docetaxel ± nintedanib, Docetaxel ± ramucirumab	Gemcitabine, vinorelbine, erlotinib, anlotinib
	Carbo + nab-paclitaxel + atezolizumab	Docetaxel ± nintedanib, Docetaxel ± ramucirumab	Gemcitabine, vinorelbine, erlotinib, anlotinib
	Nivolumab + ipilimumab	Platin-based doublet	Docetaxel ± nintedanib, Docetaxel ± ramucirumab
	Platin + pemetrexed	Atezolizumab, nivolumab, pembrolizumab	Docetaxel ± nintedanib, Docetaxel ± ramucirumab
PD-L1 ≥ 50%	Pembrolizumab; atezolizumab	Platin + pemetrexed	Docetaxel ± nintedanib, Docetaxel ± ramucirumab
High EGFR	Cisplatin + vinorelbine + cetuximab	Atezo, nivo, pembro	Docetaxel ± ramucirumab

Table 2 Treatment of advanced driver-negative squamous NSCLC.

	First-line	Second-line	Third-line
All	Platin-based CT + pembrolizumab	Docetaxel ± ramu, afatinib	Afatinib, gemcitabine, vinorelbine, anlotinib
	Carbo + nab-pacl + atezolizumab	Docetaxel ± ramucirumab	Afatinib, erlotinib, gem, vinorelbine, anlotinib
	Nivolumab + ipilimumab	Platin-based doublet	Docetaxel ± nintedanib, Docetaxel ± ramucirumab
PD-L1 ≥ 50%	Pembrolizumab; atezolizumab	Platin-based doublet	Docetaxel ± ramucirumab
All	Platin-based CT	Atezo, nivo, pembro	Docetaxel ± ramucirumab
High EGFR	Platin + gemcitabine + necitumumab	Atezo, nivo, pembro	Docetaxel ± ramucirumab

maintenance or consolidation therapy after completion of first-line chemotherapy.

Patients who progress after platinum-based chemotherapy are treated with docetaxel plus/minus ramucirumab, docetaxel plus/minus nintedanib, pemetrexed, erlotinib or afatinib.[33,54–56] Those patients who had not been treated with an immune checkpoint inhibitor in the first-line setting should receive one of them as second-line therapy.

Table 3 Treatment of advanced *EGFR*-mutant NSCLC.

First-line	Second-line	Third-line
Osimertinib	Chemotherapy	
Gefitinib, erlotinib afatinib, dacomitinib	Osimertinib (T790 M positive)	Chemotherapy
	Chemotherapy	

Advanced driver mutation-positive NSCLC

The characterization of driver mutations and the subsequent establishment of corresponding TKIs as standard first-line treatment for patients with advanced driver mutation-positive NSCLC have been milestones in the treatment of patients with lung cancer. EGFR mutations, ALK translocations, ROS1 aberrations and BRAF mutations are currently routinely assessed in advanced NSCLC, particularly in adenocarcinomas. Other molecular aberrations are assessed dependent on availability of tests and corresponding drugs. While tumor tissue is currently the main source for molecular analyses, liquid biopsies will gain importance for diagnosis and particularly disease monitoring in the future.[57]

EGFR TKIs have established themselves as standard first-line treatment for patients with advanced EGFR mutation-positive NSCLC (Table 3). First- and second-generation EGFR TKIs resulted in superior progression-free survival compared to chemotherapy among patients with advanced EGFR mutation-positive NSCLC (for review see Refs.[58–60]). Osimertinib, a third-generation TKI, improved progression-free and overall survival compared to gefitinib or erlotinib in previously untreated patients[61] and, therefore, has become the preferred first-line therapy.

Several ALK inhibitors have also been established for patients with advanced ALK-positive NSCLC (for review see Refs.[62,63]). They include crizotinib, alectinib, ceritinib, brigatinib and lorlatinib. Crizotinib was the first ALK inhibitor to be approved.[64,65] Second-generation ALK inhibitors have broader efficacy as well as better penetration into the brain and have become the preferred first-line therapy.[66–68] Alectinib and brigatinib resulted in longer progression-free survival compared to crizotinib in the first-line setting.[66,67] The third generation inhibitor lorlatinib has shown efficacy in treatment-naive patients and

Table 4 Treatment of advanced ALK-positive NSCLC.

First-linec	Second-line	Third-line	Fourth-line
Alectinib Brigatinib[a] Ceritinib	Lorlatinib	Chemotherapy	
Crizotinib	Alectinib Brigatinib	Lorlatinib	Chemotherapy

[a] Not approved in first-line in EU.

patients who have developed resistance to crizotinib or second-generation ALK inhibitors.[69] Therefore, lorlatinib has recently been approved for patients whose disease has progressed after alectinib or ceritinib, or after crizotinib plus at least another ALK inhibitor. A proposal for treatment of ALK-positive patients is shown in Table 4. In routine clinical practice, the selection of an ALK inhibitor should be based on its availability as well as re-imbursement, presence of brain metastases, doctor's judgement and patient preference. The optimal sequencing of ALK inhibitors, however, has yet to be determined within clinical trials.

Treatment of SCLC

Patients with extensive stage SCLC are now treated with platinum plus etoposide in combination with an immune checkpoint inhibitor. This change from chemotherapy to chemoimmuntherapy is based on results from two phase 3 trials which demonstrated increased overall survival for chemotherapy plus atezolizumab or durvalumab compared to chemotherapy alone among patients with extensive stage SCLC.[70,71] Patients with limited stage SCLC continue to receive first-line therapy with cisplatin plus etoposide and thoracic radiotherapy. Patients should also be considered for prophylactic cranial irradiation. At the time of disease progression, topotecan is established as standard therapy.

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REVIEW

Electronic cigarettes and vaping associated pulmonary illness (VAPI): A narrative review

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Abstract
Background: Electronic (e-) cigarettes are used to heat liquids producing aerosols for inhalation. Recently there have been reports of a large number of adverse outcomes relating to e-cigarette consumption (vaping), which has been referred to as ''vaping associated pulmonary illness'' (VAPI).
Aim: This review provides an overview of clinical, radiological and pathological features of VAPI in the literature. We also describe a case of VAPI, presenting with symptoms of bronchiolitis, responding well to azithromycin in addition to the usual treatments provided for such cases.
Methods: We searched original papers, observational studies, case reports, and meta-analyses published between 2000 and 2019 in English in PubMed database using the keywords: e-cigarette, ''vaping associated pulmonary illness'', VAPI, EVALI, vaping AND ''lung injury''. We also used data of the Centers of Disease Control (CDC) website.
Results: From an initial search of PubMed, 62 potential articles were identified, and another 9 studies were identified from the bibliographies of retrieved articles. In this search we found 7 case series and 16 case reports, which were included in the review. In this search we also found 4 review articles.
Conclusion: VAPI is a syndrome presenting with isolated pulmonary or combined pulmonary, gastrointestinal and constitutional symptoms and can be rapidly progressive, leading to respiratory failure, often requiring invasive respiratory support. There is an urgent need for more research on VAPI especially relating to etiology, treatment and prevention.

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Introduction

Electronic cigarette consumption, also called vaping, is done with a hand-held device, powered by a battery, producing aerosols by heating liquids (or e-liquids) containing various components. Compared to the first-generation devices, the second, third and fourth generation devices have higher voltages and frequently include a rechargeable lithium-ion battery. The third and fourth generation devices allow adjustments of voltage and temperature, providing a different type of aerosolization, which can create new compounds.

Aerosols from e-cigarettes. The liquids mainly consist of propylene glycol, glycerin, flavorings and in most cases nicotine. The liquids may also contain tetrahydrocannabinol (THC), the psychoactive component of cannabis. E-cigarette aerosols contain heavy metals and volatile organic compounds. The origin of the heavy metals is assumed to be the metallic coil used to heat the liquid, and also the liquids themselves. With the exception of cadmium, the number of metals is greater than in conventional tobacco cigarettes. Many other constituents of e-cigarette aerosols have been detected, such as acetone, formaldehyde, nitrosonornicotine and tobacco-specific nitrosamine. The long-term health effects of these aerosol components are largely unknown. Other contaminants in e-cigarettes are strongly dependent on different brands of commercially available e-cigarettes or on self-made mixtures with products from the illegal street market or online sales. The e-cigarette is also used for illicit drug delivery. THC and cannabinoid (CBD) oils are popular drugs. Other liquid components are synthetic cathiones, benzoylmethylecgonine (cocaine), gamma-hydroxybutyric acid (GHB), heroin, fentanyl, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine.[1]

E-cigarettes for stopping or reducing tobacco smoking. E-cigarettes have mainly been promoted as a way of stopping or reducing tobacco smoking in smoking adults, especially in the early years after its first appearance in 2003. In a recent randomized trial of e-cigarettes versus nicotine-replacement therapy, the e-cigarette was shown to be more effective compared to nicotine-replacement therapy for smoking cessation, when both strategies were accompanied by behavioral support.[2] Amongst young adults, the most important reason for e-cigarette use is experimentation, followed by stopping smoking.[3]

Presentation of VAPI. Although vaping has been promoted commercially as a safer alternative to traditional tobacco cigarettes, it has been shown to be associated with a large spectrum of lung injury. Symptoms may be limited to one organ such as the lung or cardiovascular system or combined respiratory, gastrointestinal and systemic. Dyspnea can be severe and rapidly progressive, leading to severe respiratory failure requiring intubation and/or extracorporeal membrane oxygenation ECMO and in some cases even resulting in a fatal outcome in previously healthy adolescents and adults. The Centers for Disease Control CDC has recently reported an epidemic of a spectrum of pulmonary diseases, associated with the use of e-cigarettes. Until December 2019 2409 cases of vaping associated pulmonary illness VAPI have been reported in the United States, also known as E-cigarette Vaping Associated Lung Injury EVALI, of which 52 2% had a fatal outcome.[4]

Aim of the review. This review aims to report what is currently known about vaping-associated pulmonary illness and includes the first reported case of VAPI in Switzerland.

Methods

We searched original papers, observational studies, case reports, meta-analyses published between 2000 and end of 2019 in English in the PubMed database using the keywords: e-cigarette, v̈aping-associated pulmonary illness, VAPI, EVALI, vaping AND ''lung injury''. We also used data of the Centers of Disease Control (CDC) website and searched the reference lists of the retrieved articles.

Results

From an initial search of PubMed, 62 potential articles were identified, and another 9 studies were identified from the bibliographies of retrieved articles. In this search we found 7 case series, 16 case reports, and 4 review articles. No randomized controlled studies were found. Available evidence on presenting features, imaging and pathology results as well as treatment strategies, are summarized in the descriptions below and in the respective tables (Tables 1–3).

Definitions

VAPI (and EVALI) is a diagnosis of exclusion. There are no specific clinical, laboratory, radiological or pathological markers of disease. There are case definitions, which are likely to evolve, as more information becomes known about the etiology and pathogenetical mechanisms involved. It is a potentially fatal complication of vaping and it can mimic or be associated with respiratory infections, and present with a great variety of symptoms (Table 1, Table 2).

For surveillance purposes, not for clinical diagnosis, the CDC described case definitions for p̈robable casesänd c̈onfirmed cases:.[5] A ''probable case'' includes ''using an e-cigarette (vaping) or dabbing in 90 days before symptom onset; and pulmonary infiltrate, such as opacities on plain film chest radiograph or ground-glass opacities on chest CT; and infection identified by means of culture or PCR, but the clinical team caring for the patient believes that this is not the sole cause of the underlying respiratory disease process; or as the minimum criteria, to rule out pulmonary infection not met (testing not performed) and clinical team caring for the patient believes that this is not the sole cause of the underlying respiratory disease process''.[5]

The case definition of ''confirmed case'' includes the same definition as above, but there should be ''absence of pulmonary infection on initial workup: the minimum criteria include negative respiratory viral panel and influenza PCR or rapid test if local epidemiology supports testing. All other clinically indicated testing for respiratory infectious disease (e.g., urine antigen testing for *Streptococcus pneumoniae* and legionella, sputum culture if productive cough, bronchoalveolar lavage culture if done, blood culture, and

Table 1 Main references limited to original papers and case reports (excluding reviews, meta-analyses or commentaries).

Author, ref. and date	Study	No. of patients (median) age, sex	Type of e-cigarette	Specific treatments if present	Main outcomes	Hospitalization (days)
Lozier[43] 12/2019	Case Series	N = 2.291 24 yrs. 67% male	most THC-containing products	N/A	48 (2%) deaths of whom 54% male, median age 52 yrs.	Unknown
Sakla[44] 10/2019	Case Report	N = 1 25 yrs. Female	unknown	Azithromycin, ceftriaxone, levofloxacin, intubation, 3 weeks VV ECMO	ARDS, survived	>21
Casanova[45] 11/2019	Case Report	N = 1 31 yrs. Female	Nicotine salts	Ceftriaxone, azithromycin, methylprednisolone 40 mg daily, increased to 80 mg daily, after 12 days oral prednisolone tapering dose	Bilateral pneumonia with pleural effusion	12
Landman[46] 11/2019	Case Report	N = 1 17 yrs. Male	Flavored e-liquids and THC	Mechanical ventilation, VV ECMO, high-dose steroids	Life-threatening bronchiolitis Remaining limited exercise capacity and fixed airflow obstruction with gas trapping	47
Kalininskiy[47] 11/2019	Case Series	N = 12 27 yrs. (21-35)(21–35), 58% male, 42% female	92% THC 58% nicotine 8% cannabidiol	67% ICU admission Antibiotics (92%) Steroids (67%) High flow 50% Mechanical ventilation 8% BiPAP 8% Nasal cannula 33%	Bilateral GGO (100%) Pleural effusions (9%) Fibrotic features (18%) Mediastinal lymphadenopathy (27%) No deaths 50% resolution of previous chest CT findings and normal spirometry	7 (7–8)
Blagev[48] 11/2019	Case Series	N = 60 80% male, 20% female 27 years (22-6)	67% e-nicotine 78% THC, 48% both e-nicotine and THC, 5% e-cannabidiol oil	90% antibiotics 95% steroids 88% supplemental oxygen 47% high flow nasal cannula 28% NIPPV 17% mechanical ventilation 55% ICU admission	Pneumothorax and pneumomediastinum, SIRS, ARDS, chemical pneumonitis, hypersensitivity pneumonitis, inhalational injury, lung abscess, infected pneumatocele. 3% died (vaping considered a contributing factor but not the cause of death) 10% readmission rate to ICU or hospital < 2 weeks (of whom 50% relapsed with vaping) residual abnormalities on chest radiographs (67%) and lung function (67%) 29% discharged on supplemental oxygen	5 (3–8)

Table 1 (*Continued*)

Author, ref. and date	Study	No. of patients (median) age, sex	Type of e-cigarette	Specific treatments if present	Main outcomes	Hospitalization (days)
Davidson[22] 09/2019	Case Series	N = 5 18-35 yrs. (sex unknown)	THC (5), nicotine (3)	I.v. methylprednisolone (120—500 mg daily)	Lipoid Pneumonia No deaths N = 3 ICU, N = 1 mechanical ventilation	Unknown
Flower[17] 04/2017	Case Report	N = 1 33 yrs. Male	''Tsunami White Spirits vaporizer E-Liquid E-Juice''	Quit vaping	RB-ILD, resolution after cessation of vaping	N/A
Sommereld[10] 06/2018	Case Report	N = 1 Age 18 yrs. Female	Unknown	PICU admission Broad-spectrum antibiotics 40 mg methylprednisolone twice daily Mechanical ventilation for 5 days Vasopressor support with norepinephrine	Hypersensitivity pneumonitis and ARDS	Unknown
Moore[12] 09/2015	Case Report	N = 1 Age 43 yrs. Male	Unknown	2L nasal oxygen Antibiotics (not specified) Nebulized albuterol-ipratropium	Bilateral pneumonia and pleural effusions	2
Khan[13] 12/2018	Case Report	N = 1 Age 40 yrs. Female	Unknown	Steroids	Organizing pneumonia	Unknown
Agustin[16] 09/2019	Case Report	N = 1 Age 33 yrs. Male	Unknown	Steroids	Diffuse alveolar hemorrhage Symptoms improved with complete resolution of alveolar hemorrhage on chest CT scan after 2 weeks	Unknown
Khanijo[50] 12/2019	Case Series	N = 24 Age unknown	THC	Unknown	Unknown	Unknown

(*Continued*)

Author, ref. and date	Study	No. of patients (median) age, sex	Type of e-cigarette	Specific treatments if present	Main outcomes	Hospitalization (days)
Sharma[49] 10/2019	Case Report	N = 1 Age 35 yrs. Male	''Heavy Hitters – Cold filtering cartridge'', mixture of 89% active cannabinoids, 86% THC with ''distilled oil and terpenes''	Methylprednisolone 40 mg twice daily for 5 days followed by oral prednisolone Also, VATS with bleb removal and right-sided parietal pleurectomy	Chemical pneumonitis and pneumothorax Survived	Unknown
Buus[51] 10/2019	Case Report	N = 1 Age 23 yrs. Male	marijuana	Prednisone 60 mg in tapering dose, and doxycycline	Diffuse tree-in-bud and nodular infiltration Survived	Unknown
Qarajeh[52] 11/2019	Case Report	N = 1 Age 47 yrs. Male	THC	Methylprednisolone Iv furosemide Ceftriaxone, azithromycin, vancomycin, piperacillin-tazobactam, levofloxacin	Multifocal GGO and nodular opacities with interlobar septal thickening, small pleural effusion Survived	Unknown
Conuel[53] 11/2019	Case Series	N = 5 Age 36 yrs. (23–55) 80% male	CBD oils THC oils Marijuana	Methylprednisolone and oral corticosteroids	Bilateral GGO with subpleural sparing All survived	80% hospital/ICU admission (3–7 days) 20% supportive care at home
Abeles[54] 11/2019	Case Report	N = 1 Age 18 yrs. Male	THC oils	Azithromycin Levofloxacin BiPAP	Bilateral GGO Survived After admission slightly reduced diffusion capacity (DLCO/VA 61%)	25 d
Ocampo-Gonzalez[55] 11/2019	Case Report	N = 1 Age 20 yrs. Male	THC oils, nicotine and marijuana	Steroids	survived	Unknown
Triantafyllou[56] 12/2019	Case Series	N = 6 Age unknown 100% male	Cannabis and nicotine	Antimicrobial therapy and corticosteroids	Multilobar GGO with subpleural sparing	8d (median), ICU 2d (median)
He[40] 03/2017	Case Report	N = 1 Age 54 yrs. Male	Cannabis	Antimicrobial therapy, high flow oxygen therapy	Focal airspace opacities and centrilobular nodular pattern (tree-in-bloom)	5d

Table 2 Clinical presentations.

Physical examination	References
Temperature $\geq$38 °C	5,35,36,24,37,6,45,46,47,48,22
Auscultatory crackles	12,38,36,39,45,46
Auscultatory wheezing	12,13,38,24
Auscultatory squeaks	Case report
Hypoxemia SpO2 < 95% (ambient air)	10,12,13,38,40,16,5,35, 36,24,39,37,45,46,22
Heart rate >100 beats/min	10,13,6,45,46,47
Respiratory rate >20 breaths/min	10,12,13,38,40,5,45
Respiratory symptoms	
Cough	10,38,5,35,36,24,39,37, 6,45,46,47,48
Thoracic pain	10,12,13,5,35,37,6,47,48
Dyspnea	10,12,13,38,40,16,17,5, 35,36,24,39,37,6,45,46,47,48,22
Hemoptysis	40,16,5,47,48
GI Tract	
Abdominal pain	5,24,6,47,48,22
Nausea	38,5,24,37,6,47,48,22
Emesis	5,24,6,47,48,22
Diarrhea	5,37,6,47
Constitutional symptoms	
Weakness	36,24
Myalgias	24,45,47
Night sweats	35,24
Fatigue or malaise	5,24,45,47,48
Chills	5,36,24,6,47,48
Weight loss	5,24,6,48
Diaphoresis	12,5,24,47
Headache	38,48

Table 3 Radiological presentations.

Hypersensitivity pneumonitis (HP)[10]
Acute eosinophilic pneumonia (AEP)[41,42]
Pneumonia with pleural effusions[12]
Organizing pneumonia (OP)[13]
Acute lung injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)[38,40,5,15]
Diffuse alveolar hemorrhage (DAH)[16]
Respiratory bronchiolitis-associated pneumonitis (RB-ILD)[17]
Giant-cell interstitial pneumonitis (GIP)[14]
Acute lipoid pneumonia (LP)[39,37]
Bronchiolitis (our case report),[46]

Table 4 Pathology features.

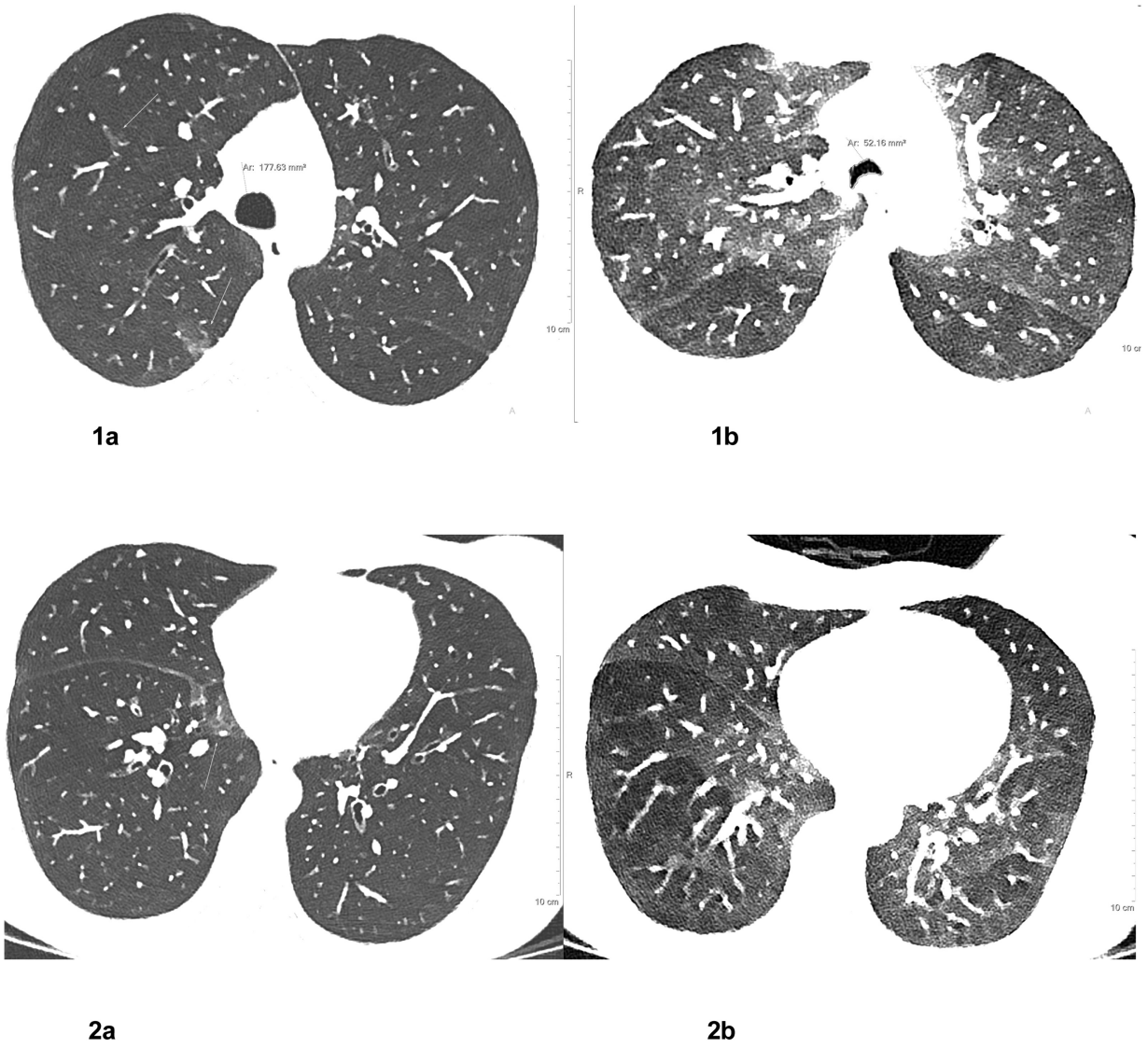
Cytology: bronchoalveolar lavage (BAL)	References
Lipid-laden macrophages	10,22,24,28,37,39,45,53,54,55
Foamy macrophages	28
Neutrophil predominant	10,16,24,28,53
Eosinophil predominant	42
Hemorrhagic	16,40
Non-diagnostic	17,35,40,46,48,49
Histology: Transbronchial biopsy (TBB)	
Acute alveolitis with intra-alveolar fibrosis	15
Diffuse alveolar damage (DAD)	28
Organizing pneumonia	28,40
Non-diagnostic	17,46
Histology: surgical biopsy	
Organizing pneumonia	13,28
Respiratory bronchiolitis-associated pneumonitis (RB-ILD)	17
Desquamative interstitial pneumonitis (DIP)	17
Diffuse alveolar damage (DAD)	24
Lipoid pneumonia	35

presence of HIV-related opportunistic respiratory infections if appropriate) must be negative''.[5]

In both ''confirmed'' and ''probable'' cases, there should be no evidence in medical record of alternative plausible diagnoses such as cardiac, rheumatologic or neoplastic process (Table 4).

Clinical presentations

According to data of the CDC, 95% (323/339) of patients diagnosed with VAPI initially experienced respiratory symptoms (e.g., cough, chest pain, or shortness of breath), and 77% (262/339) had gastrointestinal symptoms (e.g., abdominal pain, nausea, vomiting, or diarrhea).[6] As documented in the CDC data, gastrointestinal symptoms preceded respiratory symptoms in some patients.[6] Respiratory or gastrointestinal symptoms were accompanied by constitutional symptoms such as fever, chills, and weight loss in 85% (289/339) of patients to date.[6] Of these patients, 47% were admitted to the ICU, and 22% needed intubation and mechanical ventilation.[6] The clinical presentations are described in Table 2. On the other hand, there has been some concern about the association between the use of e-cigarettes and the reporting of a diagnosis of COPD in adults.[7] Perez et al. found a significant association between using e-cigarettes every day or only sometimes and the reported diagnosis of COPD, even after adjusting for the use of combustible tobacco products and other risk factors associated with this condition. The subgroup analysis showed an association between the use of e-cigarettes and reporting COPD among subjects 35 years and older, 45 years and older and 55 years and older. There were also increased odds of reporting a COPD diagnosis for a subgroup of respondents who only used e-cigarettes and no combustible cigarettes.[7] However, some results relating to the COPD development do not confirm this observation: One small 3.5-year prospective observational study, with nine daily e-cigarette users who had never smoked combustible cigarettes and a reference group of twelve smokers, did not show significant changes in blood pressure, heart rate, body weight, lung function, respiratory symptoms, exhaled breath nitric oxide, exhaled carbon monoxide nor high-resolution computed tomography findings in the lungs for both groups studied.[8] The length of the observation period is certainly important when studying the effects of irreversible airway obstruction.



Figs. 1 and 2 Lipid laden macrophages, Oil Red O staining. Chest CT 1 week after treatment onset: Corresponding axial CT images in inspiration (left row, Fig. 1a and 2a) and forced expiration (right row Fig. 1b and 2b) at 2 levels show small residual pulmonary ground-glass opacities (yellow arrows) in the medio basal right upper lobe and posterior right upper lobe, bronchial wall thickening, significant dynamic airways collapse (measurements of tracheal caliber, green) and mosaic attenuation with hypodense air trapping (images on the left).

Radiological presentations

The radiological patterns (Table 3) may depend on the frequency, dose and chemical characteristics of the inhaled substances, but also on the vaping device used.[9] Generally, chest CT-scans can demonstrate bilateral ground-glass opacities (GGO), with sparing of the lung periphery, and centrilobular ground-glass nodules. Also, a crazy-paving pattern can be seen. The following interstitial pneumonias have been described in VAPI cases;

a) **Hypersensitivity pneumonitis** has been described after vaping, in which the chest CT scan showed dependent opacities in both lung bases, with superimposed smooth interlobular septal thickening, and pleural effusions.[10]

b) **Acute eosinophilic pneumonia** has been shown to present with ground-glass opacity and pleural effusion in 133 (97%) patients and 121 (88%) patients, respectively.[11] Interlobular septal thickening and centrilobular nodules were present in 93 (68%) and 71 (52%) patients, respectively. Other findings were air-space consolidation in 51 (37%) patients and thickening of bronchovascular bundles in 24 (18%) patients. Interestingly, air-space consolidation was more frequently observed in patients with respiratory failure, and thus may be a prognostic marker of severity of the condition.

c) **Pneumonia with pleural effusions** has been described in a patient who had been smoking e-cigarettes for 3 days and had taken hundreds of puffs each day, using the electronic cigarette all day long without stopping until bedtime.[12]

d) **Organizing pneumonia** has been described after using e-cigarettes for 1 month, leading to respiratory failure with intubation and mechanical ventilation in a 40-year-old female.[13] The most typical findings are bilateral patchy ground-glass opacities, consolidation, or both in a peripheral or perilobular distribution.[14]
e) **Acute lung injury** and **Acute Respiratory Distress Syndrome (ARDS)** have also been associated with vaping and VAPI.[15]
f) **Diffuse alveolar hemorrhage (DAH)** has mainly been associated with cocaine and cannabis use unrelated to vaping practices. One case report has related DAH to vaping, in a thirty-three-year-old male presenting to the emergency department with worsening dyspnea and hemoptysis.[16] He admitted vaping for the past 2 months with overtly increased exposure time and had experimented new flavors. This male had no previous history of recreational drug use. The diagnosis of DAH was confirmed by bronchoscopy with BAL, ruling out other causes such as infection and vasculitis, and a right-sided wedge resection lung biopsy revealed bland pulmonary hemorrhage with no evidence of capillaritis or diffuse alveolar damage. Chest CT scan showed diffuse GGO and bilateral patchy consolidations, resulting in severe hypoxia requiring noninvasive ventilation. After treatment with corticosteroids the symptoms improved with complete resolution of alveolar hemorrhage on a chest CT scan two weeks after admission.
g) **Respiratory bronchiolitis-associated pneumonitis (RB-ILD)** was diagnosed in a 33-year-old male after 3 months of vaping while continuing to smoke 10 traditional cigarettes per day.[17] This patient had a 10 PY smoking history. Chest CT showed multiple new poorly- defined pulmonary nodules with fluffy parenchyma opacification along the terminal bronchovascular units. Video-assisted thoracoscopy with lung biopsy of the right upper and middle lobes were performed, with microscopical confirmation of the radiological findings of RB-ILD. This interstitial lung disease was clearly linked to e-cigarette use, since the patient had had multiple CT scans previously due to prior treatment of a mixed germ cell tumor. It had also been documented that during treatment with bleomycin and continued smoking of traditional cigarettes, the CT scans had never shown evidence for RB-ILD in any of his previous chest CT scans.
h) **Giant-cell interstitial pneumonia** is a pneumoconiosis from exposure to hard metal.[18] This rare diagnosis was made on the basis of findings in a surgical biopsy of the lung. The findings in this patient were attributed to hard metal (cobalt) contamination in her vape pen. The biopsy showed fibrosis characterized by peripheral reticulation, GGO and mild traction bronchiectasis. The patient's symptoms improved after cessation of vaping.[19] On the chest CT scan it is presented as GGO, architectural distortion and linear opacities in a peribronchiolar distribution.[20]
i) **Acute lipoid pneumonia (ALP)** has also been studied in pediatric patients with pneumonia caused by aspiration of oil-based substances. The predominant findings in chest CT scans were areas of consolidation. There were no case fatalities, and in the follow-up between 2 weeks to 6 months, all patients with clinical symptoms experienced remission. The CT scans of most of the cases had normalized by 1–3 months after the cessation of exposure with the exception for two patients who only showed complete improvement 6 months after treatment.[21] In e-cigarettes the inhaled aerosolized oils can be deposited in the distal airways and alveoli, leading to an acute lipoid pneumonia by provoking a local inflammatory response that impairs vital gas exchange.[22] Although not present in all cases, macroscopic fat attenuation within the consolidations (<-30 HU) are considered diagnostic for ALP.[14] Typically, CT scans show ALP findings in the dependent lung, including GGO, consolidation, crazy-paving, or a combination of these.[14]
j) **Bronchiolitis**, with signs of air-trapping, inspiratory squeaks on auscultation are described in our case report (see below).

Pathogenesis

In general, the e-cigarette aerosol particles contain droplets in the 200 μm size range.[23] Although only ultrafine particles, defined as particles smaller than 0.1 μm, have the ability to reach the blood circulation by passing through the lung tissue, the e-cigarette aerosol particles can at least reach the respiratory bronchioles which can lead to various outcomes.

Routes of aerosol particles

One possible route is removal by mucociliary clearance and phagocytosis by macrophages. In BAL samples macrophages have been shown to be lipid-laden, seen with Oil Red O staining (Fig. 3).[10] The pathophysiological significance of these lipid-laden macrophages and their relation to VAPI are not known, but they may be a useful marker of this disease.[24]

Alternatively, these particles remain in the lung tissue or reach the regional lymph nodes. The depositing and clearance of these particles occurs in an inhomogeneous manner.[25]

Pathophysiological responses

As yet, there is little information on the interaction of these particles with the pulmonary epithelium, regional lymph nodes, phagocytes or cytokines.

a) *Cytokine responses and oxidative toxicity*

One study showed measurable oxidative and inflammatory responses in lung cells, by exposure to vaporizing liquids, which caused in the human airway epithelial cells *in vitro* increased secretion of proinflammatory cytokines, such as IL-6 and IL-8, and lung fibroblasts exhibited stress and morphological changes.[26] Moreover, in response to a specific flavored liquid (cinnamon), the airway epithelium secreted increased IL-8, and cells were shown to be susceptible to loss of cell viability.[26] In mice, exposure of aerosols from e-cigarettes diminished lung glutathione levels, which are critical in maintaining cellular redox balance.[26] The oxidative toxicity and inflammatory response, due to radicals and alteration in glutathione levels, probably have

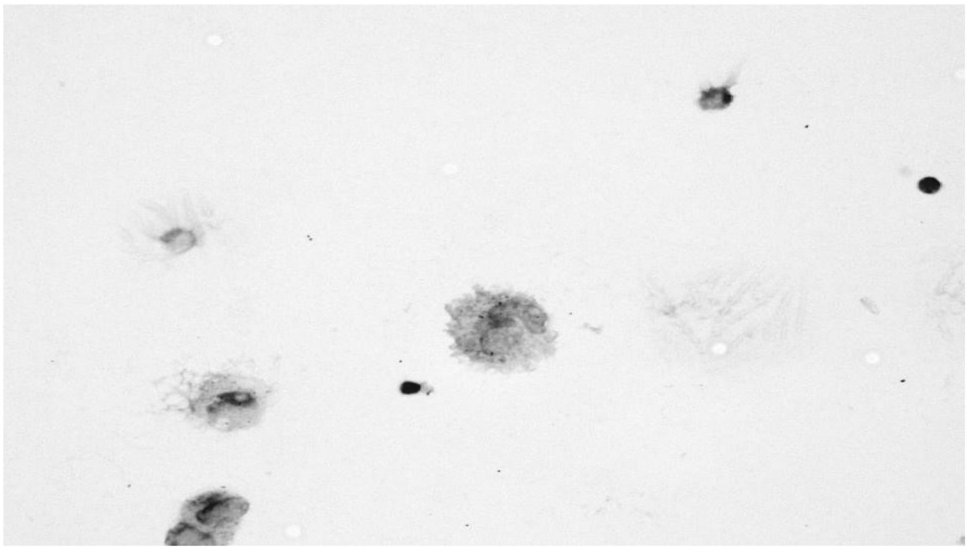


Fig. 3 Lipid-laden macrophages in bronchoalveolar lavage fluid. Oil Red O staining.

the same magnitude as in conventional tobacco cigarettes. The conventional cigarettes and e-cigarettes have approximately 10^{15} free radicals in a puff, as well as heavy metal nanoparticles. Although not proven yet, interaction of these particles with airway epithelium and phagocytes might lead to inflammation with clinically manifest flow limitation and chronic interstitial pulmonary fibrosis.

b) *Lung injury*

A recent study including lung biopsies (seven transbronchial, one surgical) showed acute lung injury including organizing pneumonia and/or diffuse alveolar damage.[27] Common features were fibroblast plugs, hyaline membranes, fibrinous exudates, type 2 pneumocyte hyperplasia and interstitial organization, with macrophages present within the airspaces in all cases.[27] Another study, reviewing the pathology of lung biopsies from 17 patients with confirmed or probable VAPI, showed histopathological patterns of acute lung injury, including acute fibrinous pneumonitis, diffuse alveolar damage, or organizing pneumonia, usually bronchiolocentric and accompanied by bronchiolitis.[28] There were foamy macrophages and pneumocyte vacuolization in all cases.

c) *Possible causative agents*

Although no definitive conclusions can be drawn yet, nicotine products, tetrahydrocannabinol (THC), cannabidiol (CBD) and vitamin E are among the most suspected ingredients with a strong link to the pathogenesis of VAPI. However, a recent animal study showed that propylene glycol, as ̈carrier fluidïn e-cigarettes, induced rapid lung damage in just 3 days of e-cigarette use.[29] In this study, mice were exposed to e-cigarette aerosols for two hours per day on three consecutive days. Comparable lung damage could be seen in mice inhaling e-cigarette aerosols with nicotine, and e-cigarette aerosols with only propylene glycol, showing that propylene glycol alone can lead to acute lung damage in mice. Female mice showed stronger inflammatory responses than males. Another study in mice has implicated nicotine as the cause for emphysema development.[30] This to date has not yet been reproduced. The rapid lung damage was also described in a case report of a former smoker, who started excessive vaping 3 days before presenting to the emergency department and developed a bilateral pneumonia with pleural effusions.[12] Recently, vitamin E has been found in BAL fluid samples (or samples of fluid collected from the lungs) from 29 patients with VAPI, while THC was found in 82% of the samples, and nicotine in 62%.[31] Interestingly, also two flavorants, diacetyl and 2,3-pentanediol, could interfere with cilia and cytoskeletal processes in normal human bronchial epithelial cells, by interaction with gene expression pathways in cilia and cytoskeleton.[32] The pathophysiology of VAPI remains largely unknown, but recent publications have helped to unravel some of the characteristic findings in these patients and vitamin E acetate seems to be one of the main culprit substances.

Diagnosis

The diagnosis of VAPI is a diagnosis of exclusion. Other diagnoses need to be excluded first.

a) *History and physical examination*

A detailed history is important and should include respiratory, gastrointestinal and systemic symptoms, smoking history, the vaping product (device), liquids and self-mixed liquids, especially asking for THC oils and possibly vitamin E containing products. On physical examination, beside vital signs including pulse oximetry, there can be signs of bronchial obstruction (wheezing) and bronchiolitis (end-inspiratory squeaks).

b) *Laboratory and microbiological investigations*

Laboratory investigations can be used to exclude other diseases and may show signs of infection. The routine investigation should include C-reactive protein and procalcitonin. In most patients generally there is a leukocytosis with predominant neutrophilia without eosinophilia, and an elevated C-reactive protein. Blood cultures, sputum Gram staining and sputum culture, arterial blood gas measurement should be considered. A urine drug screen, including testing for tetrahydrocannabinol (THC), as well as urine for *Legionella* and *Pneumococcus* antigen should be part of the routine examination if VAPI is suspected. A respiratory multiplex PCR (mPCR) to test for viral infections (depending on the season) including *Influenza virus*, may be considered for bronchoalveolar lavage fluid or nasopharyngeal swab or brush samples.

c) *Radiological imaging*

Radiologic imaging is mandatory, and at least one chest X-ray should be performed as an initial investigation. The chest X-ray can show bilateral infiltrates, sometimes additionally a pleural effusion. Interestingly, a case report of secondary spontaneous pneumothorax induced by vaping has been published[49] and in the study of Blagev et al. there was pneumothorax and pneumomediastinum in 11 (18%) of 60 patients with VAPI.[48] Since interstitial patterns can be very subtle or absent on chest X-ray examinations, a chest CT scan will be performed in most patients with progressive respiratory symptoms, especially when X-ray findings are discrete with a discrepancy to the severe clinical condition of the patient. The chest CT scan is useful to help choose the site of sampling during the bronchoscopy with bronchoalveolar lavage (BAL) or transbronchial biopsy. The chest CT scan also helps rule out other pulmonary diseases, such as infection or malignancy. If bronchiolitis is suspected, additional expiratory scans should be requested to document air-trapping.

d) *Bronchoscopy*

Bronchoscopy is useful to obtain pulmonary samples. However, depending on the condition of the patient, it may not be immediately possible and might lead to a further deterioration and intubation. Once intubated or on ECMO, bronchoscopy is advisable, since sampling results may help exclude or diagnose alternative diagnoses and thus influence treatment options. Bronchoscopy is likely to influence management of patients with atypical radiological findings, such as cavitation or large nodules, recent exposure to unusual pathogens, immunocompromised patients or in those already intubated. The decision when to perform a bronchoscopy will also depend on the clinical stability of the patient. In the series of Layden et al. only 45% of the patients underwent a bronchoscopy.[5] In addition to the standard BAL fluid analysis the Oil Red O or Sudan black staining should be considered in order to detect lipid-laden macrophages. The relevance of this finding is currently not known but it has been described in a number of VAPI cases.[24] In the case of DAH a Prussion blue iron staining should be considered.

e) *Clinical monitoring*

Hospitalized patients need frequent monitoring, as lung injury in VAPI can lead to rapid deterioration within 24—48 h. This is in line with the CDC recommendation, that patients, who are not admitted to the hospital, should be scheduled for follow-up within 24—48 h. In hospitalized patients, consulting a critical care specialist is advised, because the risk of rapid deterioration leading to admission to an intensive care unit (ICU) and subsequent need of intubation with mechanical ventilation is high. In the CDC report, there was a 47% ICU admission rate (159/342 patients) and a 22% mechanical ventilation rate (74/338 patients).[6]

Treatment

Treatment of VAPI has so far been largely empirical (Table 1). There are no published trials investigating the state-of-the-art treatment of VAPI. First of all, patients should immediately refrain from vaping. Secondly, patients should receive oxygen support as needed, by nasal cannula, an oxygen mask, high-flow nasal cannula, non-invasive ventilation, mechanical ventilation or even ECMO. Thirdly, high dose systemic corticosteroids (e.g. initially intravenous methylprednisolone, followed by 1 mg/kg prednisolone daily) should be considered (Table 1). As shown by the CDC data of 140 patients with corticosteroid treatment, there was clinical disease improvement in 82%.[6] Early initiation of antimicrobial coverage (e.g. cephalosporines i.v. and macrolides p.o.) for community-acquired pneumonia should always be considered for patients with severe clinical symptoms, as VAPI can be associated with concurrent respiratory infections. If clinically and/or radiologically suspected, monotherapy with macrolides may be a useful treatment option in case of bronchiolitis. In patients with severe bronchial obstruction, ipratropium/salbutamol inhalations will be useful. Prognosis is relatively good, even in severe disease, although fatalities have been described (see above). The mean duration of hospitalization overall was 6.7 days; in the age group of $\geq$ 51 years it was 14.8 days.[6]

Case report

A 44-year-old female former cigarette smoker with a 3 pack-year smoking history, was referred to our hospital because of severe dyspnea (mMRC 3–4), coughing with yellowish phlegm, wheezing and dyspepsia, not responding to high doses of corticosteroids and a trial of amoxicilline-clavulanic acid. She quit smoking by using a nicotine-containing liquid and a 3rd generation vaporizer.

The initial symptoms started two months after using e-cigarettes with nicotine-free liquids. The GP had been treating her for several months with high dose inhaled fluticasone propionate/formoterol, montelukast and multiple oral steroid courses, interpreting her symptoms as newly diagnosed adult-onset asthma, with spirometry showing an obstructive ventilatory pattern of variable severity (FEV1 ranging from 52%–102% on various occasions). She was afebrile and normotensive. Furthermore, lung auscultation revealed bilateral upper and lower zone end-inspiratory squeaks, suggesting a bronchiolitis. Pulmonary function tests showed a severe obstructive ventilatory defect (FEV1

0.94L, 42%), FeNO-measurement was attempted but was not feasible due to severe dyspnea. Blood gas showed a respiratory alkalosis with metabolic compensation, with relevant hypoxemia (pO2 7.3 kPa). The patient, who refused hospitalization, was instructed to stop vaping immediately. A 7-day course of azithromycin 500 mg once daily and salbutamol/ipratropium with an electrical nebulizer was initiated. The laboratory findings showed no elevated infection parameters (C-reactive protein <1 mg/l, no leukocytosis). At this time the patient was already on high dose systemic corticosteroids. The electrolytes, liver- and renal function were within normal limits. CT imaging, which was performed 7 days after presentation in our clinic and a 7 days abstinence from e-cigarettes, treatment with azithromycin, high dose oral corticosteroids and one intravenous methylprednisolone dose, demonstrated air-trapping and residual ground-glass opacities. (Figs. 1 and 2). Bronchoscopy showed lipid-laden macrophages by Oil Red O staining and normal eosinophils, neutrophils and lymphocytes in the BAL (Fig. 3). Transbronchial biopsy demonstrated local chronic inflammation with thickening of the basal membrane and fibroelastosis.

The respiratory multiplex PCR (mPCR), able to detect multiple respiratory viruses in a single assay, revealed a human metapneumovirus (hMPV) in the BAL specimen. Bacterial examination showed normal flora in both BAL and bronchial washes. After cessation of vaping, the initiated therapy including continued corticosteroids and the addition of azithromycin and salbutamol/ipratropium nebulisations, led to fairly rapid improvement of symptoms within 10 days, and the lung function showed complete normalization at follow-up.

Discussion

This paper provides an update on the current knowledge of VAPI and a case report of a probable case of VAPI in Switzerland. VAPI can present various degrees of severity and a variety of clinical and radiological patterns.

a) *VAPI classification according to CDC, Naranjo ADR and CTCAE*

Although not meant for clinical diagnosis, according to the case definition of the Centers for Disease Control and Prevention, the interstitial lung disease in our patient can be classified as a ''probable case'' of severe pulmonary disease associated with e-cigarette use.[5] In this patient, the 4 criteria of a ''probable case'' were met. First of all, the patient was using an e-cigarette within 90 days before symptom onset. Secondly, the chest CT shows ground-glass opacities. Thirdly a pulmonary infection was not the sole cause of the underlying respiratory disease process. The patient did not respond to broad-spectrum antibiotics and had severe dyspnea, with a discrepancy between the severe dyspnea and the amount of the pulmonary ground-glass in the chest CT. The bronchoalveolar lavage culture was negative for bacteria and viruses except for detection of hMPV. There is no evidence in the medical record of alternative plausible diagnoses such as cardiac, rheumatologic or neoplastic processes.

In addition, on the Naranjo ADR Probability Scale, used for scoring the risk of adverse drug reactions (ranging from Score 0, D̈oubtfulẗo Score 9 Ḧighly Probable¨), the e-cigarette would be classified as Score 3 (Possible).[33]

The severity of the dyspnea would be classified as Grade 4 (severe) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 of the U.S. Department of Health and Human Services.

b) *Acute bronchiolitis in VAPI: potentially life-threatening*

The diagnosis of VAPI remains challenging. Specific clinical, laboratory, radiological or bronchoscopic findings have not yet been identified, despite analysis of many aspects so far, and many symptoms are similar to those of other lung conditions. In this respect the clinically and radiologically detected signs of bronchiolitis in our patient might be of special interest. The e-cigarette aerosol particle distribution is not homogeneous. Especially in the respiratory bronchioles, concentrations typically are 25–100 times the concentration seen in the mainstem bronchus, and similarly, in one publication,[34] high concentrations were found in the large airway carinas. Extremely high concentrations of e-cigarette aerosol might have provoked the clinical manifestations of bronchiolitis, which was the striking finding in our patient at presentation in our clinic. The patient had a productive cough, and the e-cigarette particles could have interacted with airway mucus secretion, further increasing local inflammatory responses resulting in airway obstruction. Bronchiolitis has also been an important histopathological pattern found in lung biopsies of patients with VAPI.[28] Acute bronchiolitis in VAPI is very rare. There is recent case publication of a 17-year-old patient with a life-threatening bronchiolitis related to electronic cigarette use, which was treated with ECMO.[46]

c) *Additional investigations in VAPI*

As reported in literature, laboratory findings in patients with VAPI are non-specific. Many patients show elevated infection parameters, such as leukocytosis and elevated C-reactive protein or erythrocyte sedimentation rate. However, our patient had been pretreated with multiple courses of high doses of corticosteroids and also short courses of antibiotics which possibly explain the absence of systemic inflammatory signs. Another explanation could be the abnormal behavior of inflammatory markers in VAPI. High false positive rates of procalcitonin and C-reactive protein has been observed in VAPI, limiting the use as infection parameter. It has been shown to normalize relatively rapidly and has been suggested as a supplementary diagnostic tool in the evaluation of patients with VAPI.[50]

Radiological findings can show a wide variety of lung injury patterns as discussed above (Table 3).[20] In the study of Layden et al., patients with VAPI showed an abnormal chest radiograph in 91%.[5] In our patient, after cessation of e-cigarette use no specific radiological pattern could be diagnosed, with the exception of ground-glass opacification in the mediobasal right lower lobe and diffuse air-trapping.

Bronchoscopy with BAL and/or transbronchial biopsy, should be performed to rule out infection, if the condition of the patient allows these investigations. In our patient, bron-

choscopic findings are in line with the literature, reporting a median neutrophil value of 65% (range, 10–91) and a total of 7 of the 14 cytology reports on BAL specimens noted lipid-laden macrophages with Oil Red O stain, as observed in our patient.[5]

Although there is a continuing effort in this area, the elucidation of the pathogenetic mechanisms is an unmet need and is key to guiding treatment decisions. In the meantime, healthcare providers should strongly discourage patients from using these heavily marketed devices and warn their patients of the dangers of VAPI. While there is limited evidence that e-cigarettes are an effective strategy to quit smoking, there are alternative evidence-based methods that are safe and effective.

In summary, we describe the clinical and radiological presentations of VAPI cases published to date with a summary of the likely pathogenetical mechanisms leading to this clinical syndrome. The current treatment strategies used so far to address those patients presenting with signs of respiratory failure are summarized. We report a case of probable VAPI, presenting with symptoms and imaging compatible with a bronchiolitis with a complete recovery, following cessation of vaping in combination with corticosteroid, azithromycin and symptomatic treatment measures to address the imminent respiratory failure and severe airway obstruction in a previously healthy woman.

Conclusion: the authors' view

Some patients experience negative pulmonary and systemic adverse effects from using vaping devices. The definitive causative agent has yet to be determined. A number of possible culprit factors (including vitamin E acetate) have been suggested and empirical treatment strategies have emerged including cessation of vaping, corticosteroid, anti-infective and supportive measures.

Conflicts of interest

The authors have no conflicts of interest to declare.

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REVIEW

The impact of exercise training on fatigue in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis

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KEYWORDS
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Abstract
Introduction and Objective: Fatigue can be divided in perceived fatigue, the feeling of exhaustion or lack of energy, and performance fatigue, the reduction in muscle force/activation during a given task. This meta-analysis evaluates the impact of exercise training on fatigue, compared with normal care in patients with COPD.
Material and Methods: We searched randomised controlled trials on MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL databases from their inception to December, 31st 2019 using the terms COPD, Fatigue, Fatigability, Muscle activation, Muscle endurance, Muscle Performance, Voluntary Activation, Motoneuron excitability, Force Development, Exercise, AND Rehabilitation.
Results: We evaluated 494 potential articles. Sixteen, all evaluating perceived fatigability, satisfied the inclusion criteria and were included. Twelve studies (463 patients) assessed fatigue by the Chronic Respiratory Questionnaire showing that intervention improved significantly more than the control group [SMD 0.708; 95% CI 0.510, 0.907; $p < 0.001$; $I^2 = 34.3\%$; $p = 0.116$]. Two studies (68 patients) using the Fatigue Impact Scale, did not find any significant differences between groups [SMD −0.922; 95%CI −2.258, 0.413; $p = 0.176$; $I^2 = 83.9\%$; $p = 0.013$]. Two studies (82 patients) assessed perceived fatigue by the Fatigue Severity Scale: the intervention improved significantly more than the control group [SMD −2.282; 95%CI −2.870, −1.699; $p < 0.001$; $I^2 = 64.6\%$, $p = 0.093$]. No study evaluating performance fatigue was found.

Abbreviations: SMD, Standardized Mean Difference; CI, Confidence Interval.

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Conclusions: This study provided low-quality evidence of a positive impact of different exercise training programs on perceived fatigue in patients with COPD. Further studies are needed to assess the effects of exercise training on fatigue and to test tailored programs.

Introduction

More than half of patients with chronic obstructive pulmonary disease (COPD) experience fatigue which may have a substantial impact on functional impairment, physical activity, health related quality of life (HRQL), mortality, morbidity, hospitalization rate and length of hospital stay.[1,2] Lower limb muscles of patients with COPD may show reduced endurance capacity and are more prone to fatigue, due to disuse, the presence of limb muscle dysfunction,[3] and exercise vasoconstriction induced by respiratory muscle fatigue.[4,5] These mechanisms may be responsible for the onset of the symptom fatigue during daily life.[6]

It can be divided into perceived fatigue or performance fatigue.[7] The first one is a normal response to exercise or stress, a multidimensional perception defined as ''the subjective feeling of tiredness, exhaustion or lack of energy, which occurs on a daily basis''.[7] However, fatigue may also occur during the performance of a given task, and is defined as performance fatigue: an objective and measurable domain, consisting of the reversible reduction in force generated by the muscles during a given task[8] such as a constant load exercise.[9] It could be distinguished as central, defined as a progressive reduction in the voluntary activation of muscle during exercise,[10] and peripheral fatigability, described by the reduction of muscle activation in or distal to the neuromuscular junction.[11]

The reduction of fatigue should be one of the aims of comprehensive management of patients with COPD.[12] Exercise training is strongly recommended in COPD, being effective in reducing dyspnoea and improving exercise capacity and HRQL.[13–15] However, the effects of exercise training on fatigue as a primary aim in patients with COPD have been rarely studied,[16,17] and to the best of our knowledge, there is no systematic review of the literature about the effectiveness of exercise training on fatigue in patients with COPD.

Therefore, the aim of this systematic review and meta-analysis of randomized controlled trials (RCTs) in patients with COPD, was to evaluate the impact of interventions including exercise training on perceived and performance fatigue, as compared to ordinary care or education alone.

Methods

This study conforms to all Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and reports the required information accordingly (Supplementary Checklist, http://links.lww.com/PHM/A364).

Data sources and search strategies

We searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature, from their inception to December, 31st 2019, with no language restriction. We also reviewed the references of retrieved articles for additional studies. The search was limited only to RCTs using the terms: COPD, Fatigue, Fatigability, Muscle activation, Muscle endurance, Muscle Performance, Voluntary Activation, Motoneuron excitability, Force Development, Exercise, and Rehabilitation.

Patients

We included RCTs involving patients with COPD according to the Global Initiative for Chronic Obstructive Lung Disease recommendations in all stage of severity.[18] We excluded studies involving patients with (1) an acute exacerbation within 4 weeks before starting the intervention; (2) major comorbidities such as chronic heart failure, asthma, and sleep-related disorders.

Interventions

We included studies administering exercise training programs, with the following characteristics:

- Involving in- or out-patients, and home- or community-based programs;
- Programs of 2 week minimum duration;
- Endurance and/or strength training of lower and/or upper limbs;
- Comparing exercise training with usual care, (defined as conventional medical care without any prescription of exercise training or physical activity) and/or education.

Outcome measures

We included any study assessing:

- Perceived fatigue: by means of scales or questionnaires evaluating subjective perception of fatigue;
- Performance fatigue: by means of objective measures evaluating changes in muscle performance after a fatiguing task such as muscle force or electromyography trace during a maximal voluntary contraction (MVC) or stimulated muscle resting Twitch.

Data collection and analysis

Two investigators (LB, MP) independently conducted the search of the databases, screening all titles and/or abstracts for the inclusion criteria. Reviewers then retrieved abstracts and/or full-text papers of all potentially eligible studies and maintained records of all studies not meeting the inclusion criteria. They also provided the reasons for their exclusion.

The investigators inserted the data of potentially eligible articles in a Microsoft Excel (2013 version, Microsoft, Redmond, WA) dedicated database. Disagreement between investigators about eligibility was resolved by discussion and consensus. If consensus could not be reached, a third investigator (MV) adjudicated. All data were checked for accuracy. Missing data were requested by e-mail to the authors. An investigator (LB) retrieved the full-text of the included studies and inserted their data into a dedicated electronic database. Another investigator (MP) independently extracted data from the same studies.

The information collected included the background characteristics of the research reports: characteristics of participants in the study; number of participants who dropped out or withdrew from the study; a full description of the exercise training programs (setting, components, duration, and characteristics); assessments, and associated results. If a study reported multiple group comparisons (e.g., exercise training plus free walking vs exercise training alone vs conventional care), treatment groups performing exercise that could be relevant to outcomes were combined into one virtual intervention group, and this group was compared to the group receiving conventional care.

The investigators assessed papers for bias using the Cochrane Collaboration's tool for assessing risk of bias in RCTs.[19] Risk of bias was assessed according to the following domains: sequence generation; allocation concealment; blinding of participants; blinding of personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting, and other biases.

Statistical analysis

Statistical analysis was performed using STATA version 11.2 software (Stata, College Station, TX). All data were extrapolated from the corresponding full-text studies. For outcome, we recorded mean and standard deviation (SD) of variation from baseline to the end of the study. When SD was not available, we calculated them from standard errors, confidence intervals, or t-values or contacted the trial authors by email for clarification. We excluded studies with data other than mean and SD.[20]

The standardized mean difference (SMD) was calculated. Heterogeneity of studies was assessed by performing the Q-test considering values of $P < 0.01$ as significant. The first step of the evaluation was conducted by fixed-effect models using the Mantel-Haenzel method. If a significant heterogeneity among studies was found, a random effect evaluation by the Der-Simonian and Laird method approach was performed.[21] Forest plots were used to detect publication bias for meta-analysis evaluation including more than 8 studies.[22] For the meta-analysis, only the outcome measures included in at least two studies were analysed.

Table 1 Demographic, anthropometric and clinical characteristics of included patients.

Clinical characteristics	No. studies (No. Participants)	Pre-intervention Mean (SD)
Age, years	15 (596)	64.2 (7.7)
BMI, kg/m^2	7 (288)	27.7 (4.7)
FEV_1, % of predicted	13 (481)	45.6 (15.2)
FVC, % of predicted	4 (168)	63.6 (15.6)
FEV_1/FVC, % of predicted	6 (249)	47.0 (11.1)
RV, % of predicted	4 (173)	165.5 (44.1)
PaO_2, mm Hg	3 (124)	72.5 (8.0)
$PaCO_2$, mm Hg	3 (124)	42.8 (5.6)
MIP, % of predicted	2 (86)	77.7 (26.7)
MEP, % of predicted	2 (86)	65.9 (19.3)
6MWT, m	8 (315)	348.3 (77.1)
CRQ fatigue domain	9 (348)	11.1 (3.4)
FIS units	2 (68)	53.5 (32.3)
FSS units	2 (82)	45.3 (11.1)
CAFS units	1 (65)	53.8 (17.1)
SGRQ units	4 (143)	52.6 (14.8)

BMI, Body Mass Index; FEV_1, Forced Expiratory Volume in the 1st second; FVC, Forced Vital Capacity; RV, Residual Volume; MIP, Maximal Inspiratory Pressure; MEP, Maximal Expiratory Pressure; CRQ, Chronic Respiratory Questionnaire; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; CAFS, COPD and Asthma Fatigue Scale; SGRQ, St. George's Respiratory Questionnaire.

Results

We identified 494 potentially relevant articles. Of these, 405 were excluded after the abstracts were read and 89 full-texts were analysed for inclusion criteria. Sixteen out of the 48 studies evaluating perceived fatigue satisfied the inclusion criteria and were included in the meta-analysis[23–38] (Fig. 1). No study out of the other 41 evaluating changes in performance fatigue satisfied the inclusion criteria.

Table 1 shows the baseline characteristics of the included subjects. They suffered from moderate-to-severe COPD. Table 2 shows the main characteristics of all interventions carried out in the studies included.

Settings

Seven studies[24,26,28,32–34,36] were conducted mainly in an out-patient setting, six at home [25,27,30,31,37,38] and three studies[23,29,35] in both settings.

Schedules

The total duration of programs ranged from 6 to 24 weeks. There were two to seven sessions per week. The duration of each session ranged from 30 to 90 min in eleven studies[23–28,30,32,33,35,36] and lasted two and a half hours in one study.[34] Four studies[29,31,37,38] did not report any duration.

Table 2 Characteristics of the interventions.

Reference	Duration, weeks	Withdrawal/ dropouts	Participants, n	Intervention and Control	Intervention Details
Wijkstra[23]	12	2	28	Intervention: outpatient (2 days/week) and home based cycle ergometer and upper limb training, 2 times/day +inspiratory muscle training and education session	30 min of training; cycling at 60% of Wmax, gradually extended to a maximum of 75% of Wmax
			15	Control: usual medical care	
Cambach[24]	12	23	15	Intervention: outpatient training, 3 days/week + education session	90 min of cycle ergometer/rowing machine/stair-walking training (twice a week) at 60–75 % Wmax; 45 min of recreational activities such as swimming/cycling/hockey (once a week)
			8	Control: usual medical care	
Larson[25]	16	77	28	Intervention: cycle ergometry training at home, 5 days/week + Inspiratory muscle training	Interval training protocol with 4 work sets of 5 min separated by rest intervals (2–4 min); intensity of 50% of peak work rate, evaluated weekly with progressive increases as tolerated
			12	Control: education	
Guell[26]	24	13	24	Intervention: cycle ergometer training, 5 days/ week + breathing exercise ad education session	30-min of cycle ergometer at 50% of the maximal load (Wmax); load increased in increments of 10 W provided according to symptoms
			23	Control: usual medical care	
Hernandez[27]	12	23	20	Intervention: home-based walking training, 6 days/week	1 hour of walking raining at 70% of the maximum speed attained in the SWT
			17	Control: usual medical care	
Man[28]	8	8	18	Intervention: aerobic and strength training, 2 days/week + education session	1 hour walking/cycling and strength training for the upper and lower limb
			16	Control: usual medical care	
O'Shea[29]	12	10	20	Intervention: resistance exercise, 3 days/week (1 at hospital, 2 at home)	6 resistance exercises against elastic bands of increasing resistance; 3 sets of 8 to 12 repetition maximum
			24	Control: usual medical care	
Moore[30]	6	7	10	Intervention: video exercise at home, 4 days/week + education session	30 min of upper and lower limb strengthening and aerobic exercise
			10	Control: usual medical care	

Table 2 (*Continued*)

Reference	Duration, weeks	Withdrawal/ dropouts	Participants, n	Intervention and Control	Intervention Details
Ghanem[31]	8	0	25	Intervention: home-based endurance and strength training, 7 days/week + breathing exercise	Walking/cycling training + 6–10 upper-body and lower-body strength exercises with
			14	Control: usual medical care	
McNamara[32]	8	8	30	Intervention: water-based and land-based exercise, 3 days/week	60 min of exercise at intensity rating of 3–5 on modified Borg scale for dyspnea and perceived
			15	Control: usual medical care	
Roman[33]	12	21	36	Intervention: Low intensity peripheral muscle training and breathing exercises, 3/week + education program	15 minutes breathing exercises and 45 minutes of abdominal and upper and lower limb exercises
			14	Control: usual medical care	
Wadell[34]	8	7	17	Intervention: graduated exercise training for upper and lower limbs, 3 days/week + education session	2.5 hours of graduated walking/cycle ergometer training, arm ergometer and strength exercises for upper and lower limbs, at highest attainable work rate for the longest tolerable duration
			24	Control: education	
Theander[35]	12	4	12	Intervention: multidisciplinary pulmonary rehabilitation programme, 2 days/week + home training programme	10–15 minutes of bicycle training + strength exercise
			14	Control: usual medical care	
Duruturk[36]	6	5	29	Intervention: all-body callisthenic exercise and cycle ergometer training, 3 days/week + education session	20/45 min of exercise and 20–30 min of continuous cycling at 50–70% of VO2max; intensity adjusted to maintain a perceived difficulty level of 4–7 on the Modified Borg Scale
			13	Control: education session	
Arslan[37]	8	15	32	Intervention: individualized exercise home program + walking program, 3 days/week	Walking outdoors on a flat surface
			33	Control: usual medical care.	
Mohammad[38]	7	0	20	Intervention: home-based training program, 3 days/week+ breathing exercise and education session	Walking training
			20	Control: usual medical care	

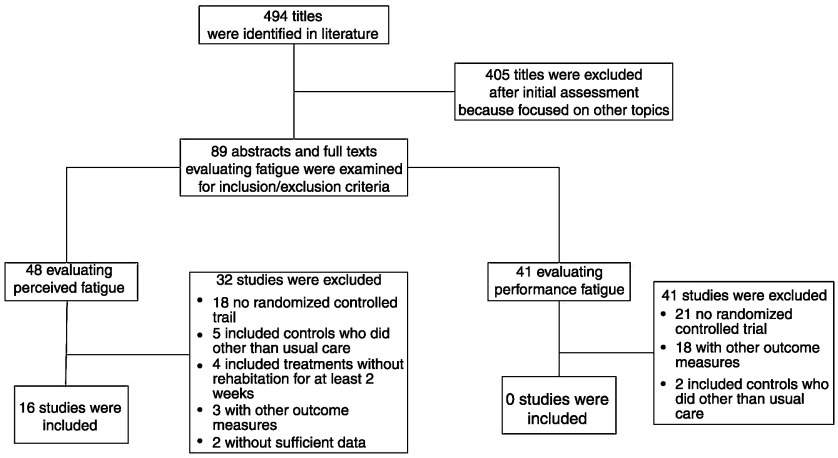

Figure 1 Flow chart of the study.

Interventions

Thirteen studies included exercise training of locomotor muscles: cycling in five studies,[23,25,26,35,36] walking in three[27,37,38] and a combination of these in five.[25,28,31,32,34] In three studies the intervention consisted only of calisthenics exercises.[29,30,33]

All the studies included endurance training. The intensity ranging from 50% to 75% of either the maximum workload or oxygen consumption (VO_2) reached during incremental tests in five studies.[23–26,36] McNamara et al.[32] used the Borg scale[39] to set the intensity of the exercise (from 3 to 5 on modified Borg scale) and Hernandez et al.[27] used the 70% of the maximum speed attained in the Incremental Shuttle Walking test (ISWT);[40] nine others studies[28–31,33–35,37,38] reported no training intensity.

In six studies[23,24,26,34,35,36] patients performed continuous training on a cycloergometer, while only one[25] used the interval training.

Additional components of exercise training

In four studies[26,31,34,38] breathing exercises were administered in addition to the exercise program (e.g.: pursued lip breathing and diaphragmatic breathing). In eleven studies[23–26,28,30,33–36,38] educational sessions were also administered. Inspiratory muscle training was added in two studies[23,25]

Outcomes

Twelve studies[23–34] (463 patients: 271 study group and 192 controls) evaluated perceived fatigue by means of the dedicated domain of the chronic respiratory questionnaire (CRQ).[41] Only in three studies[35,37,38] (18.8%) was fatigue measurement the primary outcome. Fig. 2-Panel A shows the related forest plot: the intervention improved significantly more than the control group [SMD 0.708; 95% CI 0.510, 0.907; $p < 0.001$; $I^2 = 34.3\%$; $p = 0.116$]. Figure 1SM describes funnel plot for studies on fatigue item in CRQ.

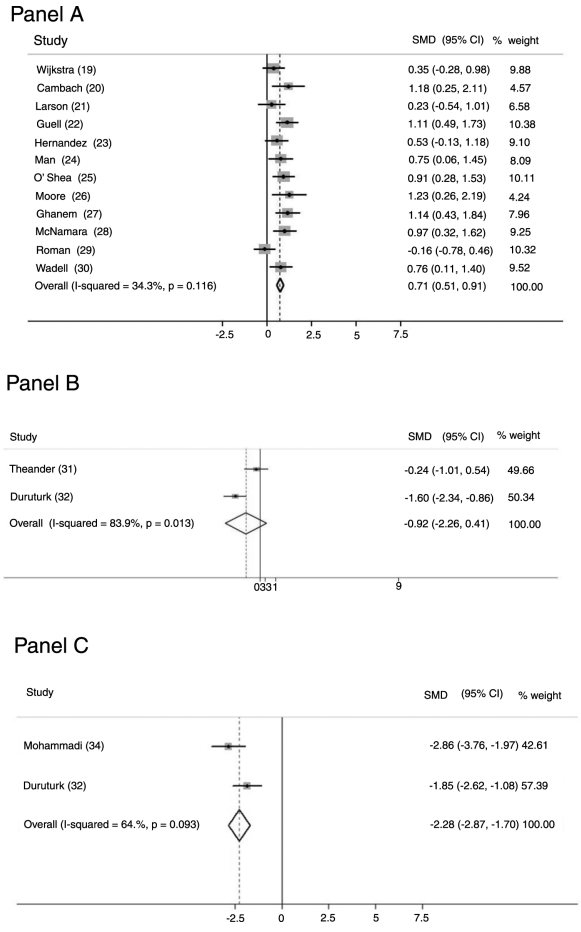

Figure 2 Forest plot of effect of training on: fatigue item in CRQ scale (Panel A), Fatigue Index Scale (Panel B) and Fatigue Severity Scale (Panel C).

Two studies[35,36] (68 patients: 41 study group and 27 controls) used the Fatigue Impact Scale (FIS), which examines patients' perceptions of their limitations caused by fatigue on the cognitive, physical, and psychosocial domains.[42] Fig. 2-Panel B describes the related forest plot: owing to the high heterogeneity in the ''fixed analysis

model'' (P = 0.0001), a random effect model was performed. No differences between intervention and control group were found. [SMD-0.922; 95%CI −2.258, 0.413; p = 0.176; I^2 = 83.9%; p = 0.013].

Fig. 2-Panel C describes the forest plot for two studies[36,38] (82 patients: 49 study group and 33 controls) assessing fatigue by the Fatigue Severity Scale **(**FSS), a 9-item scale assessing disabling fatigue. Each question evaluates patients' perception in the form of 7-point modified Likert Scale.[43] The intervention group improved significantly more than the control group [SMD -2.282; 95%CI −2.870, −1.699; p < 0.001; I^2 = 64.6%, p = 0.093]. Only one study[37] used the COPD and Asthma Fatigue Scale.[44]

Risk of bias

The assessment of the risk of bias by funnel plots on CRQ revealed high variability in the results of the included studies. Table 3 shows results of the risk of bias assessment. Half of the studies[23,25,27,28,31,33,34,38] did not report any detail on randomization and allocation modalities, and there was a high detection bias rate. Almost all studies included showed a high risk of bias for the blinding of participants and personnel.

Discussion

This systematic review investigated the current evidence of exercise training on fatigue in patients with COPD. The analysis of the 16 RCTs included evaluating the effects on perceived fatigue[23–38] showed high heterogeneity of study design, patient sampling, exercise training schedules, and outcome measures assessed. All studies showed a high risk of bias. As a whole, the studies showed low-grade evidence of positive effect of exercise training on perceived fatigue. No study evaluated the effects on performance fatigue.

Fatigue is an important debilitating symptom affecting all chronic respiratory diseases, including COPD. A four-year observational study on fatigue in patients with COPD reported that severe fatigue doubled in patients with mild to severe COPD despite optimal care.[45] Fatigue is a leading cause of consultations with major clinical implications. Despite its well-acknowledged negative impact on patient's life, fatigue is still a misunderstood and underdiagnosed symptom in COPD. As a consequence, there is currently no specific intervention to treat all aspects of this symptom which is quite often considered a secondary outcome in interventions aiming primarily to increase physical fitness and/or HRQL.[46]

Spruit et al.[9] have proposed a model of fatigue in patients with COPD. Moderate to severe fatigue can be the results of systemic, physical, psychological and behavioural factors. Fatigue can be precipitated by infectious COPD exacerbation and its treatment. This model suggests that the fatigue of these patients is not simply the result of COPD and cannot be predicted by the sole degree of airflow obstruction but would be the consequence of multiple factors that may act alone or in interaction, at rest and during/after exercise.[10]

Rather interestingly in our systematic review, the positive impact of pulmonary rehabilitation on perceived fatigue was found in studies using the CRQ and the FSS but not the

Table 3 Risk of bias assessment.

Bias	Random sequence	Allocation	Blinding of participants	Blinding of outcome	Incomplete	Selective	Modified by Jadad Scale
Wijkstra[23]	Low	Unclear	High	High	Low	Low	2
Cambach[24]	Low	Low	High	High	Low	Low	3
Larson[25]	Unclear	Unclear	High	Low	Low	Low	2
Guell[26]	Low	High	High	Low	Low	Low	2
Hernandez[27]	Low	Unclear	High	Low	High	Low	2
Man[28]	Low	Unclear	High	High	Low	Low	3
O'Shea[29]	Low	Low	High	Low	Low	Low	3
Moore[30]	Low	Low	High	High	Low	Low	3
Ghanem[31]	High	Unclear	High	High	High	Low	1
McNamara[32]	Low	Low	High	Low	Low	Low	3
Roman[33]	Low	Unclear	High	Low	Low	Low	3
Wadel[34]	Unclear	Unclear	High	Unclear	Low	Low	2
Theander[35]	Low	Low	High	High	Low	Low	3
Duruturk[36]	Unclear	Low	High	Unclear	Low	Low	2
Arslan[37]	High	High	High	High	Low	Low	1
Mohammadi[38]	Low	Unclear	High	Unclear	High	High	2

FIS. Antoniu and Ungureanu[46] identified 8 multidimensional scales which are commonly used to assess fatigue in COPD but 75% of RCTs included in our analysis evaluated fatigue by means of the dedicated domain of the CRQ.[41] Houben-Wilke and colleagues recently showed that the item 'energy' of the COPD assessment test improves with the greatest effect on size after pulmonary rehabilitation.[47] A commonly used multi-dimensional scale to evaluate fatigue is the subjective fatigue subscale of the checklist individual strength (CIS-Fatigue)[48] and Peters and colleagues reported a significant mean improvement in CIS-Fatigue score following 12-week of pulmonary rehabilitation in patients with COPD.[49] The use of different tools in papers prevents accurate comparisons between studies as the scores produced by the scales show poor to moderate correlations between them.[50]

It should be noticed that we analysed exercise training, just one (although the main) component of pulmonary rehabilitation which is a comprehensive multidisciplinary intervention including, but not limited to it.[13] Therefore the results of our systematic review should not be generalised to pulmonary rehabilitation programs.

On the subject of performance fatigue, it is rather interesting to note that, despite the fact that there are some observational studies describing high prevalence in patients with COPD,[51] we were unable to include any RCT of the effects of exercise training on this impairment.

Different tests have been used to evaluate performance fatigue, which depends on the ability of the peripheral muscles and the central nervous system to meet the demands of a prescribed task. Both systems can exhibit abnormal changes in response to exercise and contribute to increased performance fatigue:[52,53] we can test it by the changes in stimulated resting Twitch for peripheral involvement and by MVC for the central ones.[53] Thereafter, specific methods to train the muscles and reduce the central and/or peripheral component of performance fatigue, such as the maximal strength training[54] or neuromuscular electrical stimulation,[55] should also be thoroughly investigated in subjects with COPD.

Conclusion

This systematic review has provided low-quality evidence of a positive impact of different exercise training programmes on perceived fatigue in patients with COPD. Further studies with better standardisation and scientific validity are needed to assess the effects of exercise training on fatigue and to test dedicated programs. No study of the efficacy of exercise training on performance fatigue was found.

Authors' contributions

LB, MP and CS contributed to data acquisition; LB, MP and CS contributed to data analysis; MP, MVi, MVe, CS, SS, FS and NA prepared article draft or critically revised it for important intellectual content; all authors gave contribution to conception and design, data interpretation, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material associated with this article can be found in the online version available at doi:https://doi.org/10.1016/j.pulmoe.2020.02.004.

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LETTER TO THE EDITOR

Treatment of lung cancer during pregnancy

Cancer treatment during pregnancy is a rare challenge. It is defined as the cancer diagnosed from the first day of childbearing to 1 year postpartum.[1] The incidence is approximately 1 in 1000 pregnancies[2] and in Europe annually 3000–5000 patients are diagnosed with this condition.[3] Cancer is the second leading cause of mortality in women aged 25–39 years.[4] The most frequently diagnosed cancers are those more commonly seen during the reproductive age of a woman, particularly breast cancer, cervical cancer, Hodgkin's disease, melanoma and leukemias.[5]

Worldwide, lung cancer remains the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018.[6] Tabaco use is, by far, the most important risk factor for lung cancer, being responsible for 70% of global lung cancer deaths.[7] Although lung cancer counts as one of the most common malignancies, it represents a rare tumour during gestation.[8] However, such an association is expected to rise due to delayed pregnancies as well as the increased cigarette consumption by women in developed countries.[9] In the literature, there are few cases of lung cancer during pregnancy described. Most of them are non-small cells.[10,11]

Treating a pregnant woman with cancer requires a delicate balance between maternal benefit and fetal risk.[12] The general golden rule in the management of pregnant women with cancer diagnosis is the treatment should not differ between pregnant and not pregnant women, if this is feasible.[1] The treatment goals for a pregnant woman are to try to increase survival of the mother, to treat the curable malignant disease of pregnant women and to protect the fetus and the newborn from the ill effects of cancer treatment.

Making a decision can be more difficult when cancer is at an advanced stage at diagnosis and no curative treatment is available. It is necessary to consider various factors related to treatment. The administration of chemotherapy during gestation can cause harmful effects to the fetus and to the mother. For the fetus the detrimental effects include malformations, teratogenesis, mutations, carcinogenesis, organ toxicity and retarded development; for the mother, they include spontaneous abortion and sterility,[2] along with all the other adverse effects and current challenges of chemotherapy treatment, in this case in pregnant women.

Given the lack of safety profile studies of the different chemotherapy regimens and target therapies during pregnancy, it is essential to report clinical cases and to share evidence about the use of antineoplastic therapies during the gestation period.[11]

A 32-year-old woman, 27 weeks pregnant, non-smoker, no family history of cancer, was admitted to the emergency department with complaints of dry cough with 2 months of evolution. On examination she had palpable cervical adenopathy. Thoracic CT revealed left lower lobe mass with 4 cm, multiple small diffuse round nodules and bilateral mediastinal adenopathies (Fig. 1a and b). Cervical lymph node fine-needle aspiration biopsy revealed adenocarcinoma, consistent with metastatic lung cancer [positive for cytokeratin 7 (CK7) and thyroid transcription factor-1 (TTF1)]. The patient was diagnosed as having primary lung adenocarcinoma, cT4N3M1a, stage IVa disease. To determine the optimal therapeutic strategy, an additional next-generation sequencing (NGS) testing of the tumour specimen was conducted. The test yielded a negative result for mutation of EGFR, ALK rearrangement, ROS1 and BRAF V600E but with presence of KIF5B(15)-RET(12)rearrangement. PD-L1 expression was negative.

She initiated chemotherapy at 28 weeks + 6 days of gestation with carboplatin and paclitaxel scheme (carboplatin AUC5 D1, paclitaxel 80 mg/m2 D1, D8 and D15 4/4 weeks). At 30 weeks of gestation she developed a respiratory infection and a caesarean section was performed. The patient was delivered of a normal female newborn whose birth weight was 1070 g. The Apgar scores were 7, 8, and 9 at 1, 5, and 10 min, respectively. The placenta had no disease by gross and pathological examination. She had pulmonary progression and started treatment according to the cisplatin and pemetrexed regimen having completed 4 cycles followed by maintenance with pemetrexed. After 4 cycles, she had liver biopsy-proven progression that revealed metastatic lung adenocarcinoma, now with PD-L1 > 50% (Figs. 1c and 2). She initiated pembrolizumab 2 mg/kg with hepatic progression after 3 cycles. Vandetanib was proposed, but given hepatic function worsening, treatment with gemcitabine was initiated. As complications, a deep venous thrombosis was diagnosed, and low molecular weight heparin was started. Later she had an ischemic stroke, worsening of the general state and suspension of systemic treatment. She died about 12 months after diagnosis. The baby is healthy and has a normal development for her age.

In pregnant women with lung cancer, adenocarcinoma is the most common, accounting for 80% of cases. More than 97% of the published cases are diagnosed with locally advanced or metastatic disease,[13] largely due to diagnostic delays due to attribution of symptoms to other etiologies and efforts to ensure fetal well-being. Approximately, 20–30% of malignant tumours occur in women younger than 45 years[14] as with our patient.

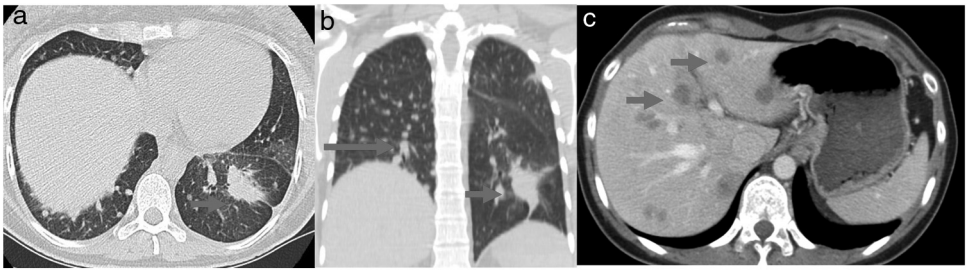

Figure 1 (a) Chest axial CT; (b) non-contrasting coronal CT shows left lower lung mass (arrow) and multiple small diffuse round nodules (long arrow) at diagnosis; (c) contrast axial abdominal CT shows multiple hypo-enhanced solid liver nodules according to diffuse liver metastases (arrows) following hepatic progression.

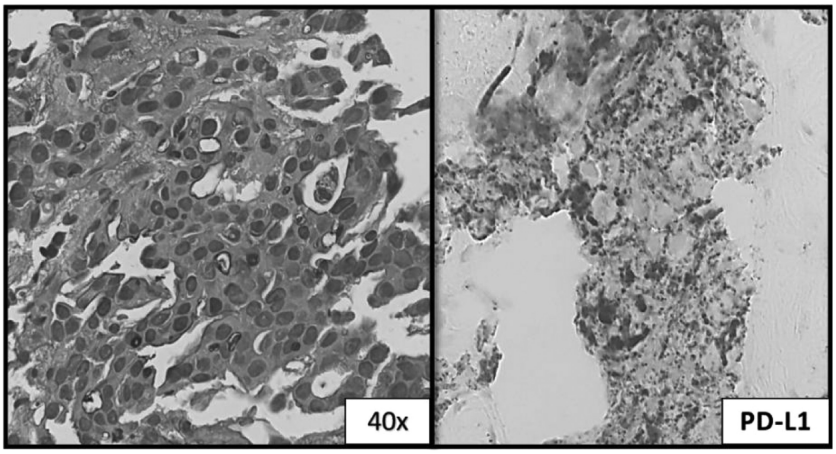

Figure 2 Liver: metastatic lung adenocarcinoma; the tumor cells show >50% PD-L1 expression.

Full-term pregnancy ($\geq$37 weeks) should be always the goal, according to all current treatment guidelines, since prematurity influences the emotional and cognitive development of children.[15] In pregnant women, cancer is often diagnosed at a later stage than in nonpregnant females. This fact might explain the poorer outcome of pregnant patients with cancer reported in some publications. However, the pathological characteristics and outcomes of patients in whom cancer is diagnosed during pregnancy are comparable to those of age- and stage matched nonpregnant patients with cancer.[16]

Metastatic transmission to the products of conception is a rare phenomenon, but 11 cases of placental metastases and 3 cases of fetal metastases were reported secondary to maternal lung cancer.[17–19] The most likely way for dissemination is through the hematogenous route. The rarity of this dissemination is probably due to the placental barrier and the fetal immune system.[20] The placenta of our patient was normal.

The main concerns for these patients are to choose the proper treatment and the overall survival from the disease. In the meantime, it is of great importance to take into consideration the consequences of the chemotherapeutic drugs on the developing fetus, as well as the long-term complications after in utero exposure to anticancer therapy.[1]

Nowadays we need to focus on those tumours that require systemic treatment since it is now widely acknowledged that surgery may be administered to pregnant women with no damage to the foetus in any phase of pregnancy. Chemotherapy is the treatment of choice in most cases of lung cancer in pregnancy.[14] Drugs with a molecular weight of less than 500–600 cross the placenta, whereas those with molecular weights greater than 1000 are reported to cross poorly.[3,21] Most traditional antineoplastic agents have a weight below 400, resulting in potential chemotherapy exposure to the fetus. Congenital malformations can occur in approximately 20% of cases if cytotoxic anticancer drugs are administered during the first trimester and thus should be avoided.[22] Among the therapeutic drugs, antimetabolites (aminopterin, methotrexate, 5-fluorouracil, arabinosyl cytosine) and alkylating agents (busulfan, cyclophosphamide, chlorambucil) are the most common drugs reported to induce malformation or to exert teratogenic effects. Vinca alkaloids and antibiotics seem to have no effect on the fetus; however, cisplatin is implicated in growth restriction and hearing loss, whereas etoposide is implicated in pancytopenia.[2] There are several published case reports with carboplatin plus paclitaxel treatment during pregnancy.

Since teratogenic effects of chemotherapy have been described, we can assume that at least a fraction of these drugs pass the placenta.[23] The teratogenic potential of any drug depends on a variety of factors that include the extent of its placental transfer, the dose administered, the duration of exposure, the genetic variability in drug metabolism

of the mother and fetus, and timing of exposure. Hence, pregnancy termination should be considered in pregnant patients with cancer who need chemotherapy administration in the first trimester.[24,25] Based on multiple studies, giving chemotherapy after the first trimester is safer; however, there is a relatively higher risk of premature rupture of membranes, intrauterine growth restriction and premature labour.

The pharmacology of various anti-cancer drugs may be altered by the normal physiological changes that occur during pregnancy, such as increased plasma volume, enhanced renal and hepatic elimination, and decreased albumin concentration.[26] However, it is still not clear whether pregnant women should be treated with different doses of chemotherapy, and no studies have addressed the effectiveness of treatment regimens in pregnancy.[22]

There are no data evaluating molecular and genomic characteristics for lung cancer in pregnant women. As in pregnant patients the rate of lung cancer in non-smoking females can reach more than 40% in published cases one might assume a higher incidence of cancers with targetable molecular alterations (e.g., sensitizing EGFR mutations, anaplastic lymphoma receptor tyrosine kinase gene [ALK] translocations). Dagogo-Jack et al. reported 8 cases of lung cancer during pregnancy: six patients had an ALK translocation, and two patients showed a sensitizing EGFR mutation.[27] The RET rearrangement of our patient is not described in the literature.

The most widely reported scheme of chemotherapy in pregnant woman with lung cancer is carboplatin and paclitaxel, which has been reported as well in ovarian cancer during pregnancy with acceptable toxicity. The weekly application of paclitaxel allows a lower peak plasma concentration of the drug resulting in lower maternal toxicity and possible lower placental transfer. Carboplatin seems slightly safer than cisplatin during pregnancy and hence was favoured.[12] Our patient was treated according to this scheme with optimal tolerance and without significant toxicity.

The vinca alkaloids vincristine, vinblastine and vinorelbine have been used safely after the first trimester. Three cases of vinorelbine use in pregnancy have been reported, all three infants are growing normally and were born without congenital abnormalities. The use of gemcitabine and pemetrexed should be discouraged due to the lack of data.

It should be clearly stated that there are insufficient data for the proper management of pregnant women with cancer; guidelines are mainly based on data coming from small retrospective studies or case series with limited follow-up.[28] In these cases, the multidisciplinary discussion for therapeutic decision making becomes even more important. Maternal outcome is very poor. Post-partum maternal median survival is generally poor, and the majority are known to have died within 1 year after delivery.[18] Despite all the advances in lung cancer in recent years, the outcomes in this subgroup remain scarce with survivals that do not exceed 12 months, as with this patient.

The diagnosis of lung cancer during pregnancy is rare, and often made at an advanced stage since symptoms can be easily attributed to other causes and there is the fear of carrying out diagnostic tests during pregnancy. The most studied protocols in the treatment of lung cancer during pregnancy include platinum and paclitaxel.

In a subject in which there are no randomized controlled trials, where the number of reported clinical cases is low, evidence is scarce. The clinical decision is based on knowledge of treatment in non-pregnant patients, the few cases described in the literature, the assessment of potential toxicity and the potential benefits of treatment. Decisions should always be made in a multidisciplinary group where obstetricians and neonatology are also present. Multidisciplinary management is essential to provide better outcomes for our patients. It is also important to report more and more cases, as well as the molecular and genetic studies of these tumors to increase the experience and safety of using targeted therapies.

Ethical disclosures

The submitted document is a review. It does not involve experimentation on animals or humans. The study is not a clinical trial and is not part of a trial. And all clinical case data are referred to in the discussion and conclusions.

Conflict of interests

The authors declare no conflict of interests.

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Tuberculosis screening at social solidarity institutions: a new protocol

KEYWORDS
Tuberculosis;
Latent tuberculosis infection;
Treatment;
Preventive

Dear Editor,

The diagnosis and treatment of latent infection with *Mycobacterium tuberculosis* (LTBI) significantly reduces the risk of developing active tuberculosis and disease transmission in the community. LTBI screening must include the exclusion of active disease (medical evaluation with a clinical history and chest radiography) and the assessment of immune response to *Mycobacterium tuberculosis* through currently available tests such as the tuberculin skin test and the IGRA test (interferon-gamma release assay).

Certain clinical and social conditions are associated with a higher risk of progression from latent infection to active disease, namely HIV infection, homeless people, alcoholism and drug use. Therefore, the diagnosis and treatment of LTBI are part of a strategy to eradicate tuberculosis and prevent new cases in the future.[1,2]

Long-term studies with isoniazid showed that administration at 3, 6 or 12 months reduced the risk of disease progression by 21%, 65% and 75% respectively.[3] Adherence to treatment has been recognized as a key parameter, and its efficacy is greater when associated with taking at least 80% of dose.[3,4] In order to improve treatment adherence and simultaneously treat the infection by isoniazid resistant species, several other regimens have emerged namely four months of rifampicin (R), three months of rifampicin

and isoniazid (HR), and three months of rifapentine and isoniazid.[5]

The Center of Pneumological Diagnosis of Coimbra has implemented, since 2009, a protocol for screening tuberculosis in social solidarity institutions in order to eradicate tuberculosis and prevent new cases in this risk population. The objective of our study was to analyze the results of Tuberculosis screening in residents and employees of several social solidarity institutions in Coimbra, namely ''Farol Institution'', ''Caritas'', ''Integrar'', ''Sol Nascente'', ''Casa Abrigo'', ''Ateneu'' and ''Cozinha Económica'', over 10 years.

Our study was a retrospective analysis of the clinical processes of residents and employees of these institutions, submitted to screening from the beginning of the project (10 years). Demographic and clinical data were analyzed. Statistical analysis was done using Microsoft Excel.

We included 601 individuals (559 residents and 42 employees), 58.2% male, aged 19–67 years. In our sample the risk factors for tuberculosis were HIV infection (n = 39; 7%), alcoholism and drug use (n = 246; 44%) and homelessness (n = 274; 49%). LTBI screening was done excluding active disease (medical evaluation with a clinical history and chest radiography) and the assessment of immune response to *Mycobacterium tuberculosis*. To diagnosis LTBI we used both tuberculin skin test and the IGRA test.

There were 115 cases (19.1%) of LTBI and 6 of active disease (1%). Ten individuals (1.7%) did not attend screening. All cases of LTBI and active disease were found in residents of those institutions. No cases of LTBI and active disease were observed in the employees.

The majority of the individuals with LTBI (n = 99; 86%) completed the treatment. Three individuals are still ongoing therapy, 6 were lost to follow-up and 7 developed pharmacological toxicity, namely hepatotoxicity to isoniazid.

Regarding treatment for LTBI, 68.7% (n = 79) started the regimen with HR, and 94.9% (n = 75) completed the therapy. Thirty six (31.3%) initiated only H, and 66.6% (n = 24) completed the therapy. Regarding treatment for active disease, five individuals completed the treatment with HRZE (isoniazid, rifampicin, pyrazinamide and ethambutol) and 1 HIV + person with rifabutin instead of rifampicin.

In conclusion, our study shows that the majority of the diagnoses of screening of tuberculosis in this risk population were classified as LTBI. Therapeutic adherence was better with the HR regimen. The diagnosis and treatment of LTBI should be properly controlled, and the screening of social solidarity institutions with risk populations could be a move forward in the approach to tuberculosis, as it could help to avoid new cases in the future and, consequently, reduce the transmission of the disease. The choice of treatment regimen should take into account the efficacy, compliance and associated side effects.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Insights into tuberculosis: A survival analysis of time to recurrence in Portugal, between 2002 and 2009

Recurrence of TB has been associated with poor adherence to treatment, smoking, alcoholism, unemployment, drug abuse, the severity of pulmonary cavitation, HIV infection and duration of treatment.[1] However, the risk factors can vary considerably across countries and between studies. Since little is known about risk factors for recurrence in Portugal, we aimed to identify predictors of treatment recurrence in the country. Surveillance data on TB for the period of 2002–2009 was provided by SVIG-TB, a database from the Portuguese National Health System. For this analysis, only cases of confirmed TB disease were considered, and patients that had information on the first and second TB episodes. The variables studied were chosen as TB risk

Table 1 Hazard ratios and 95% confidence intervals for TB recurrence.

Variables	β (se)	HR	CI (95%)	*p*-value
Treatment outcome	2.32 (0.197)	10.18	[6.90, 14.93]	<0.001
Prison	1.31 (0.522)	3.63	[1.41, 10.81]	0.012
HIV	0.85 (0.202)	2.34	[1.58, 3.48]	<0.001
Clinical form	0.77 (0.235)	2.14	[1.35, 3.40]	0.001
Alcohol use	0.62 (0.195)	1.86	[1.26, 2.74]	0.002
Age	−0.01 (0.006)	0.99	[0.98, 0.99]	0.033
Length of treatment	−0.12 (0.021)	0.90	[0.86, 0.93]	<0.001
Diabetes	−1.61 (1.007)	0.20	[0.03, 1.44]	0.110

se, standard error; HR, hazard ratio; CI, confidence interval.

factors according to previous reports about TB recurrence. The existence of missing data was assessed and missing data characterised (missingness between 0 and 10%). From this characterisation, we chose to explore multiple imputation using random-forest based on multivariate imputation by chained equations. We used a semi-parametric Cox regression model in which the event of interest was the second episode of TB, with time being measured from the end of treatment for a first TB episode. Patients without the second episode of TB before the end of the study were eliminated. A total of 8364 individuals were analysed, of which 145 (1.73%) had a recurrent TB episode during the time of the study.

Patients who defaulted TB treatment are ten times more likely to suffer a recurrent case of TB (Table 1). As expected,[1] HIV was positively associated with recurrence of TB disease (Table 1). Alcohol use disorders have been associated with recurrent TB, mostly by linkage to other confounding factors.[1,2] We found that even when considering treatment default, TB patients with an alcohol use disorder still had 86% increase in the risk of TB recurrence (Table 1). Incarceration is a known risk factor for TB mainly due to overcrowding, delayed diagnosis and/or inadequate treatment. Our study shows that in Portugal, the risk of TB recurrence for prison inmates is four times higher (Table 1). The standard 6-month treatment regimen is often insufficient to prevent TB relapse,[3] nevertheless, the study of treatment length as a risk factor has been mostly restricted to TB patients living with HIV.[4] Longer treatments are usually prescribed for patients with poor prognosis, potentially confounding a beneficial effect. We found a decrease of 10% in the risk of recurrence per added month of treatment, even accounting for the effect of other risk factors (e.g. HIV), which may suggest a need to reevaluate standard treatment regimens (Table 1). The inclusion of the clinical form in a study about recurrence is unusual. Most studies discard extrapulmonary TB cases since this form is much less infectious, contributing less to overall TB epidemics.[1] Nevertheless, we found that there is a two-fold increase in the risk of recurrence when suffering from an extrapulmonary form of the disease (Table 1). Driver et al.,[4] showed that in TB patients living with HIV, extrapulmonary disease increased the risk of recurrence, and Millet et al.,[2] suggested that this was true irrespective of HIV status. Interestingly, some TB risk factors have been shown to be associated with the clinical form – i.e. having HIV or being young increases the chance of having an extrapulmonary infection, while smoking and living with diabetes increases the chance of a pulmonary TB. Regardless of the association between youth and extrapulmonary TB, the role of age in TB recurrence is somewhat uncertain, with some studies[5] indicating a decrease of risk for older people while others[6] suggest a reduction for younger individuals. In Portugal, we found that an increase of one year in the age of the patient leads to a decrease of 1% in the risk of a recurrent episode (Table 1). The association between diabetes and TB incidence has been relatively established, but the association with TB recurrence is unclear.[3] Although the variable is not significant, we have estimated a decrease of 80% in the risk of a recurrent episode when having diabetes (Table 1). In this study, 55% of recurrence occurred in the first 12 months after treatment completion, suggesting that in Portugal most of TB recurrence cases were due to relapse since relapse occurs not long after the end of treatment.[7] Nevertheless, future studies should consider the inclusion of mycobacterial DNA information to distinguish between relapse and exogenous reinfection.

To the best of our knowledge, this is the only study, to date, covering risk factors for TB recurrence in Portugal. The study concerns the period 2002–2009 and, although the situation may have changed over the last decade, this cannot be assessed unless datasets linking multiple disease episodes at the individual level are made available to researchers. Understanding risk factors for TB recurrence in Portugal can help to define new guidelines to reduce the prevalence of recurrence, decreasing the chance of multi-drug resistant TB development.

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Conflict of interest

The authors reported no conflict of interest.

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Diagnostic challenges of hypersensitivity pneumonitis with autoimmune features: Dealing with more than a coincidence?

To the Editor,

Besides the well-known relationship between connective tissue diseases (CTDs) and several forms of interstitial lung disease (ILD), the recognition of autoimmune features in idiopathic interstitial pneumonias led to the establishment of the IPAF (interstitial pneumonia with autoimmune features) denomination and classification criteria in 2015.[1]

Hypersensitivity pneumonitis (HP) and several CTDs share T cell dysregulation, suggesting a greater likelihood of autoimmune disease in HP patients. A previous study of a cohort of chronic, fibrotic HP patients found that fifteen percent of these patients revealed either the presence of a defined CTD or some autoimmune features suggestive of CTD. These patients were identified as having ''HP with autoimmune features'' (HPAF) and seemed to have a worse survival rate than non-HPAF HP patients.[2]

We report a case of a 72-year old man who is followed as a Pulmonology outpatient due to obstructive sleep apnea syndrome, under home continuous positive airway pressure (CPAP) therapy, chronic obstructive pulmonary disease with mild centrilobular emphysema and mediastinal lymph node enlargement. Inhalation exposure is relevant due to former smoking habits (thirty pack-years), close contact with birds in the backyard, occasional use of sauna and Turkish Baths. As for past medical history, the patient also has arterial hypertension, dyslipidemia, unknown chronic liver disease and a previous rheumatological diagnosis of psoriatic arthritis, currently without directed therapy; a previous hospital admission happened due to community-acquired pneumonia. Chronic medications are an association of two anti-hypertensive drugs and atorvastatin.

Follow-up chest high-resolution CT scans showed progressive, unspecific, peripheral lower lung lobes intralobular reticulation (Fig. 1), as well as lymph node enlargement (14 mm) in the left paratracheal station (4 L). Endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) was performed; the 4 L station was identified and sampled and its cytological analysis was unremarkable.

Meanwhile, the patient reported worsening exertional dyspnea. Body plethysmography identified a mild obstructive ventilatory defect: FEV1/VC ratio equal to 64.2% and FEV1 equal to 2.41 L (86% of the predicted value). There was no lung diffusion impairment. Fibreoptic bronchoscopy with bronchoalveolar lavage (BAL) in the middle

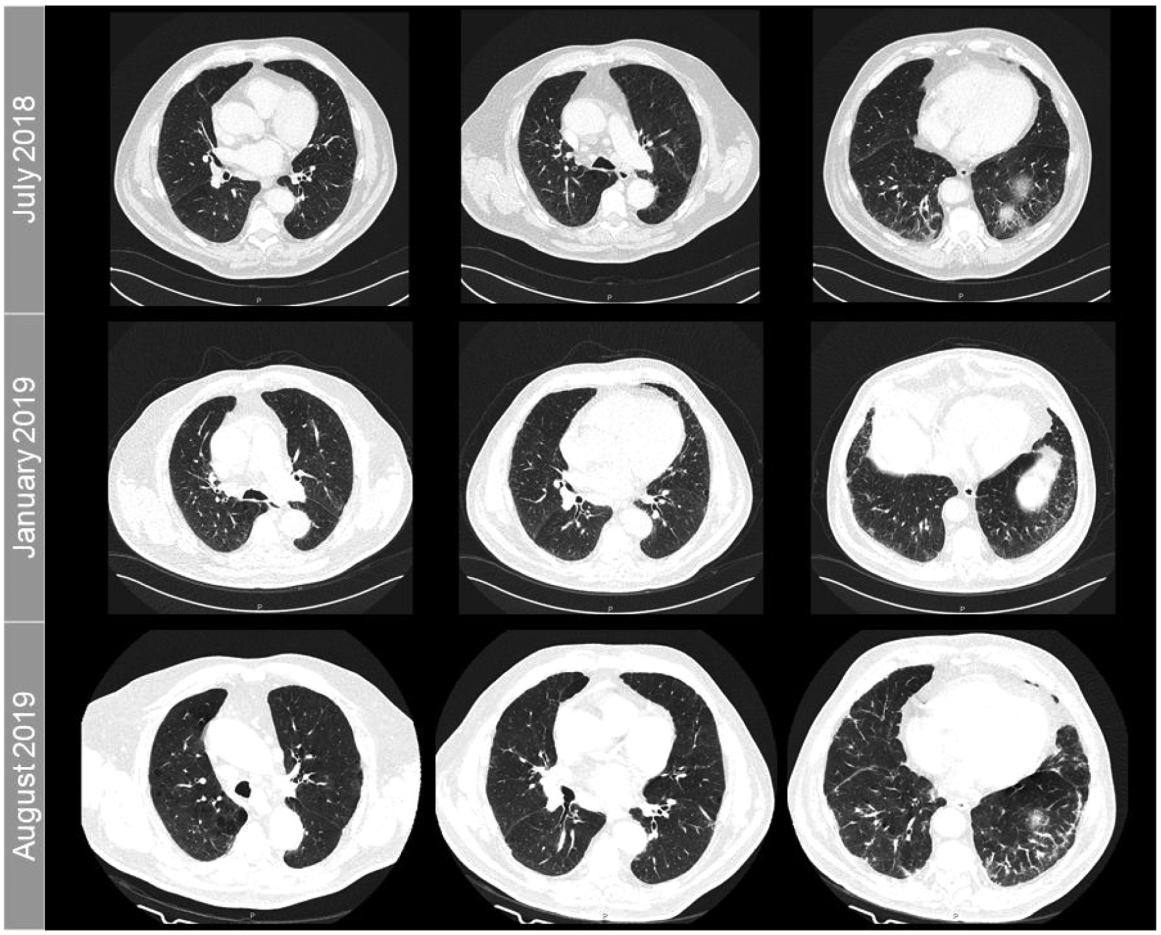

Figure 1 Follow-up chest CT scan axial images showing progressive, unspecific peripheral intralobular reticulation in the lower lung lobes. The time when the scans were performed is indicated on the left of each row of images. For comparative purposes, the images in each column correspond to identical axial planes.

lobe was performed. BAL fluid cellular analysis showed a normal total cell count, an intense lymphocytic alveolitis (55.6%) and a CD4/CD8 ratio of 1.87; bronchial wash and BAL were negative for malignant cells or microbiological agents. Serum immunological study was positive for anti-nuclear antibodies (1/1000 titer, speckled pattern).

The decision to perform transbronchial lung cryobiopsy (TBLC) was made in ILD interdisciplinary meeting for diagnostic clarification. Histological analysis of three samples from the right lower lobe showed features suggestive of both HP and autoimmunity (Fig. 2).

A working diagnosis of HPAF was established in an ILD multidisciplinary meeting.

This case report shows the diagnostic challenges of HPAF. It is still unclear whether autoimmune features in HP are a distinct HP clinical phenotype or an unrelated finding. However, we think that both HPAF and non-HPAF HP patients deserve further study in future prospective studies, specifically regarding immunosuppressive therapy outcomes.

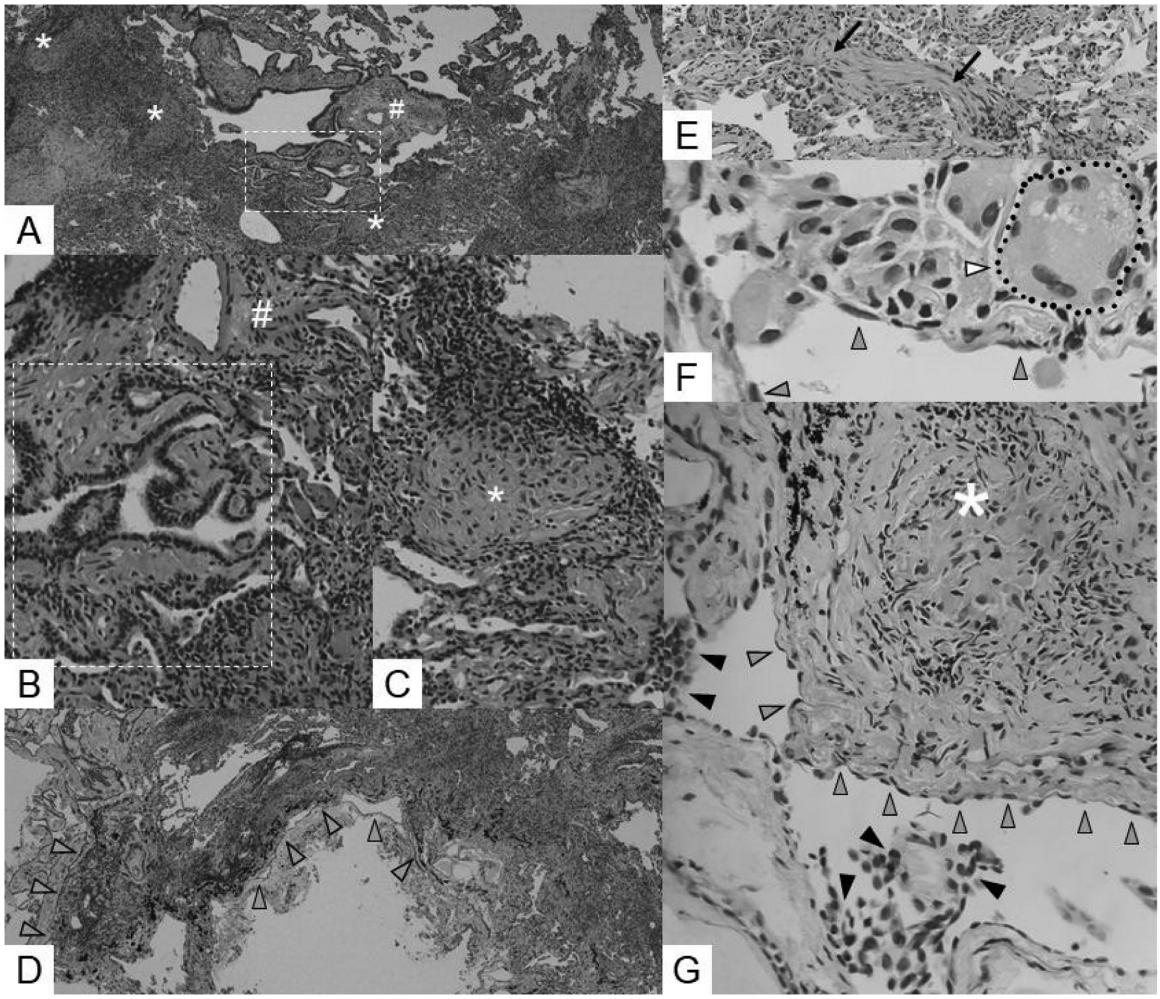

Figure 2 TBLC histopathology findings in HPAF. There are expressive peribronchiolar and subpleural changes, typical of HP and CTDs, respectively.
(A) A prominent, dense interstitial chronic inflammatory infiltrate without lymphoid follicles with a predominantly bronchiolocentric distribution is seen. There are extensive lesions of peribronchiolar metaplasia (white - - - - -) and loose aggregates of epithelioid histiocytes – epithelioid granulomas (white *). A centrilobular region is marked with white # – hematoxylin and eosin (H&E) staining, 40× magnification.
(B) Detail of a lesion of peribronchiolar metaplasia (white - - - - -), adjacent to the centrilobular region (white #) – H&E staining, 200× magnification.
(C) Detail of an epithelioid granuloma (white *) – H&E staining, 200× magnification.
(D) A moderate cellular chronic inflammatory infiltrate, extensively involving subpleural areas (▶), as well as alveolar septa, is also seen – H&E staining, 40× magnification.
(E) Detail of organizing pneumonia lesion (→) – H&E staining, 200× magnification.
(F) Detail of a multinucleated giant cell (▷and ●●●●●●●) adjacent to the visceral pleura (▶) – H&E staining, 400× magnification.
(G) Detail of a pleura-centered epithelioid granuloma (white *) and focal mesothelial reactivity (▶) interspersed with normal pleural mesothelium (▶) – H&E staining, 200× magnification.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Juvenile dermatomyositis and pneumomediastinum: a case of a very rare complication

Dear Editor,

Juvenile Dermatomyositis (JDM) is a systemic autoimmune myopathy that affects mostly the muscles and skin. It usually manifests with nonspecific systemic signs preceding typical symptoms of the disease mainly symmetrical proximal muscular weakness and pathognomonic skin lesions, i.e. heliotrope and Gottron papules. Idiopathic inflammatory myopathies are rare in the pediatric group of which the most prevalent is JDM.[1] Spontaneous pneumomediastinum (PNM) associated with Dermatomyositis (DM) is even rarer, with 81 cases reported overall,[2] 2 of those in children.[3,4]

We report the case of a 10 year-old caucasian boy, who presented to the emergency room with an eight-month history of fever, photosensitivity, cutaneous lesions on hands and face, arthralgia, proximal muscular weakness, significant weight loss (10 kg), dyspnea on minimal exertion and dysphonia. The patient was previously healthy, with no personal history of pulmonary disease or tuberculosis. Initial physical examination showed tachycardia, tachypnea, decreased breath sounds at pulmonary bases and diffuse crepitations. He also had heliotrope and Gottron's papules (on the hands, elbows and knees), malar rash, Raynaud's phenomenon, and arthritis in the 3rd right proximal interphalangeal joint (Fig. 1). The Childhood Myositis Assessment Scale(CMAS) score (which assesses the patient's overall muscular strength, with a maximum score of 52) was 15. Laboratory work-up showed elevated muscle enzymes (creatine phosphokinase and aspartate aminotransferase), negative anti-nuclear antibody, negative antibodies to extractable nuclear antigens (ENA), negative double-stranded native DNA and negative anti-neutrophil cytoplasm antibody (ANCA). Specific myositis antibodies were unavailable for testing. Based on the presumed diagnosis of JDM, he received intravenous pulse of methylprednisolone and subcutaneous methotrexate. On the first day of hospitalization, the patient suddenly developed cough, worsened respiratory distress and palpable cervical emphysema. An urgent computed tomography scan showed bilateral mild pneumothorax, extensive PNM with subcutaneous emphysema and bilateral pulmonary consolidations, more prominent in bases, associated with ground-glass attenuation areas (Fig. 2). Treatment was with conservative, as well as broad spectrum antibiotics due to impossibility of exclude infection, but respiratory distress worsened at day fifteen. Intravenous immunoglobulin was administered, with no response, and he also started sulfamethoxazole + trimethoprim due to leukopenia. The patient was submitted to orotracheal intubation and drainage of PNM, with no significant improvement. By this time, pneumothorax had improved just with conservative measures. However, despite mechanical ventilation support and management of shock the refractory hypoxemia continued and he died after 23 days of hospitalization.

Although JDM affects primarily the muscles and skin, it can involve many tissues and organs, including the lungs.[2,5–7] Lung disease can present as aspiration pneumonia, interstitial lung disease (ILD) or respiratory muscle weakness.[5] There are limited data regarding the occurrence of PNM in JDM due to its rarity; its frequency in adults with inflammatory myopathies varies in the literature, but the largest cohort reported a prevalence of 2.2 %.[5] Risk factors for the occurrence of PNM in DM are: history of ILD, early age of onset (below twenty years old), cutaneous vasculopathy, normal or slightly increased levels of muscle enzymes (amyopathic dermatomyositis), previous use of glucocorticoids and the presence of anti-MDA5[2]. There is no data for risk factors in JDM. The findings on his CT-scan were also suggestive of ILD, although infection was an important differential diagnosis. The main risk factor for DM-associated PNM is the presence of ILD, with a prevalence of 10–43 %

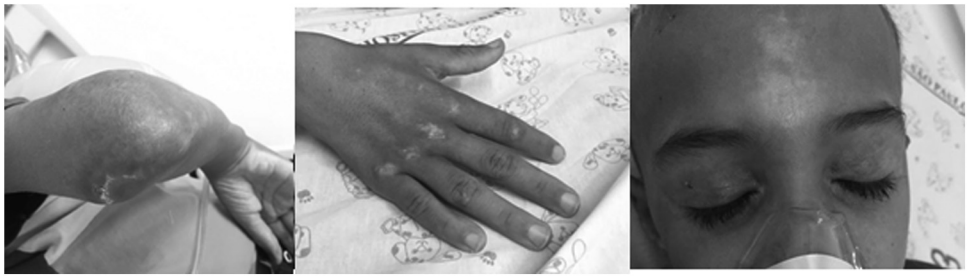

Fig. 1 Gottroń papules over the elbows (left). Gottroń papules on the hands (middle). Heliotrope (right).

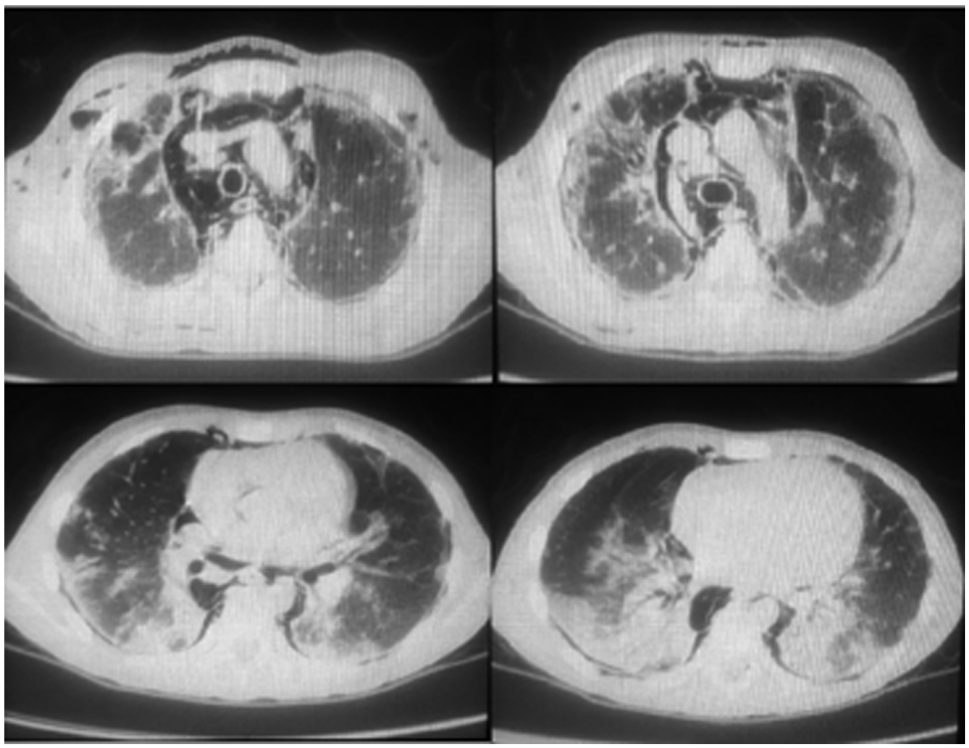

Fig. 2 Bilateral pneumothorax, extensive PNM with subcutaneous emphysema and bilateral consolidations, ground-glass attenuation areas.

in adult patients[2]; in pediatric patients, Sato et al. recently reported a prevalence of 27.6 %.[7] ILD was diagnosed in all patients with DM-associated PNM,[2,5,6] and while ILD is considered a poor prognostic factor,[2,5,6] isolated spontaneous PNM did not correlate with increased mortality.[5] The global mortality rate of DM-associated PNM is 37.5–52.5 %.[2] There is no standardized treatment for DM-associated PNM. In most cases, initial treatment was high-dose methylprednisolone, followed by numerous immunosuppressors.[2,5,6]

This case is the third pediatric case reported - previous cases were a eleven-year old girl and a nine-year old boy.[3,4] All three cases had a delayed diagnosis of JDM, varying between six and fourteen months. Corticosteroid treatment was introduced in all three cases, with significant improvement in JDM and PNM in the two cases described above, but a poor outcome in ours. In all three cases, there was concomitant pulmonary disease. Romanelli et al.[3] considered it pulmonary infection secondary to immunosuppression; in our case, though suggestive, the diagnosis of ILD was not possible because we didn't have enough time to confidently rule out infection.

ILD is an important risk factor for the onset of PNM, and those two complications combined are responsible for a high mortality rate in patients with DM.[2,5,6] As there is no data related to PNM in JDM, the extrapolated data from adult studies is important for the identification and management of patients at risk. Thus, we stress the importance of considering the diagnosis of JDM and its complications in the presence of proximal muscle weakness and nonspecific respiratory symptoms All children already diagnosed with JDM must have a thorough evaluation for subjacent lung disease.

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Competing interests

None.

Authors contribution

Active participation in patient care and the search for treatment options. Writing of the clinical case and research of articles that could support the treatment and the case report

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Severe asthma intervention in adult obese patients

Dear Editor,

Obesity and asthma are prevalent disorders, both with an important impact on public health.[1] A meta-analysis of seven prospective studies found a relationship between obesity and asthma: incident asthma OR in overweight and obese groups was 1.5 and 1.9, respectively, when compared to the normal weight group.[1] In fact, obese patients have an increased risk of asthma, and obese asthmatics have even more symptoms, frequent and severe exacerbations and worse response to asthma-specific therapies.[1–4] Weight loss has been proposed as essential in these patients, where up to 5–10% of weight loss is associated with improved asthma control and quality of life.[1,5] In this way, bariatric surgery is considered as the key option to promote a substantial weight loss.[6–8]

Here, we report the case of an obese adult woman who presented with severe allergic-predominant asthma, who really improved her symptoms and frequency of exacerbations following bariatric surgery. However, she developed a psychiatric disorder due to the non-acceptance of her new body image.

A thirty-eight-year-old woman was referred to a pulmonology department because of severe uncontrolled steroid-dependent asthma. She had frequent cough, shortness of breath, wheezing and recurrent exacerbations. She had other comorbidities, like obesity (BMI 38), gastroesophageal reflux disease (GERD) and chronic rhinosinusitis. The patient's comorbidities, exposure to allergens or other harmful agents, as well as adherence and the appropriate use of current treatment were assessed. After the evaluation, weight loss was proposed and proton pump inhibitors and intranasal corticosteroids were prescribed. Asthma treatment was reviewed and optimized (with reduction of systemic corticosteroids (SC), high-dose inhaled corticosteroids (ICS) and long-acting beta 2-agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists (LTRAs)). However, the patient continued to have uncontrolled asthma.

The patient had reduced lung function (FEV1 63% pred, Tiffeneau index 61), atopy (skin prick test positive), IgE 454 kU/L and blood eosinophils count of 890 cells/l. Based on this, anti-IgE treatment (omalizumab 525 mg, SC each 2 weeks) was started.

Over the next four years (Fig. 1), the patient was asymptomatic, had a total CARAT score of 22 (9 + 13), decreased blood eosinophil count (260 cells/l), improved respiratory function tests (FEV1 87% pred), showed a clear decrease in the number of exacerbations and did not report the need for systemic therapy with corticosteroids. After that, the patient had progressively worse asthma control, despite using specific asthma therapy. Thus, the patient's comorbidities, exposure to allergens, as well as adherence and the appropriate use of current treatment were re-evaluated. The patient gained weight, reaching BMI of 40 kg/m^2. She was diagnosed with moderate obstructive sleep apnea (OSA) syndrome (apnea-hypopnea index of 20.3 events/h) and automatic positive airway pressure (APAP) therapy was

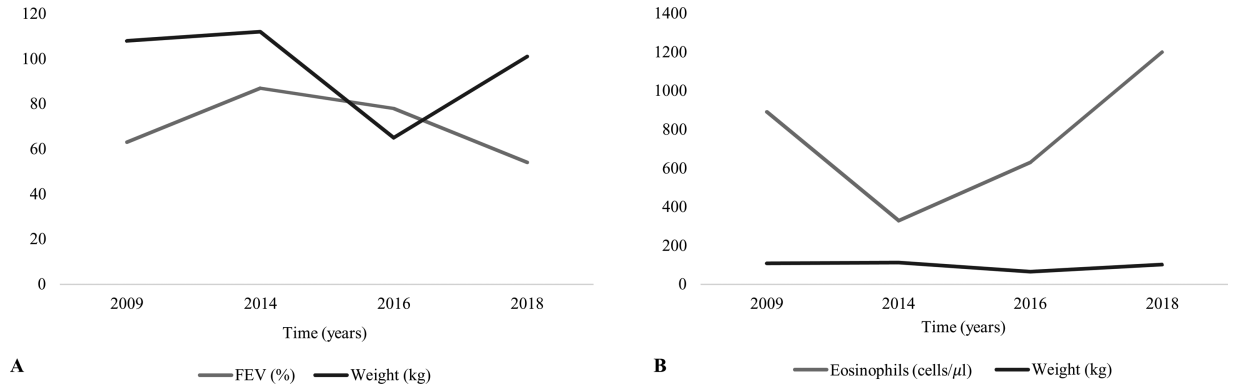

Figure 1 Variation in (A) FEV (%) and weight (kg) and (B) eosinophils count (cells/L) and weight (kg) over time following omalizumab treatment initiation.

initiated. Meanwhile, after a psychiatric evaluation, she underwent bariatric surgery. Following bariatric surgery, the patient had a rapid reduction in BMI, 65 kg in 6 months. Subsequently, the patient presented a clinical (total CARAT score of 28) and functional improvement and did not require systemic corticosteroids or omalizumab therapy. However, the patient started having depressive symptoms and lack of acceptance of her new body image, being referred for psychiatric re-evaluation. She started drug treatment and cognitive-behavioral therapy, but her weight persistently increased and asthma became uncontrolled. Thus, due to a new severe uncontrolled asthma, anti-IgE treatment was repurposed.

In fact, obesity and asthma are prevalent disorders, and there is an association between the two conditions,[1,3,4] where obesity is both a major risk factor and an asthma modifier. Patients with severe asthma usually have limiting symptoms, exacerbations and side effects of medications, especially with the prolonged and recurrent use of SC.[2,9] The adverse effects of SC include obesity, diabetes, hypertension and psychological disorders, such as depression and anxiety. Therefore, although asthma in obese patients is more commonly associated with non-type 2 inflammation,[2] obese patients with childhood-onset asthma tend to have higher markers of Th2 inflammation and more severe disease among obese asthmatics.[4,9] Studies have shown that weight loss interventions are associated with better control of asthma and respiratory function,[2,10] and that bariatric surgery promotes a rapid and sustained weight loss, and is generally associated with significant improvement in both asthma control and quality of life scores, reducing the risk of hospitalizations due to asthma exacerbation,[7,8,10] and even triggering a significant decrease in treatment step.[10] However, although obese asthmatic patients can be treated with specific asthma therapy and weight loss interventions, some patients still remain uncontrolled.

Obesity and asthma are frequently and independently associated with other conditions, which are also associated with worse asthma control, such as GERD, OSA and mood disorders.[2–4] Mood disorders, which consisted mainly of anxiety and depression, have been reported to be strongly correlated with asthma symptoms severity.[11] Thus, severe asthma management is difficult and needs a careful and multidimensional assessment.[12]

Here we report the case of an obese adult woman who presented with predominant severe allergic asthma, who truly improved her symptoms and exacerbations frequency following specific asthma therapy and bariatric surgery. However, despite all comorbidities and risk factors having been systematically assessed, their management was difficult, never allowing a longstanding asthma control. This may be due to a different type of airway inflammation, mechanical factors and other commodities that are associated with obesity.[2–4]

Specifically, although the evaluation of all comorbidities is extremely important, it must be emphasized that, in the case of mood disorders evaluation, this can have a negative impact if not appropriately recognized and treated.[11] The patient mentioned in this case started unpredictable depressive symptoms and lack of acceptance of her new body image, following a rapid reduction in BMI. Once depression was suspected, the patient was referred for psychiatric evaluation and management. She started drug treatment and cognitive-behavioral therapy, but her weight persistently increased and her asthma became uncontrolled. In conclusion, the management of this patient remains difficult, as the various comorbidities diverge and antagonize each other. Taking this into account, anti-IgE therapy was restarted.

In short, given that obesity is an important risk factor for asthma and asthma-related morbidity, weight loss interventions should be highly encouraged to ensure proper control of asthma, lung function and quality of life. However, although this aspect is extremely important, it is also essential to ensure holistic management with an appropriate approach to all comorbid conditions in obese asthmatic individuals.

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Strengths of breath-triggered inhalers in asthma management

Dear Editor,

Asthma affects the lives of several hundred million people around the World, across all age groups and Portugal is not an exception, with an asthma lifetime prevalence of 10.5%.[1] Patients, their families and the society face high direct and indirect costs, due to healthcare resources use, loss of productivity, absenteeism and presenteeism of patients. Asthma strongly influences the wellbeing and quality of life of patients. With no established curative treatment, guidelines for asthma management have identified that the primary goal of management is to achieve asthma control.[2] In asthma, pharmacological treatments mainly consist of inhaled drugs, which allow efficacy and significantly reduce systemic side effects, being the most efficacious treatments. However, lack of adherence to treatment in asthma occurs in more than half of all medical prescriptions. Furthermore, reduced adherence to treatment frequently allies with an incorrect inhalation technique, both considered major issues significantly impairing pharmacologic treatments effectiveness. Therefore, despite the efficacy of the available drugs, a high percentage of asthmatics are uncontrolled and have frequent exacerbations.

Difficulties in using inhalation methods are well-known problems that have been consistently maintained in recent decades, with the occurrence of several errors that affect treatment results with the use of both dry powder inhalers (DPIs) and pressurized metered-dose inhalers (pMDIs). Results from the Critikal study[3] analyses of the inhaler technique assessment initiative Helping Asthma in Real-life Patients (iHARP) database have helped to identify the prevalence of critical inhaler errors (those that have a definite detrimental impact on the delivery of drug to the lungs) with different devices in patients with asthma. The most common critical errors included failure to coordinate device actuation and inhalation with pMDIs, and lack of a forceful inhalation with DPIs; overall, 89% of patients made at least one potentially critical handling error and 67% made multiple potentially critical errors.[3]

Breath-actuated inhalers (BAIs) represented an evolution in inhalers' design aiming to improve the management of asthma.[4] BAIs are aerosol devices, like pMDIs, but rather than being activated manually, they automatically release a dose of drug when the patient inhales with a sufficient inhalation flow rate. In the past, BAIs had a major limitation when chlorofluorocarbon propellants (CFCs) were used and the speed of emission of the aerosol was so high that the impact of inhaled droplets in the upper airways was still very significant; nowadays, with hydrofluoroalkane propellants (HFAs), the speed of emission is considerably lower and the aerosol may be inhaled slowly being deposited more peripherally in the airways. These new devices may offer several advantages (Table 1), and were developed to overcome the most commonly seen critical errors with other inhalers, as follows: there is no need to coordinate actuation and inhalation (which is necessary for pMDIs); as active devices, BAIs emit a propelled aerosol and patients do not need to inhale forcibly to generate respirable particles (which is required for DPIs).[4,5]

BAIs are intended to simplify the inhaler technique, leading to improved inhaler use by the patients and less health

Table 2 Key attributes of the breath-triggered k-haler®.

General design	
Minimal inhalation force is required to trigger the device	• Ensures that a dose is released even if the patient has limited lung capacity and gives a 'nice feel' upon actuation
Shape	• Retains the classic 'pMDI' shape familiar to patients; the size and shape of DPIs vary considerably, which can lead to patient confusion
Orange translucent cap and silver detailing	• Helps patients to orientate the inhaler correctly and to identify the mouthpiece correctly
Small, compact size	• Easy to store and carry, and fits nicely in the hand (even small hands) • Can be used discreetly and has a comfortable fit in the mouth
Closed system	• Prevents dirt and dust from accumulating in the inhaler that could clog the device and irritate patients' airways
Usability	
Open–breathe–close operation	• Few simplified steps are required to prime and operate the device
Cap is connected to the device	• The cap cannot be lost and can be repositioned easily when priming/closing
Dose feedback	
Easy-to-read dose counter in font designed specifically by the UK Royal National Institute for the Blind	• Ensures that patients know how many doses are left
Audible 'clicks' when dosing and when closing	• Feedback that the device is primed and ready for use and also when the cap has been closed securely
Automatic release of dose when the mouthpiece cap is closed if a primed dose is not taken	• Alerts the patient that a dose has not been taken • Prevents double or multiple-dosing

care professional (HCP) time spent training patients to use the devices correctly.[4] Indeed, several studies have shown that patients find BAIs easier to use and HCP find it easier to train patients in their correct use in relation to other devices. The ease of use of BAIs may offer particular advantages in certain patient groups, such as children, the elderly or those with limited manual dexterity.[4,5] BAIs that are triggered by a low inspiratory force may offer additional advantage.[4]

An ergonomically designed breath-triggered inhaler (BTI), k-haler®,[5] was recently available. Its successful use involves only a few steps and, as an 'active' aerosol inhaler, it automatically releases a dose of the drug in a respirable form when a patient inhales, even at a low inspiratory flow (the device is triggered at an inspiratory flow rate of approximately 30 L/min). A high fine particle fraction and a plume that is less forceful than that of previous pMDIs can decrease drug impaction at the back of the throat and improve delivery to the lungs.[5] As such, k-haler® represents an added-value to improve asthma control by addressing current patients' needs and overcoming the most common lasting critical errors referred with other inhalers (Table 2).[5]

Table 1 Breath-actuated inhalers: key advantages and disadvantages.

Advantages	Disadvantages
Portable and compact • Multi-dose device • High reproducibility in the amount of drug delivered • Closed canister, so contents cannot be contaminated *Benefits over conventional pMDIs* – No need to coordinate inhalation and actuation Benefits over DPIs – Releases drug at low inspiratory force, so no need to inhale forcibly	• Available for a limited range of drugs • Suspension formulations need to be shaken before each use • Important to prime before first use, if not used for some time or if the inhaler has been exposed to cold temperatures

The simplicity of use, better inhaler handling and patient preference for BAIs are advantages that may translate into improved treatment compliance with the prescribed therapy, leading to improved lung function and asthma control compared with other devices.[4–6] Several controlled studies comparing the efficacy of drugs at equivalent nominal doses administered with different devices had demonstrated equivalence in the main clinical outcomes (mostly symptoms and exacerbations) of asthma (or chronic obstructive pulmonary disease), but this may be justified by, 1. the large number of variables affecting the clinical response to inhaled drugs, besides the inhalation technique and 2. the gap between the patients in clinical trial conditions in referral centers with specific characteristics and close monitoring, being aware that they are being evaluated, and those patients in the real world, where poor inhalation technique and low adherence to therapy are known to be more common.[3–7]

If correctly and effectively used, inhalers are excellent, safe and effective in controlling asthma, as in other chronic respiratory diseases.[7] Improving inhalers correct and effective use is therefore a global issue to overcome current

known difficulties and to move forward into achieving higher rates of asthma control.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this article.

Confidentiality of data. The authors declare that no patient data appears in this article.

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Conflicts of interest

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LETTER TO THE EDITOR

Tracheostomy at skilled nursing facilities

Sir,

We read the article by Pereira et al. on tracheostomy prevalence in skilled nursing facilities (SNFs) with great interest.[1] The authors provided us with useful information about the situation of tracheostomized patients admitted to SNFs, showed the relative omissions and insufficiencies of these facilities in performing decannulation safely and effectively and concluded that a coordinated multidisciplinary team is required to favorably perform the weaning process of the considerable size of population of tracheostomized patients admitted to SNFs.

The authors' conclusions reflect our own experience. As a medical director of a SNF in Greece, I am aware of this major deficit in numerous nursing facilities to provide proper tracheostomy care for these patients, not to mention decannulation. This is probably due to several reasons such as inadequate staff to patient ratio, poor training programs and inappropriate nursing facility management. When the above reasons do not exist and a multidisciplinary team handles the tracheostomized patients with care, there is great potential for progress to be made.[2] We report a case of a successfully performed decannulation in a COPD patient admitted to a SNF after a prolonged treatment in an ICU due to acute respiratory failure from mycoplasma pneumoniae infection. He was a kyphosis-scoliotic asthenic tracheostomized man with a suitable level of consciousness, presented with dyspnea, tachypnoea, tachycardia and oxygen saturation of 94% under a FiO2 of 40%.

The physiotherapy planning program included maintaining and improving physical activity, reducing breathlessness and the work of breathing, aid with expectoration and clearance of secretions, walking assistance with a walker and improvement of functional abilities. Evaluation of swallowing function by a speech therapist revealed the presence of effective voluntary cough and a strong coughing reflex but high volume of yellowish orotracheal discharge and wet phonation. Clinical swallowing assessment using 10 ml of water and few drops of methylene blue performed twice on the same day, revealed ability to swallow fluids (no traces of dye appeared in the subsequent bronchoaspiration), but inability to swallow semisolid foods (cream), though immediate aspiration, after administration of semisolid food with methylene blue was provided, revealed colorant material and oxygen desaturation. Needless to say assessment of the ability to swallow solid food was not performed. Therefore, decannulation was postponed and oral intake was considered improbable. In order to restore the swallowing mechanism and prevent other complications caused by nasogastric tube insertion, a surgical gastrostomy was performed a few days later. Three weeks later, following a strict physiotherapy training program, muscle strengthening and high calorie intake according to the dietitian's guidance, the patient gained weight and physical strength. The patient could be fed orally and all the above mentioned swallowing tests were performed without signs of broncho-aspiration. The fiberoptic endoscopic evaluation of swallowing performed by an otolaryngologist revealed no major abnormalities regarding swallowing function, thus attempt at decannulation was decided according to the criteria by Ceriana et al.[3] The method of immediate tube removal-instead of tracheostomy downsizing — was chosen and sterile gauze covered the opening in the neck. His condition progressed gradually, the gastric tube was removed and the patient followed his rehabilitation program until discharge five months after admission to the SNF. During his stay, his psychological state was reinforced by family members as well as by a professional psychologist.

This case highlights the importance and necessity of a coordinated multidisciplinary team dedicated to the care of tracheostomy patients, which can favorably influence the weaning process in acute-care hospitals, rehabilitation centers and last but not least in SNFs.

Conflicts of interest

The authors have no conflicts of interest to declare.

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