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# PULMONOLOGY JOURNAL


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## Original articles

*COVID-19*

Pathophysiology of light phenotype SARS-CoV-2 interstitial pneumonia: from histopathological features to clinical presentations

*Pediatric Pulmonology*

Dilation with rigid dilators as primary treatment of subglottic stenosis in pediatrics

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# PULMONOLOGY

# FÓRUM OUTONO

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EDITORIAL

# Publish or perish? Perish to publish? (Unrequested advices to young researchers)


## Writing is the painting of the voice

### Voltaire

Despite the beliefs of (S)Talk-show conductors and No-Vax people, medicine is not an exact science, it is a science of probability and the duty of a physician is to provide the best up to-date care. Optimal management results from the combination of clinical expertise, research evidence and patient preference. In recent decades Evidence Based Medicine (EBM) has stirred up great interest due to full awareness that despite long clinical experience, lack of updated knowledge may lead to inadequate clinical performance.[1] Although the use of EBM may help reduce risks of malpractice, reducing the costs and optimizing the quality of care, it can never replace individual clinical expertise.[2]

In addition, very recently the concept of EBM has been challenged by the new concept of "personalized medicine": any therapy, whenever possible, should be tailored to the unique features of the individual patient, such as age, gender, race, habit, past medical history, prognosis and disease severity, socio-economical status, literacy and her/his preferences. Of course personalized medicine does not exclude EBM, but avoids indiscriminate use of the "best" treatment in EBM with every patient, regardless of her/his individual specificity and needs. The European Union, has launched the "European Alliance for Personalized Medicine" (EAPM) including European healthcare experts, patient advocates, academia and industry involved with chronic diseases, with the aim of accelerating development, delivery and uptake of personalized medicine and diagnostics.[3]

On March 22nd, 1457, Gutemberg printed the first book. It has been stated that in the history of humanity, while writing has made possible law, contracts, history, narratives, poetry, sacred texts, the press has changed the world more than any other invention in the past two millennia.[4]

This would be enough to understand what medical writing means. Medical writing means to contribute to EBM and overall scientific knowledge. A scientific writer is not like fantasy, adventure, phylosophy, or novel writers, (writers of what is usually considered as literature). Regular medical writing is not literature, it is about getting across a message, usually in a short format. Literature writing is like a Picasso painting, a medical paper is like a photo. However, a little bit of literary skill is not such a bad thing, even in a scientific writer.

In the last few decades, and especially since the COVID-19 pandemic, there has been an increase in medical publications and in the number of (not always high quality) scientific journals. Are we fully aware of what we are doing when writing medical papers?

- Writing papers should ***not be just*** a means to developing an academic career (although in some countries some academics survive very well publishing nothing).
- ***Scientifc writing is a big scientific and ethical responsibility:*** what you write might be (hopefully or unfortunately) read by someone who might take seriously your described methods and/or results, and accordingly change his/her medical habits.
- ***No writing, no work***. If you have brilliant ideas leading to innovation in clinical practice or basic research and don't write anything about your findings/methods, your work might be useful only for yourself and (hopefully) your patients, but not for the scientific community.
- ***No medical practice/active research, no writing***. Consider your work as a potential source of scientific information, always measure what you do and collect data : in future they will give you new ideas.
- ***No data no writing***. (Unfortunately this is not completely true, given the increasingly huge amount of unsolicited narrative/systematic reviews and meta-analyses of very few randomised controlled trials (sometime only 1 or 2 !) or even of just observational, retrospective studies). A regular writing habit should result from personal solid medical practice or active research work or both. When performing clinical trials the experimental

https://doi.org/10.1016/j.pulmoe.2022.03.008

protocol and the appropriate selection of statistical tests are the most important steps for a rigorous study.

**Don't fall into the "Publish or Perish" hole**. Writing may be important for an academic career and this may lead to competition with related "*Publish or Perish*" syndrome resulting in emotional pressure, unduly hurrying research steps, shortening the appropriate and thoughtful interval between research work and reporting. As an example, the COVID-19 pandemic has been associated with a storm of information by all media ("infodemic") and with high number of paper submissions ("paperdemic") with high level of retractions.[5-7]

From one side researchers are pushed to improve their H-Index (an index to quantify an individual's scientific research production: the higher, the better),[8] on the other side Journal Editors are obsessed with increasing their Journals' impact factor (IF), *" that's the **press**, **baby**, the press! and there's nothing you can do about it, nothing! "*.[9]

However a higher H-Index (or IF) does not necessarily mean higher researcher quality. Consider this : if Albert Einstein had published just one article on relativity theory[10] his H-Index would have been only 1 (one) point, no matter how many billion citations and the consequences for humanity of his finding.

Therefore:

- Be ambitious but not too ambitious, don't overstate/underestimate the importance/quality of your paper and chose the target journal appropriately.
- Don't trust in any inverse correlation between journal IF and the probability the paper will be accepted.
- Don't be afraid of and don't be discouraged by rejection of your paper: a rejection is not Divine Judgment, it is just a misfit between your paper and the journal needs. If you believe in your research, submit to another journal.
- On the other hand, don't be arrogant, consider and respect reviewers' comments and suggestions: reviewers are supposed to be expert and have given (usually for free) their time to evaluate your work. Use their comments to grow.
- Quote and discuss with an open mind any relevant publications also those conflicting with your results.
- Use the **R**ea**L**i**S**t protocol:
  - ✓ ***Rea**ding. Writing comes from reading, and reading is the finest teacher of how to write*" (Annie Proulx).

Daily accessing medical literature is the corner stone for any researcher or practitioner: ***no reading, no research; no reading, no good medical practice (or even= malpractice), no reading, no writing***. Whenever possible, in clinical research prefer prospective rather than retrospective studies.

- ✓ ***L**earning. Once you stop learning you start dying* (Albert Einstein).

Learn from your teachers (provided they are good writers), even better, ***choose a mentor***, if necessary and if possible spend some time in excellence centers.

- ✓ ***St**art. Brevity in writing is the best insurance for its perusal* (Rudolf Virchow).

Start from simple case reports, through retrospective observational studies, to randomised controlled trials, finally to reviews. However don't write reviews on topics you have not contributed to with any personal reference.

**There is a last but not least issue**. When forgetting the ethical bases, the competition may result in inappropriate if not illegal behaviours. Researchers should be cautious when submitting data for publication, to avoid problems with data analysis or ethical issues, such as lack of authorization by the Ethical Committees or patients' permissions (even for retrospective studies). Avoid ***plagiarism***, the "appropriation" of another author's "language, thoughts, ideas, or expressions" and the representation of them as one's own original work. Avoid ***duplicate publication***, multiple publication, or redundant publication, publishing the same intellectual material more than once. These problems should be avoided by using available tools, such as appropriate softwares and by improving the efficacy of the peer-review process.

Finally an analysis of literature indicates that pulmonology research might be lacking in efforts to increase replicability.[11] Reproducible and transparent procedures should be incorporated into research. Publications should provide sufficient information about materials, protocols, raw data, statisticall analysis and other indicators. Clinical decisions may depend on replicable or refutable results.

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## Declaration of Competing Interest

Authors declare no conflict of interests

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COMMENT

# Awareness and education in lung diseases: Are we reaching the target?

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**KEYWORDS**
Google trends;
Chronic obstructive pulmonary disease;
Asthma;
Pneumonia;
Tuberculosis;
Lung cancer;
Awareness;
Sensibilization campaign

Google Trends (GT) is a free and publicly accessible tool of Google Inc. that analyses web queries made using the Google search engine and provides the proportion of searches for a user-specific term over a specific geographic region and period.[1] It has been used to study public interest and awareness in various medical topics.[2,3]

The Forum of International Respiratory Societies identified chronic obstructive pulmonary disease (COPD), asthma, pneumonia, tuberculosis, and lung cancer, as the five major lung diseases ("The Big Five") and included them in the group of the biggest killers today.[4] A previous GT search study showed how the emergence of the COVID-19 pandemic has modified online search pattern for these diseases.[5]

Every year, educational campaigns are carried out to supply the population with knowledge on prevention, control, and cure of lung diseases. To evaluate whether awareness campaigns increase public interest in lung diseases, we conducted a GT search of the "big five" measuring the Relative Search Volume (RSV) over time. RSV ranges from 0 to 100, representing search interest in a specific search term relative to its peak of popularity (RSV =100) for the given region and time. Search queries in GT were defined as topics, which includes all terms that have the same idea or semantic in every language. Our search included five topics: "Chronic Obstructive Pulmonary Disease"; "Asthma"; "Pneumonia"; "Tuberculosis"; "Lung Cancer". As awareness campaigns we considered World COPD Day (November 17th, 2021), World Asthma Day (May 3rd, 2021), World Pneumonia Day (November

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12th, 2021), World Tuberculosis Day (March 24th, 2021) and World Lung Cancer Day (August 1st, 2021).

We conducted a visual analysis of the "big five" RSV-timelines, from 1st of January to 11th of December 2021, at a worldwide level, in two American (United States of America [USA] and Brazil) and in three European (United Kingdom [UK], Germany and Portugal) countries. Afterwards, we performed an annual trend analysis (Independent samples T-test; IBM SPSS Statistics Version 25.0. Armonk, NY: IBM Corp) comparing the mean RSV in the World Day promotion month for each disease with the mean RSV in the other months.

Worldwide RSV-timelines analysis (Fig. 1) showed that pneumonia and asthma were the most popular lung diseases over the studied period. Pneumonia showed its peak in search interests in January and asthma displayed its peak in May. Tuberculosis was the third most searched with a popularity peak in March. Both COPD and Lung cancer showed a constantly low interest in worldwide searches. Countries'

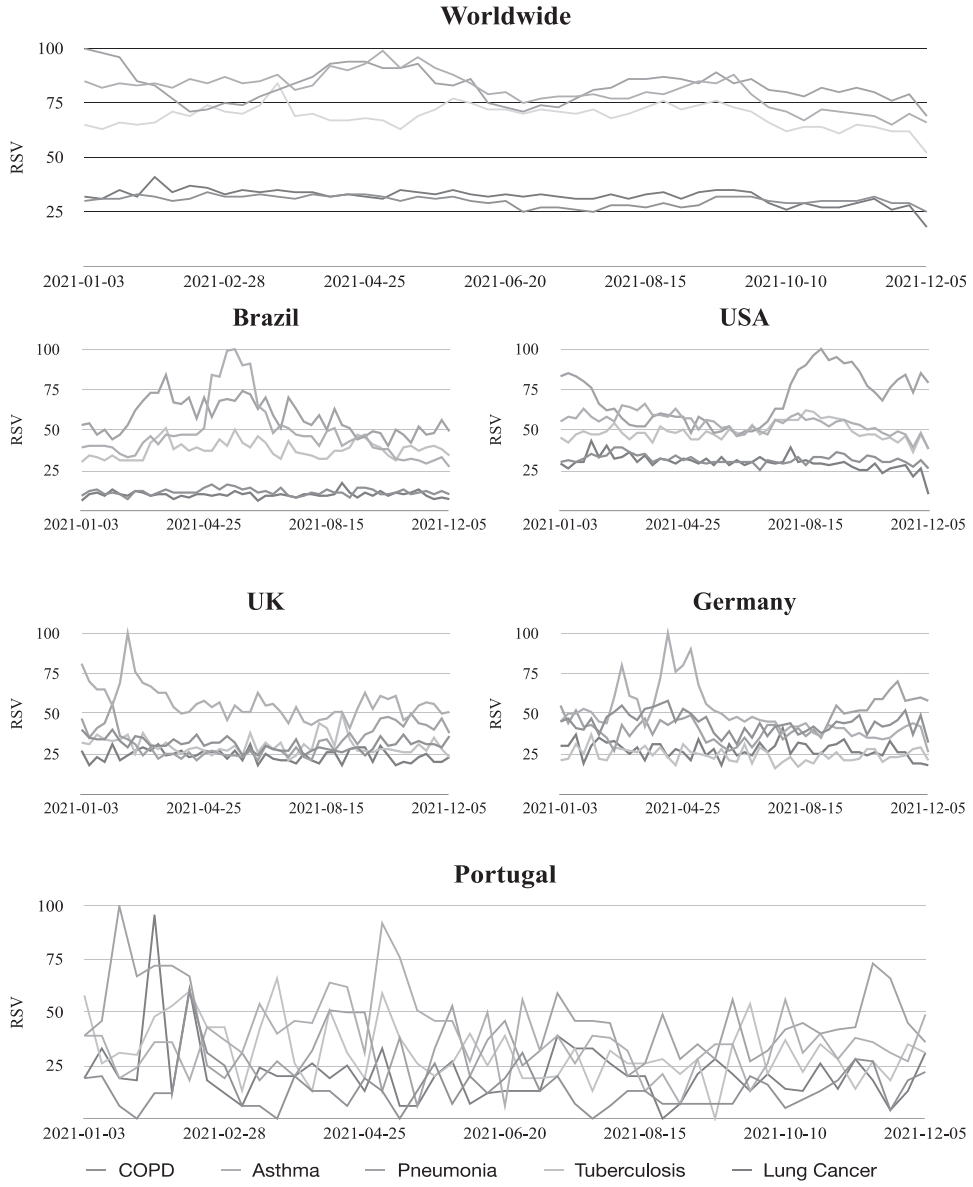


**Fig. 1** RSV over time (1st January 2021 to 11th December 2021). At a worldwide level, pneumonia was the most popular disease (maximum RSV of 100, mean ± SD 86.7 ± 7.5), followed by asthma (99, 81.1 ± 7.8), tuberculosis (84, 68.9 ± 5.3), lung cancer (41, 32.1 ± 3.5) and COPD (34, 30.1 ± 2.3). World and country trend analysis showed that awareness campaigns significantly increased the mean RSV for pneumonia in November, compared to other months, in the USA (80.8 vs. 68.3, $p = 0.007$), UK (43.5 vs. 32.0, $p<0.001$) and Germany (61.8 vs. 42.7, $p<0.001$); for asthma in May at a worldwide level (93.0 vs. 79.7, $p<0.001$), Brazil (91.2 vs. 43.1, $p<0.001$), Germany (63.2 vs. 48.1, $p = 0.033$) and Portugal (62.2 vs. 34.6, $p<0.001$); and for tuberculosis in March at a worldwide level (74.3 vs. 68.4, $p = 0.033$) and Brazil (44.3 vs. 37.2, $p = 0.009$). Lines indicate the relative daily RSV for each disease: blue (COPD); green (asthma); grey (pneumonia); yellow (tuberculosis); red (lung cancer). COPD = chronic obstructive pulmonary disease; RSV = relative search volume; UK = United Kingdom; USA = United States of America. Data source: Google Trends (https://www.google.com/trends).

RSV-timelines have different patterns in disease search over time between countries (Fig. 1).

In the trend analysis (Fig. 1), we observed that World Day awareness campaigns resulted in a significant increase in research for pneumonia in the USA, UK, and Germany; for asthma worldwide, in Brazil, Germany, and Portugal; and for tuberculosis worldwide and in Brazil. Campaigns focusing on COPD and lung cancer did not result in RSV variation.

Our analysis revealed popularity peaks related to awareness campaigns for pneumonia, asthma, and tuberculosis in some countries, and no impact in search for COPD and lung cancer. The highest worldwide RSV was seen in January for pneumonia, probably associated with the increasing number of COVID-19 cases at that time.[6] This has been previously shown by Barbosa et al.[5] and may translate people's reaction during disease outbreaks.

Boehm et al.[2] showed an annual increase in COPD search in November. Still, COPD was under-represented in Google search queries, compared to other diseases. They also observed a decrease in public's interest in lung cancer over the years, a tendency that is confirmed by our results. Lastly, they refer to breast cancer campaigns and the pink ribbon concept as a role model in awareness promotion since they have resulted in annual cyclic RSV peaks during October for breast cancer, which have increased over the years.

In conclusion, the data here presented suggest that sensibilization campaigns do not consistently increase population's interest in lung diseases. The low level of population interest and the lack of effect of COPD and lung cancer awareness campaigns is of particular concern, as both diseases are highly preventable, but their prevalence and mortality remain high. We must strive to elaborate new strategies to increase the effectiveness of sensibilization campaigns, and consequently, population's awareness in lung diseases.

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SPECIAL ARTICLE

# Pathophysiology of light phenotype SARS-CoV-2 interstitial pneumonia: from histopathological features to clinical presentations

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**KEYWORDS**
COVID-19;
ARDS;
Cryobiopsy;
Ventilation perfusion ratio;
Respiratory failure;
Prone position

**Abstract** Little is known about the light phenotype of SARS-CoV-2 pneumonia, which behaves in an unusual way, unlike other known respiratory diseases. We believe that the histopathological features of early COVID-19 could be considered the pathophysiological hallmark of this disease.

Lung cryobiopsies show almost pristine alveoli, enlarged/hyperplasic alveolar capillaries along with dilatation of the post capillary pulmonary venules. Hypoxemia could therefore be explained by a reduction of the normal V/Q ratio, due to blood overflow around well ventilated alveoli.

This could clarify typical manifestations of type L COVID-19, such as happy hypoxemia, response to awake prone positioning, response to PEEP/CPAP and platypnea orthodeoxia.


## Introduction

In early December 2019, the first cases of a pneumonia of unknown origin were identified in Wuhan, the capital of Hubei province in China. The pathogen responsible for this new disease was identified as a novel member of the RNA betacoronavirus family and was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), due to its similarities with the SARS-CoV, the virus responsible for

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the SARS epidemic in 2002–2003, and Middle East Respiratory Syndrome virus (MERS-CoV). The disease caused by SARS-CoV-2 infection was thereafter labeled as ''coronavirus disease 2019'' (COVID-19).[1,2]

COVID-19 has a wide spectrum of clinical severity. Mild disease is observed roughly in 81% of patients, whereas severe or critical forms are detected in 14 and 5% respectively.[3] Severe and critical cases usually present with bilateral interstitial pneumonia that apparently fits in with the Berlin definition of Acute Respiratory Distress Syndrome (ARDS).[4]

Italy was the first western country to be involved in the COVID-19 pandemic. The first case was identified at the end of February 2020 and shortly thousands of patients overwhelmed the hospitals in the Northern provinces. Patients often needed hospital admission, with many of them requiring supplemental oxygen, mechanical ventilation, and Intensive Care Unit (ICU) kind of respiratory support.

When SARS-CoV-2 began to spread in our country, we supposed we were facing an explosion of cases of interstitial pneumonia similar, from a pathophysiological perspective, to those induced by influenza viruses, cytomegalovirus or Pneumocystis jirovecii among others. We all had in mind patients in respiratory distress, with rapidly deteriorating clinical conditions that would require a quick referral to the ICU, where protective invasive mechanical ventilation, pronation, and even Extra Corporeal Membrane Oxygenation (ECMO) could be provided.[5]

However, as soon as COVID-19 patients started to be admitted to our hospitals, we were all surprised to face completely different patients than expected. Most of them did not even complain of dyspnea. No sense of breathlessness, no rapid shallow breathing, no need for accessory muscles of respiration, despite devastating CT scan images or dramatically low PaO2/FiO2 ratios.

The response of these patients' lungs to mechanical ventilation was also surprising. In the few cases we were forced to treat with Non Invasive Ventilation (NIV) as a bridge to intubation or for lack of other options, we found an unexpected respiratory response, as if the lungs were ''soft'', instead of ''stiff'' as they are supposed to be in ARDS.

This disease confronted us with completely unanticipated clinical and pathophysiological behaviour, which confounded our convictions.

But it was just a matter of time before these mere impressions met science. In fact, in April 2020, Gattinoni et al. published a very interesting paper in Critical Care: ''COVID-19 pneumonia: ARDS or not?''. In this article, the authors hypothesize the existence of two pathophysiological phenotypes of COVID-19 ARDS: the so called light phenotype (type L) and the heavy phenotype (type H).[6]

The light phenotype has preserved lung compliance (low elastance, *i.e.* high compliance), low ventilation/perfusion ratio (V/Q ratio), low weight and low reclutability. This phenotype is typical of the early phase of disease, but it can be seen in some severe cases as well.[7] Gattinoni himself reported a cohort of 16 critically ill patients, with relatively normal lung compliance ($50,2 \pm 14,3$ ml/cmH2O) despite a dramatically increased shunt fraction ($0.5 \pm 0,11$). Such a wide discrepancy is unlikely in typical ARDS.[8]

The type H phenotype has high lung elastance (*i.e.* low compliance), high right to left shunt, high weight and high reclutability. This phenotype is often seen in the later phase of the disease. The patients with this phenotype are usually more severe and their condition clearly resembles classical ARDS. The histopathological features of the H phenotype, documented in autoptic series, are diffuse alveolar damage (DAD) with interstitial and alveolar proteinaceous edema, hyaline membranes, alveolar type II cells hyperplasia and, later on, myofibroblastic proliferation and collagen deposition, just like in ARDS. A significant quantity of macro- and micro thrombi have been reported in different autopsy series [9,10], pulmonary embolism being the main cause of death in around one third of cases in one study.[9] Even if the significant increase of thrombotic events in DAD related to COVID-19 compared to other causes of DAD has been disputed [11], these findings suggest an important role of hypercoagulability in COVID-19, especially in the more severe disease. [9,10]

Little is known of the L phenotype, which apparently has a unique pattern of behaviour, which is not akin to other known respiratory diseases.

Several scientific papers proposed interesting pathophysiological hypotheses and brilliant inferences, however only few studies documented what is actually happening in the lung.[6,12–14] We believe that the histopathological features of early COVID-19, mirrored in HRTC scan findings[15], could help explain the pathophysiological hallmark of the L Type of SARS-CoV-2 pneumonia.

## What is happening down there in the lung?

We examined the histopathologic and immune molecular features of 12 Covid-19 patients in the earlier stages of illness (<20 days from onset of symptoms). All these patients underwent transbronchial cryobiopsy. Morphological examination of these samples showed interesting characteristics, that were substantially different from the typical DAD.[16]

Lung tissue showed hyperplasia of interstitial capillaries. Postcapillary venules were twisted and dilated, showing thickened, edematous walls, without signs of vasculitis. We also recognized other signs of endothelial dysfunction, such as overexpression of PD-L1 and indoleamine 2,3 dioxygenase-1 (IDO-1), along with aggregates of platelets, whereas microthrombi were just an occasional finding.[16]. However, all our patients were treated at least with a prophylactic dose of heparin, possibly reducing this phenomenon.

Other peculiar features were patchy alveolar type II cell hyperplasia, perivascular CD4 T lymphocyte infiltration and intra alveolar accumulation of macrophages with a hybrid phenotype.[16]

In the study by Doglioni C et al.[16] the research on expression of angiotensin converting enzyme 2 (ACE 2) receptor in lung tissue was also performed (data not published). However, ACE 2 appeared normally expressed in type 2 alveolar cells and endothelial cells.

As aforementioned, endothelial cells covering both venules and alveolar capillaries overexpressed IDO-1. This enzyme is involved in the regulation of vascular tone and remodeling. When overexpressed, it can exert a relevant role in maintaining the pulmonary venules relaxation and the capillary hyperplasia seen in our series.[17] Moreover, typical

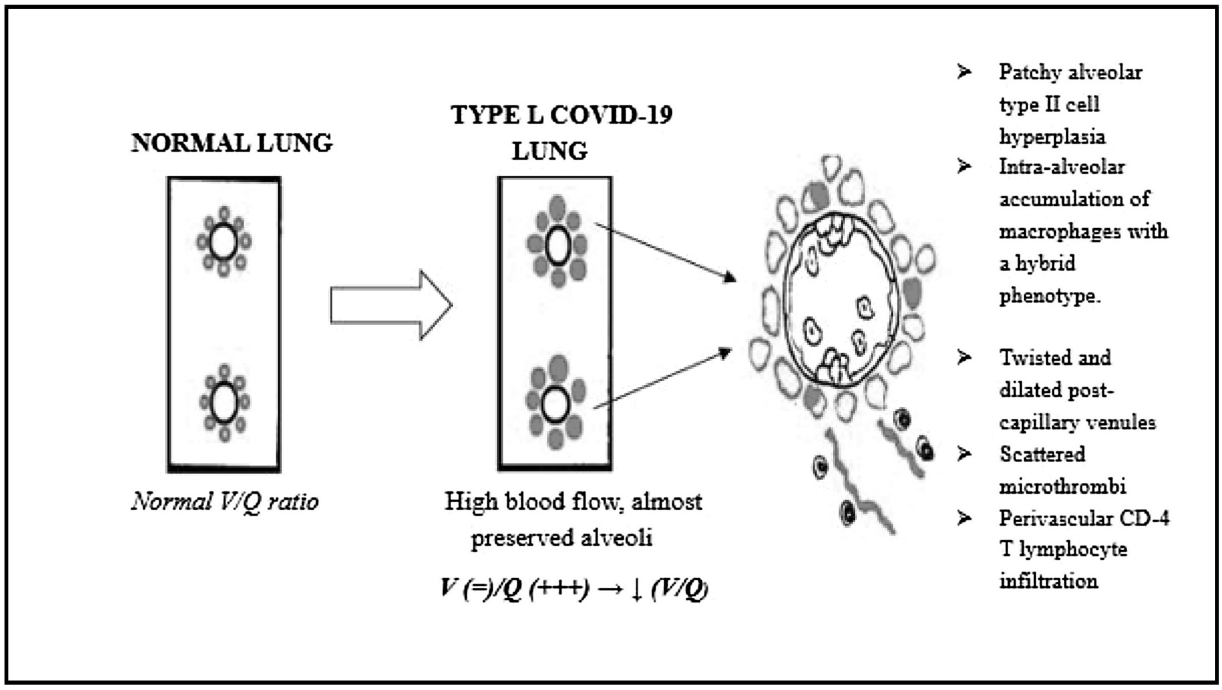


**Figure 1** Pathophysiologic considerations about type L COVID-19. This cartoon shows how the histopathological modifications, seen in lung cryobiopsies, may lead to a reduction in the V/Q ratio.

findings of DAD were rare or absent. There were no hyaline membranes and foci of intra alveolar proteinaceous oedema were spotted only occasionally.[16]

The aim of this paper is to answer this crucial question: can the histopathological hallmarks of early COVID-19 explain the pathophysiology and clinical presentation of the L phenotype? In particular, we will focus on clinical features such as the so called ''happy hypoxemia'', the response to awake prone positioning, the response to positive end expiration pressure (PEEP) or to continuous positive airways pressure (CPAP), and reports of patients with platypnea orthodeoxia.

## Can histopathologal feature explain peculiar clinical presentations of l phenotype COVID-19?

### General pathophysiological considerations

As mentioned earlier, our lung samples showed not atelectatic alveoli, with no hyaline membranes. Therefore, the alveolar side of the alveolar capillary barrier is almost preserved.

On the other hand, vascular structures appear to be substantially rearranged. The dilation and hyperplasia of alveolar capillaries, along with pulmonary venodilatation, can lead to blood overflow around these almost pristine alveoli.

Hence, the ventilation/perfusion ratio (V/Q) is reduced, since ventilation is preserved, whereas perfusion is increased. This could be the main reason for hypoxemia in the L phenotype of COVID-19 (Fig. 1).

Furthermore, alveoli appeared neither collapsed nor obliterated; therefore it is unlikely that atelectasis contribute significantly to COVID-19 respiratory failure.

The ''dead space'' effect seems to play a marginal role considering the almost complete absence of microthrombi in our lung samples, and the absence of pulmonary embolism of larger vessels on computed tomography pulmonary angiography (CTPA), as all patients underwent this exam before the cryobiopsy.[16]

This assumption is confirmed by Lang et al., as they showed, thanks to dual energy CT scan, hyper perfusion in the affected areas in the mild forms of SARS-CoV-2 interstitial pneumonia.[18]

### The ''happy hypoxemia''

This is undoubtedly one of the most interesting clinical features of COVID-19 patients. Many patients present with pronounced arterial hypoxemia, yet without proportional signs of respiratory distress. In several cases, they do not even verbalize a sense of dyspnea. This phenomenon has been labeled as ''happy dyspnea''.[13]

Tobin et al. presented 3 cases of extreme ''happy hypoxemia'', with PaO2 ranging between 36 and 45 mmHg, in the absence of increased alveolar ventilation.[19] Moreover, Guan reported dyspnea only in 18,7% of 1099 hospitalized COVID-19 patients, despite low PaO2/FiO2 ratios and abnormal CT scans.[20]

As an example of this phenomenon, we can also report one of our most plain cases of ''happy hypoxemia''. Fig. 2 refers to a 67yo woman with no significant past medical history. The CT scan was taken 15 days after the onset of symptoms, and shows bilateral ground glass/crazy paving

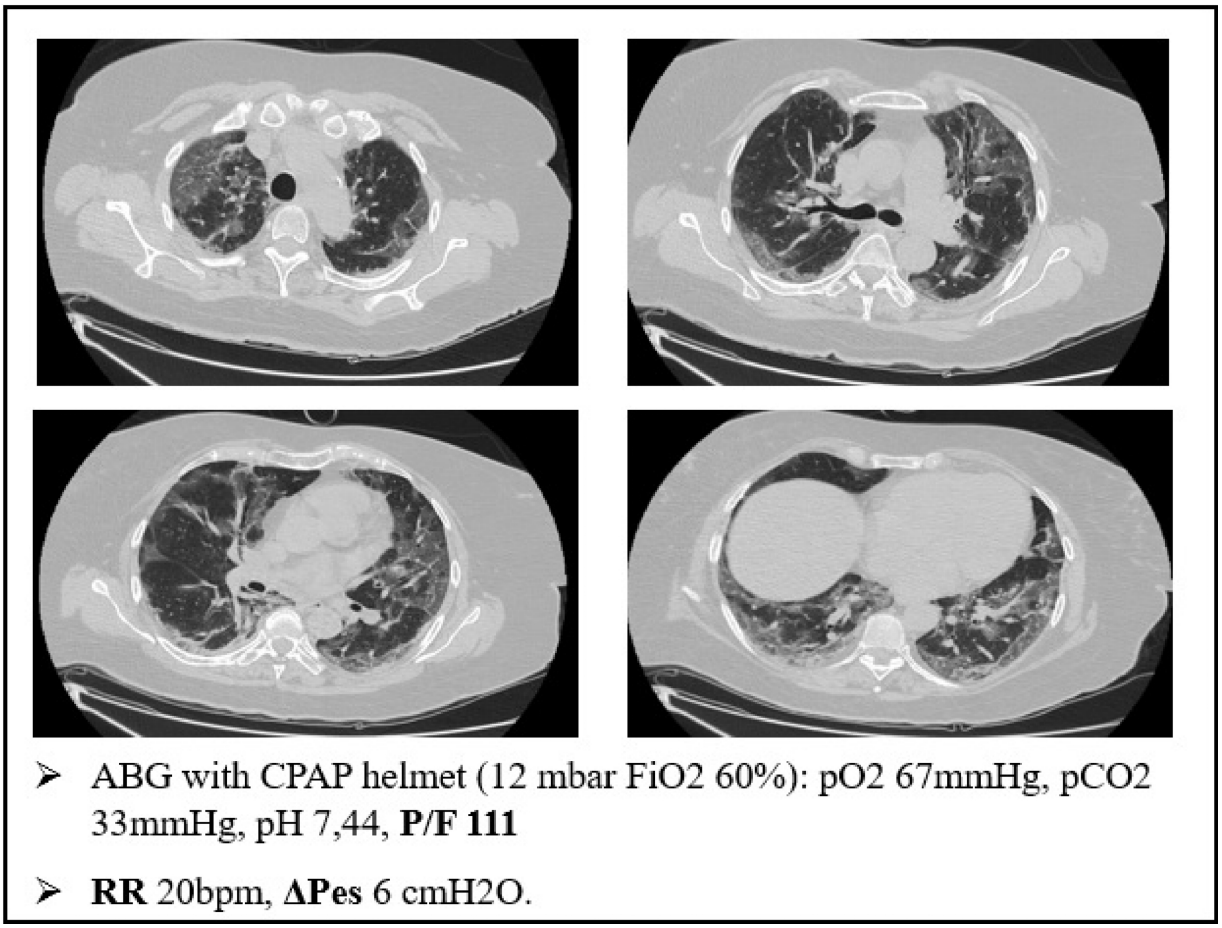


**Figure 2** A case of happy hypoxemia. ΔPes shows normal respiratory effort, even if the patient had profound respiratory failure with tachypnea. ΔPes: swings of esophageal pressure during the act of breathing.

attenuation, with a visual severity score of 16/20. The patient developed severe hypoxemic respiratory failure and CPAP treatment was started. As displayed on Fig. 2, the patient was tachypneic and ABG during CPAP treatment showed severe respiratory failure. Tidal volume could not be recorded, but we did monitor the swing of esophageal pressure (ΔPes), thanks to a multifunctional nasogastric tube with a dedicated pressure transducer (NutriVent Sidam Group). The swing of esophageal pressure, during spontaneous breathing, reflects the respiratory effort.[21] To reduce the confounding factor of breath to breath variability of the respiratory dynamic[22], we measure esophageal pressure swing in at least two daily 3 min long recordings at rest and then calculate an average ΔPes. In this case, we measured a ΔPes of 6cmH2O: a normal respiratory effort, even if the patient had profound respiratory failure with tachypnea.

The causes behind this unusual phenomenon are yet to be fully understood. However, several hypotheses have been proposed.

First of all, dyspnea is generally defined as a sensation of difficult or labored breathing. It occurs when the demand for ventilation is out of proportion to the patient's ability to respond. It is therefore different from tachypnea (rapid breathing) and hyperpnea (increased tidal ventilation).[23,24]

COVID-19 patients usually present with hypoxemia (low PaO2) and low PaCO2, caused by several confounding factors such as fever, hyperpnea due to hypoxemia, or anxiety associated to the arterial puncture itself.[13]

The respiratory chemosensors are highly sensitive to increasing level of PaCO2. Therefore, CO2 retention is one of the strongest stimuli to increase in respiratory drive and minute volume ventilation, contributing to dyspnea. On the other hand, hypoxemia alone plays a limited role in the sensation of breathlessness. Experimental models have shown that dyspnea only occurs when PaO2 drops below 40 mmHg, whereas when PaO2 ranges between 65 and 40 mmHg, the body responds with a rise in minute ventilation, increasing the respiratory rate, without dyspnea. Tachypnea and hyperpnea, not dyspnea, are therefore the clinical signs of impending hypoxemic respiratory failure.[23,24]

Tobin et al. reported a broad range in chemosensors' sensitivity to PaCO2 and PaO2 in healthy subjects, and also in the same patient when the tests were performed at a different time of the day. Older age increases this variability as well, hence setting a precise threshold of chemosensitivity for the occurrence of dyspnea might be extremely complicated.[22]

Moreover, some comorbidities, such as diabetes mellitus (reported in roughly 16% of severe COVID-19 cases by Guan

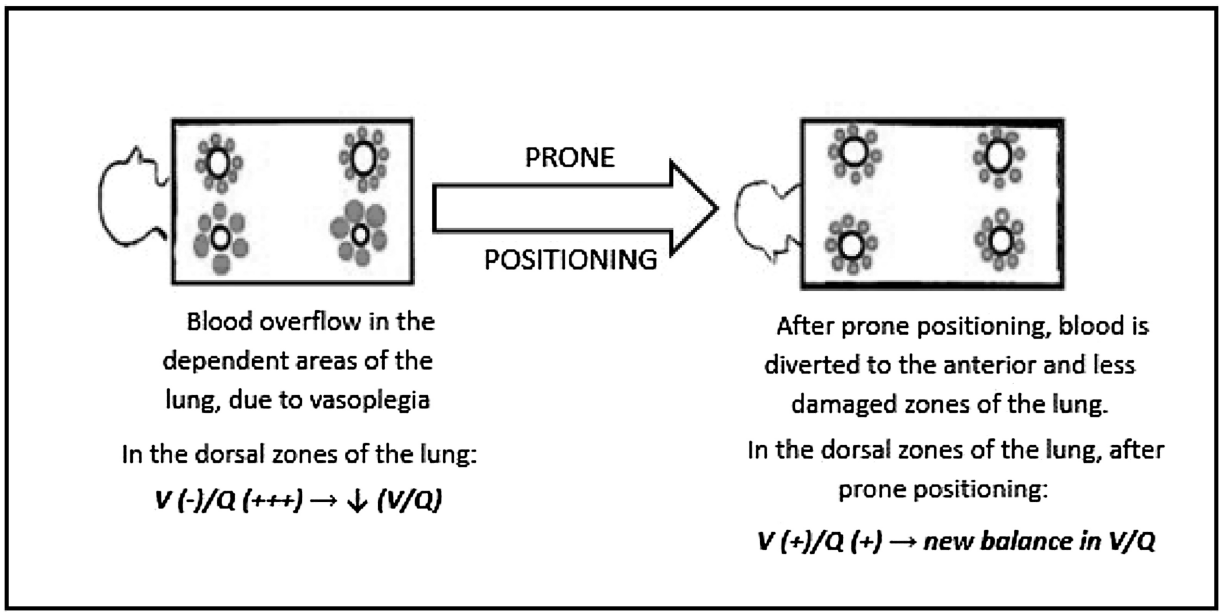


**Figure 3** Response to awake spontaneous breathing prone positioning in COVID-19. This cartoon shows that the blood is diverted from the hyperperfused areas of the lung after prone positioning. Amelioration in blood oxygenation might be explained by a new equilibrium in the V/Q ratio.

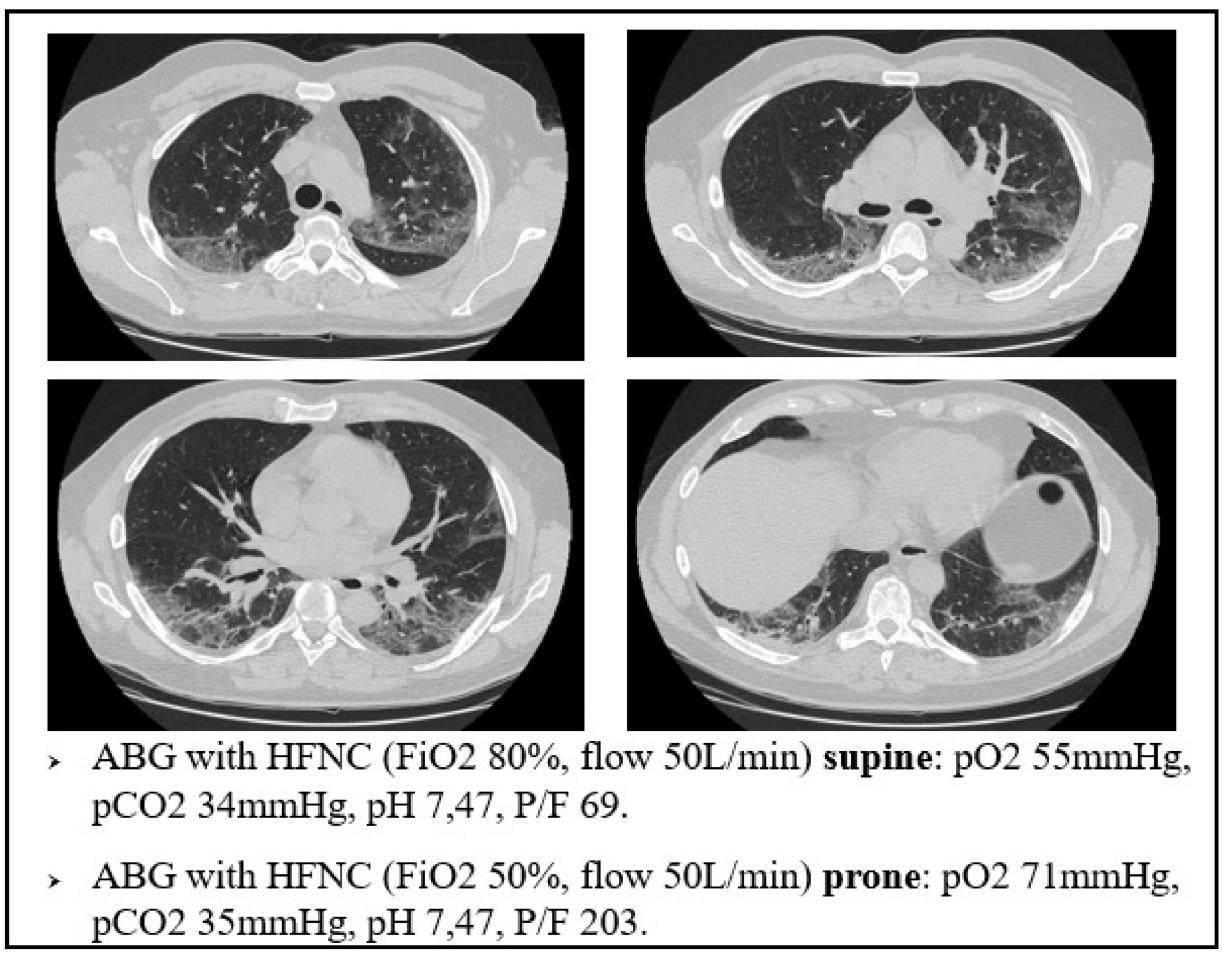


**Figure 4** A case of brilliant response to awake, spontaneous breathing, prone positioning.

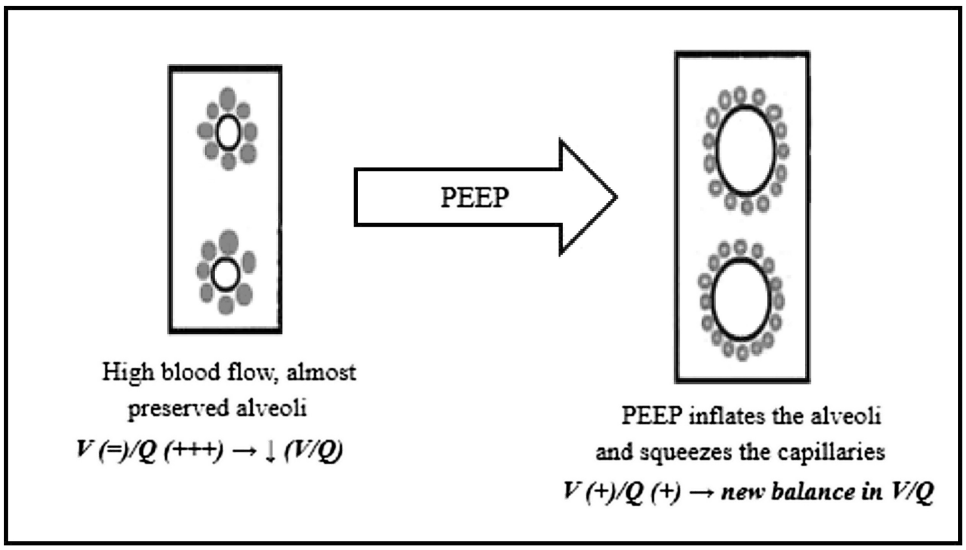


**Figure 5** PEEP/CPAP response in type L COVID-19. This cartoon shows how the alveolar inflation provided by the CPAP/PEEP therapy might lead to a new equilibrium in the V/Q ratio.

et al.[20]) might impair the perception of dyspnea.[25] This phenomenon might therefore reduce the prevalence of dyspnea in diabetic COVID-19 patients, leading to a delay in seeking medical attention.

However, dyspnea is not just a matter of central chemosensors and PaCO2 sensitivity. In fact, dyspnea can also be caused by inputs from the mechanoreceptors in the respiratory tract and chest wall, and by fatigue or weakness of respiratory muscles due to altered lung and chest wall mechanics.[24]

The compliance of the respiratory system therefore plays a significant role in the genesis of dyspnea. As aforementioned, our lung biopsies show no signs of atelectasis or alveolar edema, leaving the lung with an almost preserved compliance. During the first days of infection, there is also no increase in airway resistance, thus the breathing effort remains low in many patients without preexisting lung disease when affected by COVID-19.[13]

This also suggests that dyspnea is a very important clinical sign of deterioration in COVID-19 patients. Dyspnea tells the clinicians that lung compliance is falling, and that the patient might be evolving from an L phenotype to a more life threatening H phenotype.[13]

## The response to awake prone positioning

Prone invasive ventilation is a cornerstone of treatment of severe ARDS. It is a strategy to improve oxygenation when protective ventilation fails. In severe ARDS, prone positioning improves gas exchange by ameliorating the ventral dorsal transpulmonary pressure difference, reducing dorsal lung compression, and improving lung perfusion.[26,27] It also reduces mortality, according to several papers.[28]

However, proning awake, spontaneously breathing patients with COVID-19 pneumonia is gaining acceptance. Initially, anecdotal evidence on the benefit of awake prone positioning in COVID-19 was reported, but now evidence is growing. This was one of the first surprises of COVID-19 patients, and it was very welcome, since it is an intervention with minimal risk and requiring minimum assistance.[29–32]

It is now clear that awake prone positioning leads to a quick improvement in arterial blood oxygenation in SARS-CoV-2 pneumonia. However, as our biopsies show no significant signs of parenchimal atelectasis nor alveolar edema, it seems unlikely that the beneficial effect of prone positioning in these patients is due to a better ventilation of the dorsal region of the lung.

The vascular changes seen in our histological samples may play a role in this phenomenon. As a matter of fact, recent reviews of CT scans highlight the importance of the vascular alterations in typical radiological findings of COVID-19. For example, Lang et al., using dual energy CT scan technology, described peculiar vascular enlargement and mosaic attenuation as a pattern of inefficient vasoregulation in the affected regions, besides the typical ground glass attenuation and consolidation. The authors labeled these features as ''hyperemic halo'' pattern.[18]

Moreover, in a case series of COVID-19 patients, Piciucchi et al. described a reversibility of venous dilation and changes in parenchimal density in CT scan images acquired after moving the patient from supine to prone position. Interestingly, in this series as soon as patients switch to the prone position, enlargement of pulmonary veins appears to diminish and changes in density of the ground glass and/or crazy paving areas are observed.[15] These findings match with what we found in our biopsies. The typical ground glass attenuation/crazy paving of SARS-CoV-2 pneumonia could largely reflect the vascular changes taking place in the alveolar septa, instead of accumulation of proteinaceous edema or hyaline membranes in the alveolar spaces.

Our findings suggest that the injured areas of the lung are regions with high blood perfusion and rather normal alveoli, therefore in these areas the V/Q ratio reaches the lowest values. Prone positioning leads to a blood flow redistribution to the less damaged area, and hence to a new balance of the V/Q ratio, increasing arterial oxygen levels (Fig. 3)

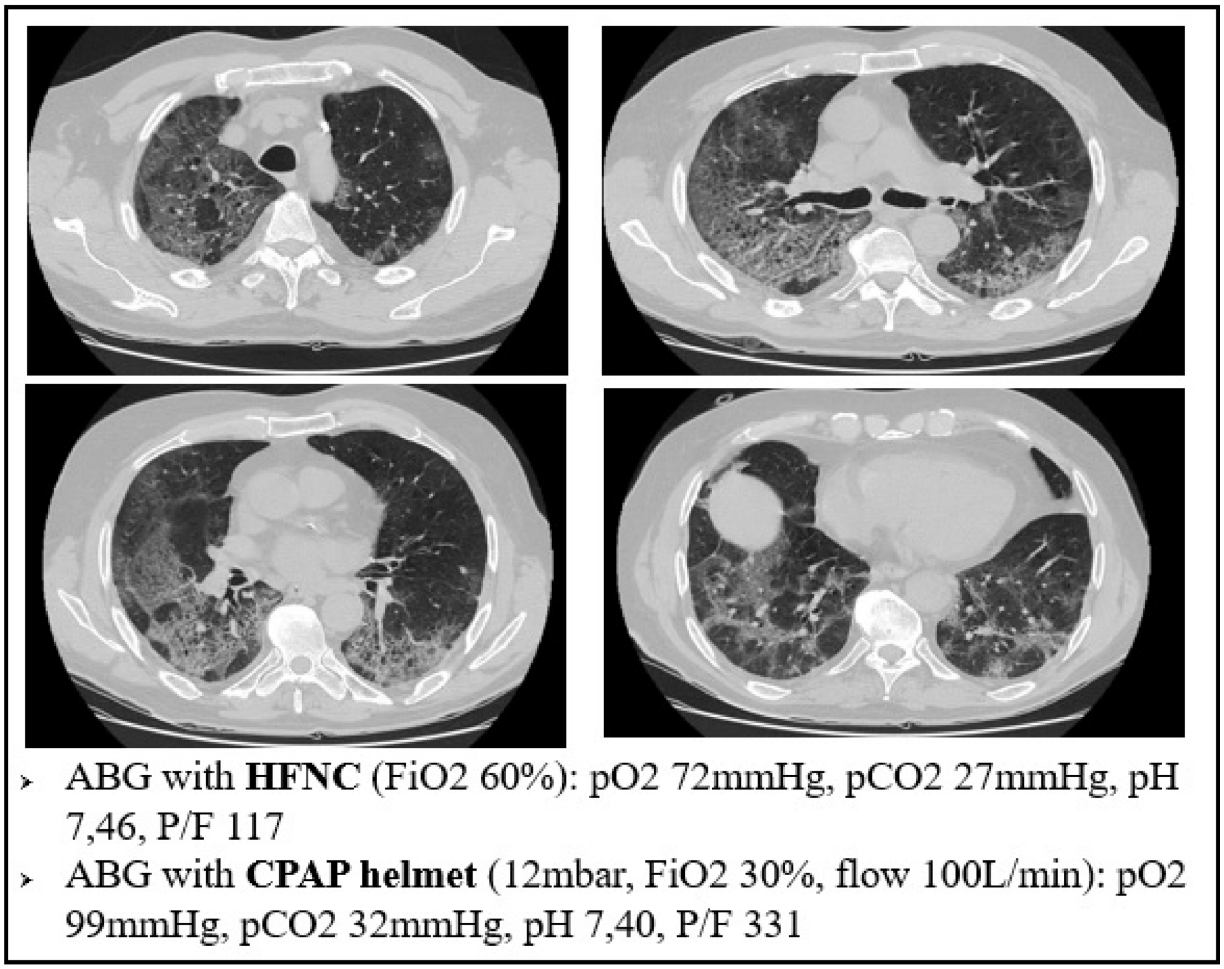


**Figure 6** A case of significant response of arterial blood oxygenation in an early COVID-19 case, after initiating CPAP therapy.

This mechanism is well represented in Fig. 4, a 49yo male with no past medical history. The CT scan was obtained after 9 days from the onset of symptoms, and displays the typical radiological findings of SARS-CoV-2 pneumonia, mainly in the dorsal region of the lungs. Visual severity score was 12/20. This was one of the patients that underwent lung biopsy. Lung tissue from the altered region of the right lower lobe showed areas of high blood flow, due to capillary hyperplasia and venous dilation, surrounding patent alveoli. Switching the patient to the prone position resulted in a rapid improvement in arterial blood oxygenation at ABGs.

## Response to PEEP/CPAP

CPAP is widely used in the COVID-19 pandemic, especially in patients treated outside the ICU. Patients treated with CPAP are usually affected by type L COVID-19.[33–35]

CPAP has been used for decades in a variety of patients to improve arterial blood oxygenation. The main role of CPAP is keeping the alveoli open: the so called ''alveolar recruitment''. In fact, CPAP can push back the transudate from the alveolar space during acute cardiogenic edema, but it can also keep the lung open when facing exudate and atelectasis due to lung infections, inflammations or classical ARDS.[36,37,5]

However, how can we explain the striking role of CPAP in type L SARS-CoV-2 pneumonia, since our biopsies showed no sign of alveolar edema, hyaline membranes or atelectasis?

Again, we can explain this phenomenon as a matter of V/Q ratio. The increased alveolar pressure given by CPAP might help by inflating the alveoli, thereby squeezing the capillaries next to them, reducing the V/Q ratio inequality (Fig. 5)

For example, Fig. 6 refers to a 76yo male, former smoker, with a past medical history of arterial blood hypertension and moderate chronic kidney disease. The CT scan was obtained after 7 days from the onset of symptoms and shows bilateral ground glass attenuation and crazy paving typical of the early phases of SARS-CoV-2 pneumonia. Visual severity score was 14/20. The high flow CPAP strongly ameliorated the arterial blood oxygenation after few minutes. The results of our biopsy suggest that such a quick improvement could be explained with a redistribution of lung perfusion, along with alveolar hyperinflation. A new balance in V/Q was reached.

## Platypnea Orthodeoxia

Platypnea Orthodeoxia refers to an uncommon condition of positional dyspnea and hypoxemia, that occur when the

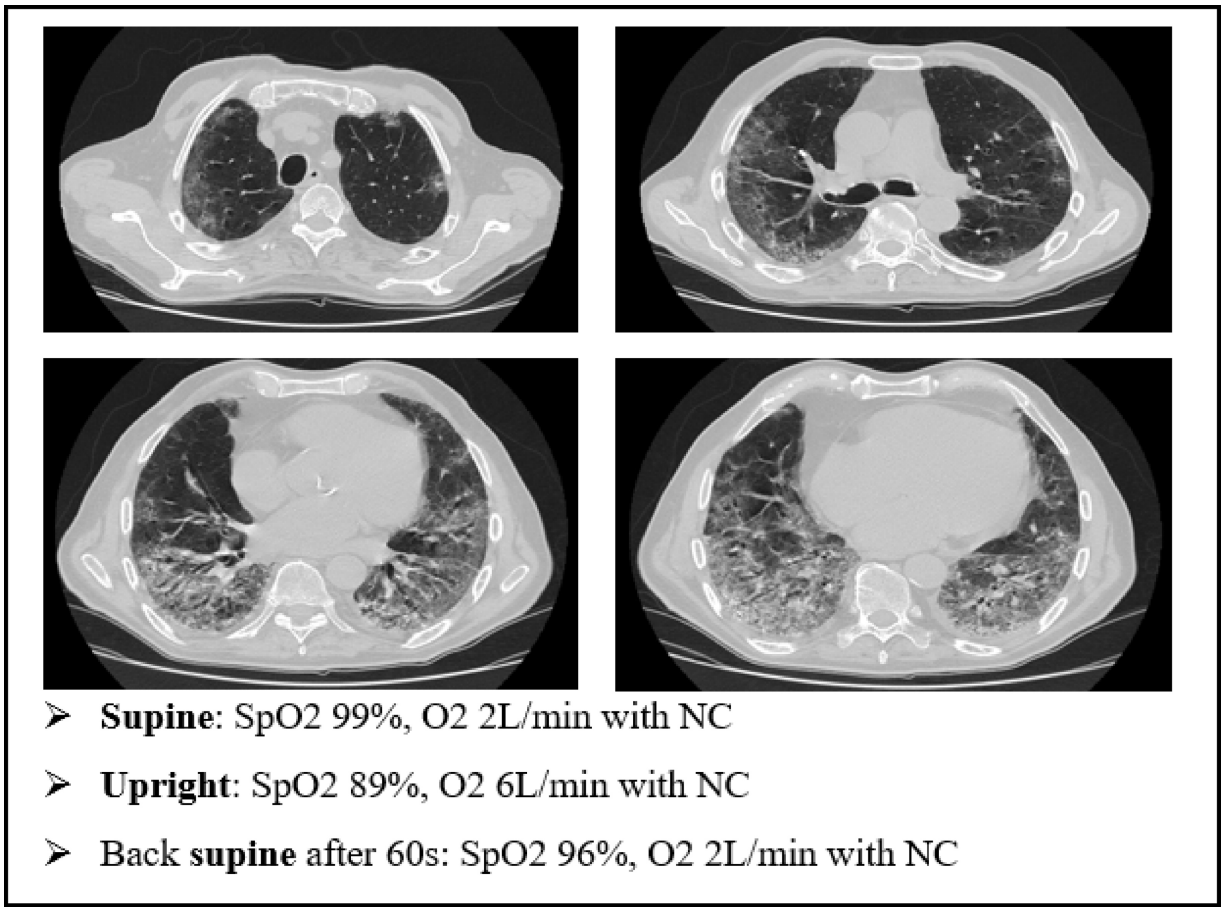


**Figure 7** A case of platypnea orthodeoxia occurred during the recovery from a severe case of COVID-19. NC: nasal cannula. platypnea orthodeoxia in type L COVID-19 (HPS like effect).

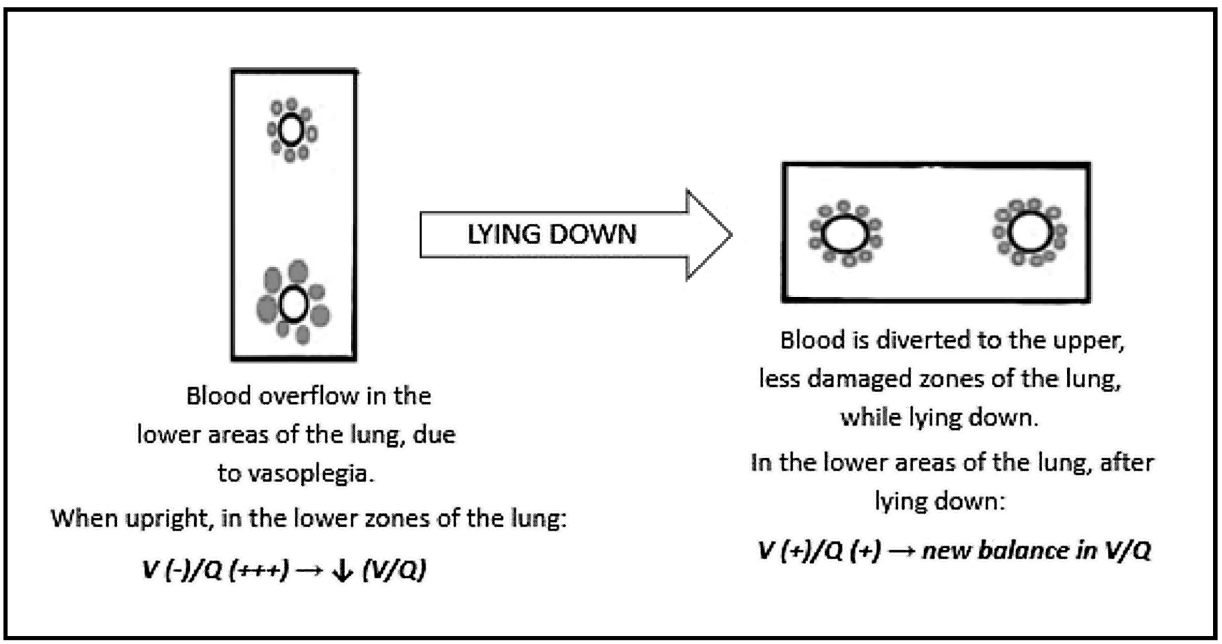


**Figure 8** This cartoon shows how blood overflow in the lower areas of the lung might explain the platypnea orthodoxia occasionally seen in COVID-19 patients. This process resembles the one seen in patients affected by HPS. HPS: hepatopulmonary syndrome.

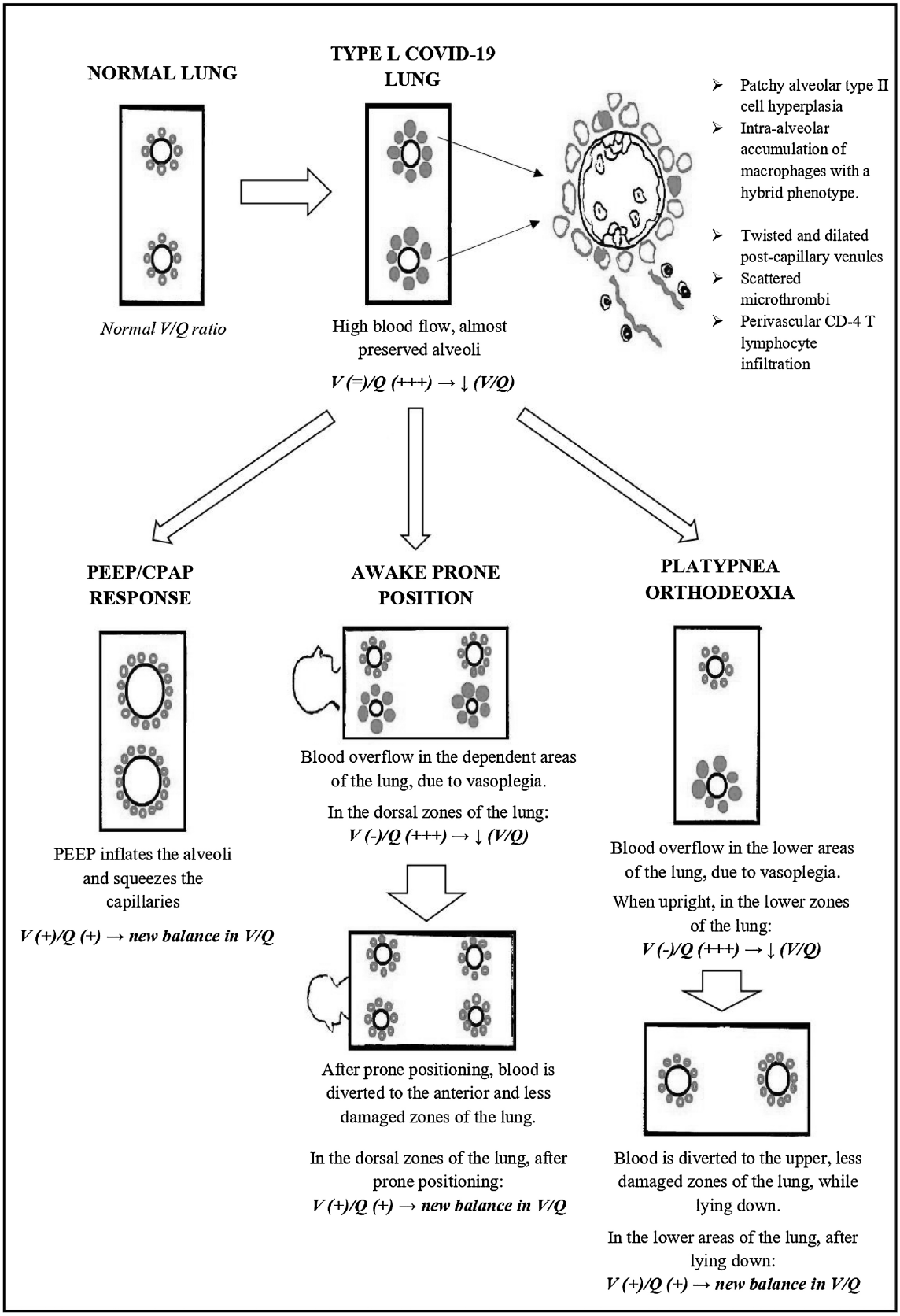


**Figure 9** A summary of the pathophysiological phenomena described in Type-L COVID-19.

patient is upright and are resolved with recumbency. This syndrome is suspected when normal arterial oxygen saturation (SpO2) is recorded while the patient is supine, followed by abrupt decline in saturations when upright.[38]

Apparently, this condition is less common in type L COVID-19 patients than the phenomena described before. Even so, some cases have been described, especially during recovery after the acute phase of SARS-CoV-2 pneumonia.[39]

We present an explanatory case as seen in our ward (Fig. 7). This is an 80 yo male, former smoker, with a past medical history of arterial blood hypertension and benign prostatic hypertrophy. He was admitted in to our Semi intensive Respiratory Care Unit for SARS-CoV-2 pneumonia and treated with CPAP for several days. After the weaning from CPAP, the patient started to develop clinical signs of platypnea orthodeoxia. As shown in Fig. 4, he needed a relatively small amount of oxygen through nasal cannula (NC) to maintain a normal level of SpO2 while lying down. However, sitting up resulted in a drastic drop in SpO2 levels, requiring increase in O2 flow.

The patient underwent a CT scan. It was 18 days since the onset of symptoms. The CT scan showed bilateral ground glass attenuation, crazy paving and consolidation, especially in the lower lobes.

How can we explain this case of platypnea orthodeoxia, considering the CT scan and the information given by our biopsy?

We could explain this phenomenon with a similar condition: the hepatopulmonary syndrome (HPS). Hepatopulmonary syndrome is characterized by impairment in blood oxygenation due to intrapulmonary vascular dilations and shunting in the context of liver disease. HPS is defined as a syndrome characterized by a clinical triad: (1) advanced chronic liver disease, (2) arterial oxygenation defect, (3) widespread pulmonary vascular dilation. The pathogenesis of this condition is yet to be fully understood. These patients have extremely dilated pulmonary vasculature, with almost preserved ventilation, and hypoxemia is caused by a reduction of the normal V/Q ratio.[40,41]

Moreover, the vascular enlargement is usually more represented in the lower regions of the lungs, leading to a sudden increase in perfusion of the dependent areas of the lung as soon as the patient stands upright. This overflow causes further reduction in V/Q ratio, hence a swift worsening of hypoxemia in sitting position (Fig. 8).[41]

We can speculate a similar mechanism in type L COVID-19 patients showing platypnea orthodeoxia. The main histopathological feature of SARS-CoV-2 pneumonia is vascular enlargement, therefore if the COVID-19 lesions are more severe in the lower areas of the lungs (as in Fig. 7), it is possible for the patient to develop the platypnea orthodeoxia syndrome, with the same mechanism of HPS.

## Conclusions

We believe that the direct knowledge of the histopathological hallmarks of early COVID-19 could provide some plausible answers to the many questions that the L phenotype as hypothesized by Gattinoni L, et al. raises.[6]

We suggest that the pathophysiology of the L phenotype might be explained by the predominance of the shunt effect and V/Q ratio reduction due to: (1) the neoangiogenesis taking place in the interalveolar septa; (2) the ''vasoplegia'' due to the loss of muscular tone of the alveolar capillaries and pulmonary venules and veins; (3) the stability of the alveoli which do not display the typical damage seen in ARDS.

This could explain interesting clinical behaviour such as the CPAP response, the response to spontaneous breathing pronation and the platypnea orthodeoxia seen in some patients as summarized in Fig. 9.

Our hope is that these observations might contribute to identify more tailored respiratory support and to investigate a possible role of drugs affecting pulmonary vascular tone in the treatment of COVID-19 pneumonia.

## Authors contributions

Stefano Oldani and Claudia Ravaglia conceived the paper and equally contributed to write the draft down. Serena Bensai, Lara Bertolovic, Cristiano Colinelli, Sara Piciucchi, Corrado Ghirotti, Silvia Puglisi, Sabrina Martinello and Siro Simoncelli helped to collect data, to analyze them and to interpret of the described phenomena. Venerino Poletti contributed in the inception of the paper, reviewed it critically and supervised all the aspects of this paper.

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## Ethical disclosure

All patients involved consented their clinical data to be used for this paper.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

# Dilation with rigid dilators as primary treatment of subglottic stenosis in pediatrics

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**KEYWORDS**
Subglottic stenosis;
Endoscopic treatment;
Rigid dilatation;
Pediatrics;
Airway

**Abstract**
*Introduction:* Acquired subglottic stenosis (SGS) occurs in 1–2% of children with a history of intubation. An alternative treatment is endoscopic dilation with rigid dilators.
*Material and methods:* Seventy-four patients with SGS grade I to III were treated between 2003 and 2017. Dilations were performed with Hegar-type rigid dilators every 2–3 weeks.
*Results:* Eighty-two percentage of patients responded to the treatment. 10% presented SGS grade I, 35% grade II and 55% grade III. Previous intubation time in successful cases was 12.4 days and it was 32 days in those that failed ($p = 0.02$). The average number of dilations was 3.23 in the group that responded and 2.98 for those that did not respond ($p = 0.51$). The presence of tracheostomy reduced the effectiveness of the treatment ($p = 0.002$). The average follow-up was 43.5 months.
*Conclusion:* The use of rigid dilators under endoscopic control is an effective minimally invasive method for treating patients with SGS grades I to III. Previous intubation time and the presence of tracheostomy were identified as poor prognostic factors.


## Introduction

Subglottic stenosis (SGS) is the narrowing or reduction of the airway lumen at subglottis level affecting the cricoid cartilage. This can be congenital or acquired. More than 90% of cases of SGS are secondary to endotracheal intubation.[1,2]

Until the 1980s, endoscopic dilations were most often used to treat subglottic stenosis. However, surgical reconstruction began to boom after the publications of Fearon and Cotton.[3] Open surgery includes laryngotracheal reconstruction with costal cartilage and partial cricotracheal resection, both with defined indications and successful results.[3–5] These are invasive and time-consuming surgeries,

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with hospitalization in intensive care units, morbidity and even mortality. Some of the patients will even require post-surgical endoscopic treatments to improve results.[6]

Endoscopic treatments include dilations with pneumatic balloons or rigid dilators, laser incisions or cold scalpel.[6] Endoscopic balloon dilations have greater acceptance due to their advantage expanding the stenotic area through their measured and controlled radial pressure.[7] Rigid dilators were sidelined because the shear forces applied in the stenotic sector hypothetically cause mucosal injury, resulting in fibrosis and worsening of the disease. Some authors have reported encouraging results with rigid metal dilators with the benefit of lowering costs by using reusable instruments over a long period of time.[8]

Endoscopic dilations were indicated for stenoses grade I and II and in those SGS recurrences in post-surgical patients with laryngotracheal reconstructions.[9] Currently, patients with SGS grade III are also candidates for dilations.[2]

The aim of this study is to evaluate the results of treatment with rigid dilators and identify factors of prognostic value.

## Materials and methods

This is an observational, analytical – descriptive, retrospective and longitudinal analysis of clinical histories of patients diagnosed with acquired subglottic stenosis (SGS) treated with dilations in a 14-year period between March 2003 and March 2017 in the Airway Department of ''Hospital de Niños de la Santísima Trinidad''.

Population: Patients with a diagnosis of SGS whose initial treatment was dilations are the subject of this analysis.

We included all patients with SGS secondary to endotracheal intubation and who were initially treated with endoscopic dilations. We excluded patients with congenital SGS, those with previous laryngeal surgery and patients with SGS grade IV.

Subglottic stenosis diagnosis was made under general anesthesia using a rigid bronchoscope zero degree lens with an appropriate caliber for the patient's age. The stenosis caliber was measured with Myer–Cotton technique and dilation was performed with Hegar-type rigid dilators with increasing diameters until reaching the patient's corresponding diameter was reached.[10] The largest caliber dilator was left in the narrow zone for a period of 2 min or until saturation fell below 92%. The result of the expansion was then evaluated with the same technique. Four operators performed all procedures.

The dilations were repeated every 2 or 3 weeks depending on the patient's clinical condition.

The patients were treated as outpatients and were discharged 6–8 h after endoscopic dilation. In all cases, empirical treatment for gastroesophageal reflux with proton pump inhibitors was indicated.

We evaluated the age (months), previous intubation time that produced the lesion (days), diagnostic interval (days from extubation to SGS diagnosis), degree of stenosis according to Myer and Cotton classification (grade I: 0–50%, grade II: 51–70%, grade III: 71–99% and grade IV: no detectable lumen), presence of tracheostomy prior to treatment, airway associated pathologies (larynx, vocal cords, trachea and bronchi), response to treatment, decannulation in tracheostomized patients and follow-up (months).

A good or ''positive'' response to treatment was considered when an adequate and stable caliber of the airway was achieved (less than 30% stenosis) and the patient remained asymptomatic and without limitations in normal activity for his or her age. Otherwise it was considered a failure or a ''negative'' result.

### Statistical methodology

An Excel-like database was created for statistical processing using data collected from clinical histories. Central and dispersion measures were calculated for the descriptive statistics of quantitative variables, and percentages for each category were calculated for the categorical variables. Variable comparison according to ''positive'' and ''negative'' results was accompanied by a Wilcoxon inferential statistical test in the case of mean comparison and a chi-square for categorical results. The level of significance used was 0.05 and it was carried out with the SPSS program.

## Results

During the period analyzed a total of $n = 74$ children with acquired SGS diagnosis were treated. Fifty-five percent of the patients were male and the remaining 45 percent were female. The mean age at diagnosis was 19.4 months (SD = 30.8), ranging from 1 month to 12 years.

As for the initial diagnosis that required patient intubation, the most frequent were bronchiolitis 31%, heart diseases 13.5%, pneumonias 10%, prematurity 9% and respiratory distress syndrome due to various causes. Eight percent of the patients had an associated diagnosis of Down Syndrome.

Mean intubation time was 16.2 days (SD = 18.8) and stenosis was grade I in 10%, grade II in 35% and grade III in 55% of cases (Fig. 1). Response to treatment was ''positive'' in 82% of cases and ''negative'' in the remaining 18% (Fig. 2).

Depending on the treatment outcome, the mean age at diagnosis was 18 months for those with a positive result and

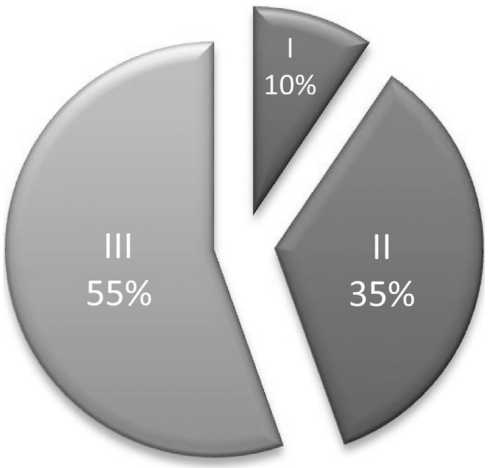


**Figure 1** Distribution of the sample by degree of stenosis ($n = 74$).

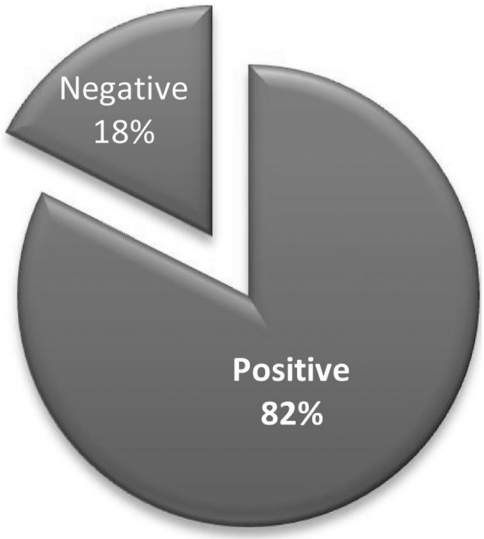


**Figure 2** Distribution of the sample by result ($n = 74$).

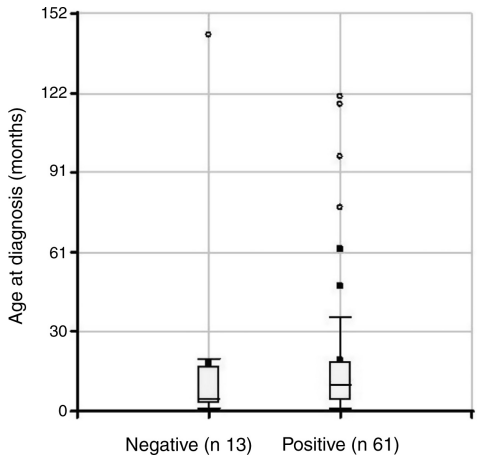


**Figure 3** Box plot of Age at diagnosis according to Result ($p = 0.2812$).

19.7 months for those who did not respond ($p$ = not significant) (Fig. 3). The intubation time in positive cases was 12.4 days and 32 days in the group where treatment failed ($p = 0.0231$) (Fig. 4).

The average number of dilations was 3.23 in the respondent group and 2.98 for non-responders ($p = 0.51$). The diagnostic interval in patients with positive results was 836.7 days ($r$: 1–31.360), of which 73% exceeded 30 days of extubation. In patients with negative results, this interval was 97.6 days ($r$: 1–540 days).

From the analysis of stenosis degree it is concluded that the majority of patients in both groups presented grade III: 62% of the negatives and 55% of the positives, while the percentages with stenosis grade II were 23% and 37% respectively (Fig. 5).

Nine patients who did not respond to dilation treatment had previous tracheostomy ($p = 0.0021$) (Fig. 6). Among the reasons for performing tracheostomy are: pulmonary pathology (broncopulmonary dysplasia, pneumonia, bronchiolitis), vocal cord paralysis, and prolonged intubation in neonatal period.

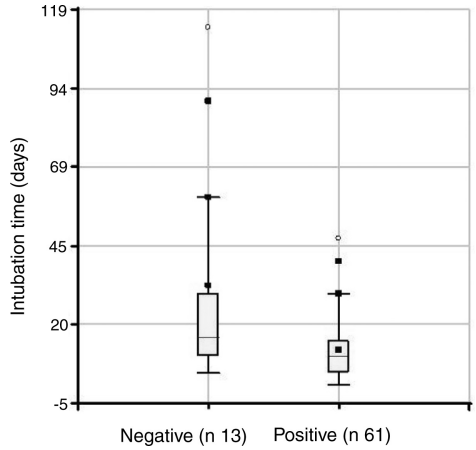


**Figure 4** Box plot of Intubation time according to Result ($p = 0.0231$).

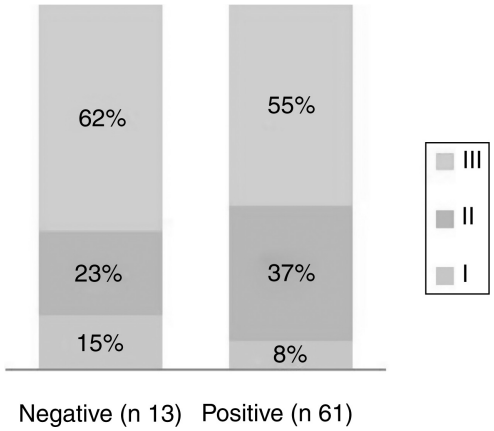


**Figure 5** Stenosis degree according to Result ($p = 0.5456$).

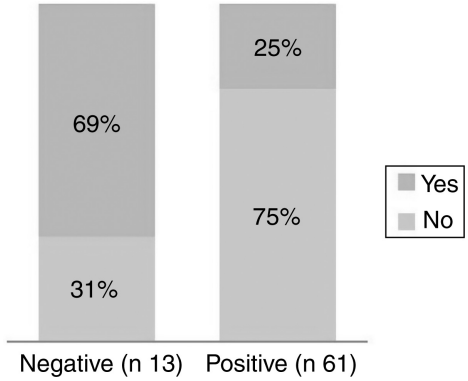


**Figure 6** Tracheostomy according to Result ($p = 0.0021$).

Eighteen patients were diagnosed with associated airway pathology including unilateral vocal cord paralysis, bilateral vocal cord paralysis, laryngomalacia, and laryngotracheomalacia among others. Fourteen patients presented airway comorbidities in the responding group and 4 patients in the group with poor outcome. Statistical analysis indicated that the difference is not significant ($p = 0.5508$). Patients with glottic or tracheal stenosis were not included.

Among the 13 patients who did not respond to treatment with dilations, eight received open surgical treatment

**Table 1** Characteristics of patients with negative results in relation to diagnosis.

| Diagnosis | Comorbility | ESG | Traqueostomy |
|---|---|---|---|
| BPD | | 95 | Yes |
| Down syndrome + BQL | Laryngomalacia | 60 | No |
| BPD | | 80 | Yes |
| BQL | | 70 | No |
| Pneumonia | | 90 | Yes |
| Prematurity | Laryngomalacia | 80 | Yes |
| BQL | | 90 | Yes |
| Pneumonia | | 50 | No |
| Cardiopaty | VC paralysis | 60 | Yes |
| Pneumonia | | 80 | Yes |
| Cardiopaty | VC paralysis | 85 | Yes |
| Prematurity | | 50 | No |
| BQL | | 90 | Yes |

BPD: bronchopulmonary dysplasia. BQL: bronchiolitis. VC: Vocal cord. ESG: subglottic stenosis, obstruction percentage.

with good results in six of them. Technically, surgery did not present complications related to previous treatment. The remaining patients are awaiting surgical resolution. The characteristics of the patients with negative results are described in Table 1.

The average follow-up for all patients was 43.5 months starting from the last bronchoscopy to the last office control (*r*: 1–86 months).

Four patients died. The causes were: tracheostomy cannula accident, sepsis, nosocomial pneumonia and complex congenital heart disease.

There were no complications attributable to the endoscopic dilation procedure with rigid dilators.

## Discussion

Subglottic stenosis is the most severe consequence of endotracheal intubation in children.[11] A simple, effective, minimally invasive therapy could be of great benefit for the treatment of this pathology. The option of dilating the narrow airway is one of them. Balloon dilations have been used with good results.[7–10,12,13] However, there are few reports of dilations with rigid or semi-rigid dilators.[8,14] Despite the increase in the implementation of treatment with dilations, no selection criteria have yet been established in order to optimize results.[15] The success rate of endoscopic treatment has varied according to the reports and the method used, ranging from 60% to 70% by balloon dilations[7,13] up to 100% reported with rigid dilations although this includes a large percentage of patients with stenosis grade 1 and a high number of procedures over a long period of time.[8]

Rigid endoscopic dilation was used on all our SGS diagnosed patients who had airway lumen that allowed a dilator to be introduced. In our case, the result was favorable in 82% of the patients treated. Age and degree of stenosis were not significant factors in predicting response to treatment, consequently it can be stated that it is a therapy applicable to all patients with SGS grade I to III.

When analyzing intubation time we noted that children who responded to treatment had an average of 12.4 days of intubation and in the group that failed it was 32 days ($p = 0.02$). This difference could be due to the fact that longer intubation time would produce a more extensive lesion in length and depth with greater alteration of the cricoid cartilage histology.[1]

We noted that an average of 3 dilations were enough to determine an outcome in both groups. We consider that other therapeutic alternatives should be considered for those patients who do not show improvement after the third dilation.

The average number of days of diagnostic interval in patients who responded to dilations was higher than in those who failed (836 vs. 97 days), which allows us to suspect that the wound healing period in which the stenosis is found does not define the response to treatment. As mentioned above, 73% of the SGSs that responded had chronic stenosis after more than 30 days of extubation. This may be due to the fact that histological changes are variable and apparently do not depend on time elapsed or severity of the stenosis.[11]

Bearing in mind that stenosis degree and diagnostic interval did not influence the response unlike intubation time which produced the lesion, we can infer that the most significant factor in predicting the response to dilations could be the depth of histological changes in the airway matrix although we do not have histological analyses to support this hypothesis.[1]

Another prognostic factor we identified as being associated with a negative response was the presence of tracheostomy. More than half the patients tracheostomized prior to the beginning of endoscopic treatment did not respond. We did not identify any significance in this relationship, since previous intubation times or association of comorbidities were no more frequent in patients with a negative response. Nor did we note lesions associated with endoscopic dilations in patients with tracheostomy.

The presence of airway comorbidities in patients who did not respond to treatment was less than in those with positive results, thus contrary to reports that relate comorbidities with poor response.[7] Despite this difference, the analysis was not statistically significant, but we suggest that the presence of associated airway pathology does not contraindicate dilation treatment.

Lang et al. report an average follow-up of 7 months in most papers when conducting a meta-analysis and systematic review in 2013.[15] We have a 43 months recurrence-free follow-up of our patients which allows us to assert that this is a treatment with good long-term results. Due to the good results obtained, we have extended the indication of dilations to increasingly severe stenosis since 2003. Among our patients, the highest percentage had stenosis grade 3 with a good response to treatment, which encourages us to implement this method in all patients who have SGS with any lumen allowing dilation.

We conclude that SGS treatment using rigid dilators under endoscopic control is a minimally invasive and effective method. Prolonged intubation time and the presence of tracheostomy were the only factors significantly related to treatment failure. We have not found any factors that contraindicate dilations and dilation with rigid dilators could be indicated as first-line treatment for SGS grade 1–3. We rec-

ommend 3 endoscopic dilation procedures and then, in the absence of response, evaluation of other treatment alternatives. Given that the patients who did not respond were subsequently operated on without any difficulty attributable to the dilations, we consider that the initial endoscopic treatment does not interfere with future surgical treatment in the event of failure.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

# Factors associated with non-completion of latent tuberculosis infection treatment in Rio de Janeiro, Brazil: A non-matched case control study

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**KEYWORDS**
Tuberculosis;
Contacts;
Latent tuberculosis infection;
Adherence

**Abstract**
*Introduction:* There are scarce data on the routine latent tuberculosis infection treatment (LTBIT) and factors associated with a non-completion in high tuberculosis burden countries. Therefore, in this study we aimed to evaluate the factors associated with non-completion of LTBIT.
*Materials and methods:* This was a non-matched case control study conducted at a University Hospital in Rio de Janeiro, Brazil. A total of 114 cases and 404 controls were enrolled between January/1999 and December/2009. Cases were close contacts who did not complete the LTBIT and controls were the contacts that completed it. Multivariate analysis was used to investigate risk factors associated with non-completion of LTBIT among contacts in two different periods of recruitment.
*Results:* Factors associated with non-completion LTBIT included: drug use (OR 23.33, 95% CI 1.83–296.1), TB treatment default by the index case (OR 16.97, 95% CI 3.63–79.24) and drug intolerance. TB disease rates after two years of follow up varied from 0.4% to 1.9%. The number necessary to treat to prevent one TB case among contacts was 116.
*Conclusions:* Non-completion treatment by the index case and illicit drug use were associated with not completing latent tuberculosis infection treatment and no tuberculosis disease was identified among those who completed latent tuberculosis infection treatment.


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## Introduction

The World Health Organization (WHO) declared tuberculosis (TB) a global public health emergency since 1993, and in 2018, in Brazil 82,409 cases were reported (new and relapses) which corresponds to an incidence rate of 45 cases per 100,000 inhabitants.[1] The state of Rio de Janeiro, has the second highest incidence rate in Brazil with an incidence rate of 66.3/100,000 inhabitants, which highlights the importance of actions for TB control and strategies to interrupt the transmission chain.[2]

Contact tracing of patients with pulmonary TB (PTB) is one of the most important strategies for interrupting the transmission and subsequent development of TB.[3] A systematic review found that the prevalence of TB in contacts is 1.4% for high income countries and 3.1% for low/middle income countries.[4] In addition, the screening of contacts helps identify contacts with latent *Mycobacterium tuberculosis* infection (LTBI), through a positive tuberculin skin test (TST) or by interferon gamma release assays (IGRA). Subjects with LTBI have a higher risk of developing TB disease and benefit from the LTBI Treatment (LTBIT). The use of isoniazid (INH) for 6–9 months is recommended for LTBIT with a 60–90% protective effect against active TB.[5]

The protective effect of INH for LTBIT varies depending on differences in treatment duration and adherence to the scheme.[6] Adherence to LTBIT is strongly influenced by clinical, social, financial, and behavioral factors. Studies evaluating factors associated with low adherence to LTBIT under routine conditions are scarce. In high income countries, the proportions of completion of LTBIT vary from 50% to 78%,[7–9] and in low/middle income countries, from 54% to 78%.[10–12]

According to the National TB program (NTP) guidelines, the Hospital TB Control Program in our hospital recommends treatment for LTBI in close contact with PTB patients once active TB is excluded.[6,7] In this context, this study aimed to analyze the factors associated with non-completion of LTBIT in contacts with patients with PTB treated at our outpatient clinic.

## Material and methods

### Settings

The Hospital TB Control Program was created in 1998 at Clementino Fraga Filho University Hospital and has coordinated the TB and LTBI diagnosis and treatment activities. From January 1999 to December 2009, INH was prescribed during 6 months (300 mg/die tablets in adults, and 10–15 mg/kg/die in children), following the National TB Guidelines for LTBIT.[5,6]

### Study design and study population

We included all contacts for whom LTBIT was recommended during the study period. In an unmatched case control study design, cases were defined as contacts who did not complete 6 months of LTBIT (contacts that started and stopped treatment at any time) and as controls the contacts who completed 6 months of LTBIT. The sample size was based on the number of contacts recruited by the TB control program. Contacts who were transferred to other Health Units or Clinical Research Unit, before starting LTBIT were excluded. The Investigational Review Board at the Clementino Fraga Filho University Hospital granted a waiver for the study and gave ethical approval for publication of the results.

### Data collection procedures

Data was collected by the researchers using data sources from the Hospital TB Control Program (medical charts and special forms used since 1998). This study evaluated two periods: January 1999 to March 2003 and April 2003 to December 2009. In the first period, the criteria for LTBIT initiation were: (i) contacts with PTB patients aged <15 years, not vaccinated with BCG and with TST $\geq$ 10 mm; (ii) contacts aged <15 years, vaccinated with BCG and with TST $\geq$ 15 mm; (iii) contacts with positive booster response (a second TST $\geq$ 10 mm with an increase in induration of at least 6 mm); (iv) HIV positive contact regardless of TST result; (v) immunocompromised contacts due to immunosuppressive drugs use or immunosuppressive diseases with TST $\geq$ 5 mm; (vi) contacts with recent tuberculin conversion (TSTC). TSTC was defined as an increment of TST $\geq$ 10 mm in respect to previous testing in non-BCG-vaccinated contacts, or $\geq$15 mm in contacts vaccinated with BCG in the previous two years.[13]

In the second period, the criterion for TST positivity changed and LTBIT was recommended to contacts of any age with TST $\geq$ 5 mm.

TB disease was assessed using the National Information System for Notifiable Diseases (Sistema de Informação de Agravos de Notificação – SINAN) records. Names and birth dates of contacts were matched with the SINAN database two years after LTBIT recommendation. In Brazil, access to TB treatment is only possible through the public health system. The TB case is notified and the patient's data (sociodemographic and clinical) are entered in SINAN. Therefore, the contact who developed active TB and initiated anti-TB treatment had his/her data entered in SINAN. We cannot ignore, however, that cases of untreated subclinical TB have occurred. SINAN evaluation was carried out by a professional assigned by the Health Secretary of Rio de Janeiro State. All data were extracted and directly entered into a Microsoft Excel spreadsheet.

Using special forms developed by the Hospital TB Control Program, the following variables were identified: co-morbidities, chronic medication use, signs/symptoms of drug intolerance to INH (rash, anorexia, nausea, vomiting, epigastric pain, arthralgia, peripheral neuritis, euphoria, insomnia, drowsiness, anxiety, headache, acne, fever), illicit substance use.

### Statistical analysis

Main outcome measures were proportion of contacts completing LTBIT (adherence to the LTBIT), variables associated with non-completion of LTBIT, TB disease rate and the number of LTBIT needed to prevent one TB case among contacts. Initially, bivariate analysis between contacts who did and

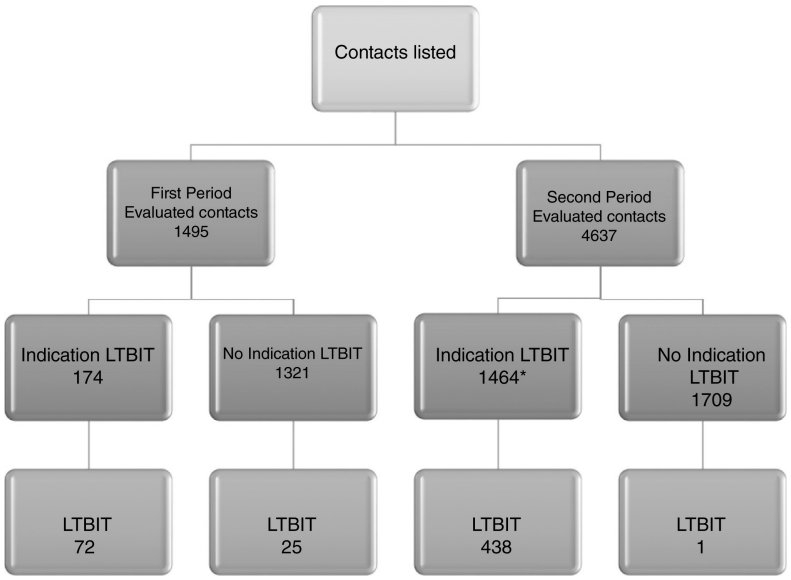


**Figure 1** Tuberculosis contacts description from 1999 to 2009. * 781 were excluded. After the exclusions, 683 remaining contacts with LTBIT indication. ILTBIT: latent tuberculosis infection treatment.

those who did not complete LTBIT and each of the potential determinants of treatment default was performed and the differences in proportion were analyzed by Chi-square or Fisher's exact tests and odds ratios (OR) with correspondent 95% confidential intervals are presented.

The variables analyzed were: sex, age, literacy, family income, occupation, origin, type of contact, co-morbidities, previously treated TB, alcohol use, illicit drug use, use of other medications, drug intolerance, drug-resistant TB in the index case (IC), non-completion treatment by the IC and the IC in clinical research. Following the National TB Guidelines, HIV testing was not routinely offered to contacts, thus the HIV status was known only if the contact informed us during the interview. In this case, it was included as a comorbidity.

Variables associated with non-completion in bivariate analysis ($p \leq 0.05$) were tested in multivariate models. Adjusted odds ratio and 95% confidence intervals for the odds ratio were estimated. To calculate the number of contacts to be treated for LTBI necessary to prevent one TB case (NNT), all contacts who started but did not complete treatment (incomplete LTBIT) or who did not start treatment were considered contacts without LTBIT that had a chance to develop TB disease and all contacts that completed LTBIT were considered contacts with LTBIT who also could develop TB disease. Analyses were performed using Epi-Info (Centers for Disease Prevention and Control, CDC, Atlanta), Statistical Package for Social Sciences (SPSS), version 20.0 for Windows (SPSS Inc., Chicago, IL, USA) and GraphPad.

## Results

According to inclusion and exclusion criteria, in the first period and in the second period, 11.6% (174/1495) and 46.1% (1464/3173) had LTBIT recommended, respectively. Among 174 contacts with LTBIT indication in the first period, 72 (41.4%) started the treatment. In the second period, among 1464 contacts with LTBIT indication, the following were excluded: 33 (2.3%) due to transfer to other health units at the physician's discretion or due to request by the contact and 998 (68.1%) were referred to a clinical trial linked to TB Trials Consortium, but among them, 250 (17.1%) came back to the Hospital Tuberculosis Program. After the exclusions, 683 remaining contacts with LTBIT indication, 438 (64.2%) started the treatment. By medical decision, another 25 contacts with LTBI in the first period and 1 contact in the second period started on LTBIT although they did not have criteria for this according to NTP, totaling 536 contacts (Fig. 1).

**Table 1** Latent tuberculosis infection treatment outcomes in first and second periods.

| Outcomes | First period*n* (%) | Second period*n* (%) |
|---|---|---|
| *Favorable* | | |
| Completed treatment | 79 (81.4%) | 325 (74.0%) |
| *Unfavorable* | | |
| Non-completion treatment | 10 (10.3%) | 104 (23.7%) |
| Tuberculosis disease | 1 (1.0%) | 0 (0.0%) |
| Transfer to another health unit | 5 (5.2%) | 4 (0.9%) |
| Death | 0 (0.0%) | 1 (0.2%) |
| Suspension by the physician | 2 (2.1%) | 5 (1.1%) |

We enrolled 114 cases and 404 controls in the study; for 18 contacts we were unable to retrieve information from Hospital TB Control Program forms. The proportion of contacts that did not complete LTBIT increased from 10.3% (10/97) in the first period to 23.7% (104/439) in the second period (Table 1). In the first period, among cases and con-

trols, females and household contacts were, respectively, 80% (8/10) and 56% (44/79), and 80% (8/10) and 81% (64/79). Median age was 12 years among cases and 10 years among controls. Ninety percent (9/10) of cases and 78% (62/79) of controls had 0 to 8 years of schooling.

In the analysis of clinical and epidemiological factors associated with non-completion of LTBIT we found that individuals who use illicit drugs were more likely to treatment default (OR 23.33, 95% CI 1.83–296.1, $p = 0.05$), which maintained after fitting the data through multivariate analysis (adjusted OR 0.04, 95% CI 0.00–0.54). However, the small number of drug users among contacts (only 3) produced an imprecise estimate with a large confidence interval (Table 2).

In the second period, females were 56% (58/104) of cases vs. 57% (187/325) among controls and household contacts were %, and 56% (58/104) and 60% (196/325). Median age was 13 and 17 years among cases and controls, respectively. Years of school were $\leq$8 for 71% (74/104) of cases and 67% (318/325) of controls. Using bivariate analysis, the following clinical and epidemiological factors were associated with non-completion of treatment: co-morbidities (OR 2.09, 95% CI 1.13-3.89, $p = 0.01$), use of other medications (OR 3.54, 95% CI 1.48-8.48, $p = 0.002$), absence of drug intolerance (OR 2.46, 95% CI 1.39-4.35, $p = 0.001$) and TB treatment default by IC (OR 16.97, 95% CI 3.63-79.24, $p = 0.00005$). However, after fitting the data through multivariate analysis, only the absence of drug intolerance (adjusted OR 2.46, 95% CI 1.39-4.35) and TB treatment default by IC (OR 9.37 95% CI 2.24-39.13) were independently associated with non-completion of LTBIT (Table 3).

Two years after LTBIT recommendation, active TB occurred in 1.0% (1/102) and 0.4% (1/245) of contacts who did not start treatment in the first and the second period, respectively. In the first period, TB disease was not observed among contacts who completed and did not complete the LTBIT. In the second period, no active TB occurred among contacts who completed the LTBIT, but active TB did occur in 1.9% (2/104) of contacts who started but did not complete the LTBIT.

After LTBIT indication in both periods, active TB occurred in 0.6% (2/347) of the contacts who were not treated, there was no active TB among contacts who completed the LTBIT and active TB occurred in 1.8% (2/114) of contacts with incomplete LTBIT (Table 4 In the first period, 112 LTBIT were required to prevent one active TB case. In the second period, 117 LTBIT were required to prevent one active TB case. In both periods, 116 LTBIT were required to prevent one active TB case (Table 4).

## Discussion

Early screening and treatment of LTBI in contacts of pulmonary TB cases are among the priorities launched by the End TB strategy.[15] And studies that evaluate the factors associated with completion of LTBIT in high TB burden countries become even more relevant.[16,17]

The proportion of completed LTBIT is variable between authors, Sharma et al. evidenced in a clinical trials conducted in research centers, this value is high (□90%),[18] but in a recent meta-analysis, Alsdurf et al. after evaluating 70 distinct cohorts pointed out several gaps in the diagnostic and treatment cascades; the general estimate is around 50% of people with medical indications completed LTBIT.[19]

However, under routine conditions, LTBIT completion rates range from 50% to 78%.[8–12] LTBIT, for both children and adults contacts of active pulmonary TB patients, has been recommended by PNCT since 2010.[20] However, in the IDT-HUCFF hospital complex of UFRJ, LTBIT became a priority target in 1999, after Hospital TB Control Program implementation. Therefore, it was possible to evaluate the impact of LTBIT under field conditions in a high burden urban area. Non-completion LTBIT rates (10.3% in the first period and 23.7% in the second period) were lower than those described in other series.

Evaluating the indication of LTBI treatment, we observed that there was a four times increase in the number of contacts with treatment indication in the second study period. This increase can be explained by the difference of the LTBI criteria used in each study period. The criteria changes included the treatment of adult contacts and TST positivity cut off decrease from 10 mm to 5 mm since April 2003. Using this TST positivity cutoff, the Hospital TB Program identified a higher number of infected contacts, which could be subjected to LTBIT.

We observed a significant difference in the proportion of contacts who started LTBIT between the first and second period. The increasing number of contacts who started LTBIT in the second study period could be attributed to the beginning of a clinical trial linked to TB Trials Consortium, in which contacts received incentives and directly observed treatment. These incentives may have had a positive influence on adherence to treatment onset in TB Program. Nevertheless, a majority of contacts did not start LTBIT in either cohort, and the main reason was the refusal of treatment.

The low percentages of non-completion of LTBIT observed in our study were similar to those reported by Codecasa et al., in Italy, and by Mendonça, in Rio de Janeiro and lower than the rates reported in the USA, Canada and in the state of Bahia, Brazil.[8,10–12] In Italy, where the study was performed under routine conditions, involving adults from risk groups for active TB, only 21.6% of contacts did not complete LTBIT.[9] Our study also found illicit drug use to be an important risk factor for non-completion of LTBIT, and our data are similar to a study conducted in Portugal that highlights the abuse of illicit drugs as well as alcohol for increased risk failure to complete LTBIT.[21] Mendonça observed a non-completion rate of 25% among subjects aged under 15 years of age who were treated in a reference unit from 2002 to 2009.[12] In large series in the USA and Canada, higher rates of non-completion of LTBIT were reported (40–52%).[9,22] In Salvador, Brazil, 46.5% of children and adults contacts did not complete LTBIT.[10]

Several studies have reported risk factors associated with non-completion of LTBIT. In the USA and Canada, Pettit et al. observed that among adults who initiated INH, female sex and alcohol use were independently associated with LTBIT discontinuation due to drug intolerance.[23] In another study, Horsburgh et al. identified the following as risk factors for non-completion of LTBIT: nine months treatment with INH, living in a nursing home, shelter, or prison; illicit drug use, age $\geq$15 years, and being a health care professional.[9] Our study also found illicit drug use to be an important risk fac-

**Table 2** Clinical and epidemiological factors associated with completion of latent tuberculosis infection treatment in first period

| | First period | | OR (95% CI) | *p*-Value | Adjusted OR (95% CI) |
|---|---|---|---|---|---|
| | Not completed treatment *n* = 10 *n* (%) | Completed treatment *n* = 79 *n* (%) | | | |
| *Type of contact* | | | | | |
| | 0 (0.0%) | 9 (11.4%) | | | |
| Extra-domiciliary | | | | | |
| | 8 (80.0%) | 64 (81.0%) | – | 1.0 | |
| Intra-domiciliary | | | | | |
| Unknown | 2 (20.0%) | 6 (7.6%) | – | – | |
| *Comorbidities*[a] | | | | | |
| Yes | 2 (20.0%) | 5 (6.3%) | | | |
| No | 8 (80.0%) | 74 (93.7%) | 0.27 (0.04–1.62) | 0.35 | |
| *Previously treated tuberculosis* | | | | | |
| Yes | 0 (0.0%) | 2 (2.5%) | | | |
| No | 9 (90.0%) | 73 (92.4%) | – | 1.0 | |
| Unknown | 1 (10.0%) | 4 (4.8%) | – | – | |
| *Alcohol use* | | | | | |
| Yes | 1 (10.0%) | 1 (1.3%) | | | |
| No | 7 (70.0%) | 70 (88.6%) | 0.10 (0.00–1.77) | 0.38 | |
| Unknown | 2 (20.0%) | 8 (10.1%) | – | – | |
| *Illicit drug use* | | | | | |
| No | 6 (60.0%) | 70 (88.6%) | | | |
| Yes | 2 (20.0%) | 1 (1.3%) | 23.33 (1.83–296.1) | 0.05 | 0.04 (0.00–0.54) |
| Unknown | 2 (20.0%) | 8 (10.1%) | – | – | |
| *Use of other medications*[b] | | | | | |
| Yes | 1 (10.0%) | 6 (7.6%) | | | |
| No | 9 (90.0%) | 73 (92.4%) | 0.73 (0.07–6.86) | 1.0 | |
| *Drug intolerance*[c] | | | | | |
| Yes | 2 (20.0%) | 20 (25.3%) | | | |
| No | 6 (60.0%) | 58 (73.4%) | 0.96 (0.18–5.18) | 1.0 | |
| Unknown | 2 (20.0%) | 1 (1.3%) | – | – | |
| *Drug resistant tuberculosis in index case* | | | | | |
| Yes | 0 (0.0%) | 2 (2.5%) | | | |
| No | 0 (0.0%) | 3 (3.8%) | – | 1.0 | |
| Unknown | 10 (100%) | 74 (93.7%) | – | – | |
| *Non-completion treatment by index case* | | | | | |
| No | 8 (80.0%) | 67 (84.8%) | | | |
| Yes | 1 (10.0%) | 4 (5.1%) | 2.09 (0.20–21.11) | 1.0 | |
| Unknown | 1 (10.0%) | 8 (10.1%) | – | – | |

[a] Comorbidities – presence of one or more any additional diseases.
[b] Medications – any other additional medications.
[c] Drug intolerance – presence of one or more of that: nausea, vomit, purities, acne, arthralgia, paresthesia, myalgia, anorexia, epigastric pain, gastric fullness, abdominal pain, diarrhea, headache, somnolence, dizziness.

tor for non-completion of LTBIT, despite the small sample analyzed. Machado et al. identified the presence of drug intolerance and the need to take two buses to reach the hospital as risk factors for non-completion of LTBIT.[10]

In contrast to the observations of Machado et al., we found that the absence of drug intolerance was a risk factor for a non-completion LTBIT.[10] A possible reason for this finding could be the differentiated care offered by the Hospital TB Program's multidisciplinary team in the presence of drug intolerance, positively influencing the adherence to LTBIT and encouraging contacts not to abandon the treatment. However, this association may be biased as drug intolerance

**Table 3** Clinical and epidemiological factors associated with completion of latent tuberculosis infection treatment in the second period.

| Factors | Second period | | OR (95% CI) | *p*-Value | Adjusted OR (95% CI) |
|---|---|---|---|---|---|
| | Not completed treatment *n* = 104 *n* (%) | Completed treatment *n* = 325 *n* (%) | | | |
| *Type of contact* | | | | | |
| Extra-domiciliary | 36 (34.6%) | 113 (34.8%) | | | |
| Intra-domiciliary | 58 (55.8%) | 196 (60.3%) | 0.92 (0.57–1.49) | 0.76 | |
| Unknown | 10 (9.6%) | 16 (4.9%) | – | – | |
| *Comorbidities*[a] | | | | | |
| Yes | 14 (13.5%) | 80 (24.6%) | | | |
| No | 90 (86.5%) | 245 (75.4%) | 2.09 (1.13–3.89) | 0.01 | 0.90 (0.38–2.09) |
| *Previously treated tuberculosis* | | | | | |
| Yes | 1 (1.0%) | 5 (1.5%) | | | |
| No | 101 (97.1%) | 319 (98.2%) | 0.63 (0.07–5.46) | 1.0 | |
| Unknown | 2 (1.9%) | 1 (0.3%) | – | – | |
| *Alcohol use* | | | | | |
| Yes | 7 (6.7%) | 36 (11.1%) | | | |
| No | 95 (91.3%) | 288 (88.6%) | 1.69 (0.73–3.93) | 0.21 | |
| Unknown | 2 (1.9%) | 1 (0.3%) | – | – | |
| *Illicit drug use* | | | | | |
| No | 101 (97.1%) | 320 (98.5%) | | | |
| Yes | 1 (1.0%) | 4 (1.2%) | 0.79 (0.08–7.16) | 1.0 | |
| Unknown | 2 (1.9%) | 1 (0.3%) | – | – | |
| *Use of other medications*[b] | | | | | |
| Yes | 6 (5.8%) | 58 (17.8%) | | | |
| No | 98 (94.2%) | 267 (82.2%) | 3.54 (1.48–8.48) | 0.002 | 0.37 (0.10–1.31) |
| *Drug intolerance*[c] | | | | | |
| Yes | 17 (16.3%) | 109 (33.5%) | | | |
| No | 83 (79.8%) | 216 (66.5%) | 2.46 (1.39–4.35) | 0.001 | 2.46 (1.39–4.35) |
| Unknown | 4 (3.8%) | 0 (0.0%) | – | – | – |
| *Index case in clinical study* | | | | | |
| Yes | 17 (16.3%) | 56 (17.2%) | | | |
| No | 87 (83.7%) | 269 (82.8%) | 1.06 (0.58–1.93) | 0.83 | |
| *Drug resistant tuberculosis in the index case* | | | | | |
| Yes | 9 (8.7%) | 37 (11.4%) | | | |
| No | 36 (34.6%) | 110 (33.8%) | 1.34 (0.59–3.05) | 0.47 | |
| Unknown | 59 (56.7%) | 178 (54.8%) | – | – | |
| *Non-completion treatment by index case* | | | | | |
| No | 71 (68.3%) | 241 (74.2%) | | | |
| Yes | 10 (9.6%) | 2 (0.6%) | 16.97 (3.63–79.24) | 0.00005 | 9.37 (2.24–39.13) |
| Unknown | 23 (22.1%) | 82 (25.2%) | – | – | – |

[a] Comorbidities – presence of one or more any additional diseases.
[b] Medications – any other additional medications.
[c] Drug intolerance – presence of one or more of that: nausea, vomit, purities, acne, arthralgia, paresthesia, myalgia, anorexia, epigastric pain, gastric fullness, abdominal pain, diarrhea, headache, somnolence, dizziness.

**Table 4** Development of tuberculosis disease two years after LTBIT recommendation.

| | Development of TB disease up to two years later | | Total | NNT |
|---|---|---|---|---|
| | No | Yes | *n* (%) | *n* (%) |
| **First period** | | | | |
| *LTBIT*[a] | | | | |
| | 101 (99.0%) | 1 (1.0%) | 102 (100%) | |
| Recommended but not performed | | | | |
| Complete | 79 (100%) | 0 (0.0%) | 79 (100%) | 112 |
| Incomplete | 10 (100%) | 0 (0.0%) | 10 (100%) | |
| **Second period** | | | | |
| *LTBIT* | | | | |
| | 244 (99.6%) | 1 (0.4%) | 245 (100%) | |
| Recommended but not performed | | | | |
| Complete | 325 (100%) | 0 (0.0%) | 325 (100%) | 117 |
| Incomplete | 102 (98.1%) | 2 (1.9%) | 104 (100%) | |
| **Both periods** | | | | |
| *LTBIT* | | | | |
| | 345 (99.4%) | 2 (0.6%) | 347 (100%) | |
| Recommended but not performed | | | | |
| Complete | 404 (100%) | 0 (0.0%) | 404 (100%) | 116 |
| Incomplete | 112 (98.2%) | 2 (1.8%) | 114 (100%) | |

[a] Latent tuberculosis infection treatment.

prevalence was low and all cases fulfilled the minor criteria, which do not usually lead to non-completion of LTBIT. Maciel et al., when analyzing different risk groups who had undergone LTBIT, observed the following factors to be associated with LTBIT default: being a health care professional, HIV positive, and a contact of a TB patient. Being a contact of TB patient increased the odds of non-completion of LTBIT by 2.65-fold and, possibly, the concentration of family efforts around the care of patient with TB disease leads to a lower priority given to LTBI.[11]

In our study, non-completion of TB treatment by the IC was associated with non-completion of LTBIT in the second study period. In this period, the contacts who underwent LTBIT were referred from other Health Units where IC were treated. Default of treatment by the IC possibly had a negative effect on the priority given by their contacts to LTBIT.

In neither period, two years after enrollment in the study, were there any cases of TB disease among contacts who completed LTBIT. On the other hand, TB disease was found in 1.8% of contacts who did not start LTBIT and 0.6% of those who started but did not complete it. In New York city, Anger et al. reported similar results, with higher TB disease rates among contacts who did not start LTBIT (1.5%) than among contacts who started LTBIT (0.4%).[24] In Brazil, in other series involving contacts with LTBIT indication, slightly higher rates of TB disease were described, ranging from 2.3% to 3.2%.[14,25]

The low rates of TB disease found in our study may be due to reasons other than the efficacy of INH therapy itself. Among these, we can cite: (a) hospital setting in a metropolitan area from middle income country, (b) contacts living in a urban area have lower risk for TB development (2.1–2.8%), as cited by Blok[26], (c) shorter follow-up period (2 years after the LTBIT recommendation), compared to the other series that followed-up contacts for 5 years.[14,25]

Overall, the NNT was similar in both periods. Therefore, it was not possible to state in which of the two cohorts the recommendation for LTBIT was more appropriate. Anger et al. observed results slight lower than to the ones found in our study, with 88 LTBITs required to prevent one TB case.[24]

The main limitations of the present study include the differences in the screening cascade of contacts in the two study periods, the limited sample size (particularly in the first study period) that could have precluded the emergence of other significant associations, the use of secondary data to diagnose TB disease among contacts, and no qualitative or economic analysis carried out to evaluate the barriers for implementation and impact of LTBIT.

## Conclusions

When analyzing the variables associated with non-completion of LTBIT, we found that illicit drug use and non-completion of TB treatment by the IC were the main risk factors. TB disease rates among contacts who did not start LTBIT or who started and did not complete it were lower than described in the literature and treatment completion of LTBIT may be a protective factor against the development of active TB. The high NNT observed in both periods among contacts who attended a university hospital from urban area

suggests that LTBIT may have lower relevance than expected in preventing a TB case.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

# Clinical profile and microbiological aetiology diagnosis in adult patients hospitalized with community-acquired pneumonia

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Antimicrobial treatment

**Abstract** Early introduction of appropriate antibiotherapy is one of the major prognostic-modifying factors in community acquired pneumonia (CAP). Despite established guidelines for empirical therapy, several factors may influence etiology and, consequently, antibiotic choices. The aims of this study were to analyze the etiology of CAP in adults admitted to a northern Portugal University Hospital and evaluate the yield of the different methods used to reach an etiological diagnosis, as well as analyze of the impact of patient demographic and clinical features on CAP etiology.

We retrospectively analyzed 1901 cases of CAP with hospitalization. The diagnostic performance increased significantly when blood and sputum cultures were combined with urinary antigen tests. The most frequent etiological agent was *Streptococcus pneumoniae* (45.7%), except in August, when it was overtaken by gram-negative bacilli (GNB) and *Legionella pneumophila* infections. Viral infections were almost exclusive to winter and spring. A negative microbiological result was associated with increasing age, non-smoking and lack of both blood/sputum cultures. Younger age was a predictor for *S. pneumoniae*, Influenza and *L. pneumophila* infections. Active smoking without any previously known respiratory disease was a

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risk factor for legionellosis. COPD was associated with *Haemophilus influenzae* cases, while dementia was typical in GNB and *S. aureus* patients. Diabetes mellitus (DM) and heart disease were negative predictors of *S. pneumoniae* and *H. influenzae*, respectively. *P. aeruginosa* was an independent risk factor for mortality (OR 13.02, 95% CI 2.94–57.7).

This study highlights the importance of a comprehensive microbiological diagnostic workup and provides clues to predicting the most probable CAP causative agents, based on a patient's clinical profile. These may be taken into account when establishing first line antibiotherapy.


## Introduction

Community-acquired pneumonia (CAP) remains a major cause of morbidity and mortality cause in Western countries, despite significant advances in antimicrobial and supportive therapy.[1] In Portugal, disease burden has been increasing in the last decade, especially among the elderly. According to the latest data, pneumonia is the main cause of respiratory hospitalization, accounting for 3.7% of all hospital admissions in Portugal between 2000 and 2009, with an intrahospital mortality rate of 20.4%.[2]

Early introduction of appropriate therapy figures as one of the major prognostic modifying factors.[3] The choice of initial antimicrobial treatment is usually empirical and it is essential that it is broad enough to cover all the likely pathogens. Despite international guidelines recommending specific empirical regimens, local differences in etiological pathogens have been found.[4] More recently, the emergence of antibiotic-resistant agents has created new concerns for a more judicious use of broad-spectrum antibiotics, which poses important challenges in initiating early therapy.[5] For this reason, and in order to propose the most appropriate treatment in a specific context, it is crucial to establish microbiological epidemiology data within different healthcare settings.

Respiratory bacteria are the major causative microorganisms, *Streptococcus pneumoniae* being the most common etiological CAP agent.[4] Other frequently identified pathogens are *Haemophilus influenzae*, Gram-negative enteric bacilli and respiratory viruses.[6] However, certain clinical features of patients have been associated with the risk of infection by multidrug-resistant (MDR) pathogens.[7] Some of these cases have been designated as healthcare-associated pneumonia (HCAP), which includes patients living in nursing homes, who are immunosuppressed, had recent hospitalization, undergo chronic dialysis or home-based infusion therapy. This differentiation was supported by the contrasting observed outcomes, with higher mortality rates among those with pneumonia acquired in the hospital or associated with healthcare environments.[8] However, this is a controversial term, given that a few European studies have shown etiology patterns in HCAP patients similar to those found in CAP patients,[9] which contrasts with data from the USA.[9] Moreover, etiological agents may have a seasonal distribution.[10] These variables must be taken into account when approaching the patient diagnosed with pneumonia.

The primary aim of this study was to describe the etiology of CAP in adults admitted to a northern Portugal University Hospital. Secondary aims are the evaluation of the yield of the diagnostic methods applied as well as the analysis of the impact of patients' demographic and clinical features on CAP microbiological etiology.

## Methods

### Study design

Retrospective analysis of hospitalized adults due to CAP at a northern Portugal University Hospital from January 2013 to December 2015. CAP was diagnosed in accordance with the IDSA/ATS guidelines as the presence of (i) at least one of the clinical symptoms of cough, sputum, fever, dyspnea, and pleuritic chest pain, (ii) elevated inflammatory biomarkers and (iii) new or evolving pulmonary infiltrate on chest radiography.[11] These criteria had to be present within 48 h of admission. Exclusion criteria were: age under 18 years; active tuberculosis; noninfectious diseases such as pulmonary infarction and pulmonary edema; hospital-acquired pneumonia (occurring $\geq$48 h after admission); or patients presenting features that were historically associated with HCAP (hospitalization for $\geq$2 days in the 90 days before admission, outpatient infusion therapy or chemotherapy, home wound care in the previous 30 days, admission from a nursing home or long-term care facility, or chronic dialysis in a hospital or clinic).[7]

The study was approved by the Health Ethics Committee of the hospital (approval number 2019-CE-P002). The requirement to obtain informed written consent from each individual was waived, as the study was limited to the review of existing medical records. To ensure confidentiality, each case was anonymized by the assignment of a random identification number.

### Microbial sample collection and analysis

Before commencing antibiotic therapy, the common practice in the hospital is to obtain from every patient hospitalized with CAP at least two blood cultures (BD BACTEC FX™ Blood Culture System, Sparks, Maryland, USA), urine sample for specific antigen detection and, whenever possible, sputum specimens for Gram stain and culture. During

flu season, recommendations also included performance of nasopharyngeal swab based on clinical suspicion. Bronchoalveolar lavage (BAL) and diagnostic thoracentesis were performed on medical indication, based on clinical judgement. Serological investigation was not routinely done. Bacteriological specimens were cultured on standard media. Sputum samples were considered acceptable for culture only when displaying >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per 100× power field.[12] Most agents – *S. aureus*, *S. agalactiae*, *S. hominis*, *Enterobacterales*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii and Stenotrophomonas maltophilia* – were identified by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry using the VITEK® MS analytical system, or VITEK cards (bioMérieux, France). For *S. pneumoniae* identification the test of susceptibility to the optochin were used, with bile solubility as a confirmatory test. Antimicrobial susceptibility was accessed mainly through the Kirby–Bauer method according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints, or by VITEK® cards. Urinary antigen detection tests for *S. pneumoniae* and *Legionella pneumophila* serogroup 1 were executed with the BinaxNOW pneumococcal or *Legionella* urinary antigen test (Binax, ME, USA). Nasopharyngeal swab was analyzed by real-time reverse-transcription PCR (RT-PCR) for detection of RNA viruses, namely influenza A and B viruses, and H1N1 on influenza A virus positive samples, parainfluenza viruses types 1–3, metapneumovirus, rhinovirus, enterovirus and respiratory syncytial virus. Real-time PCR detection of *L. pneumophila* and/or *Pneumocystis jirovecii* in respiratory samples was performed when medically relevant.

### Statistical analysis

All the statistical analyses were performed using the GraphPad Prism® 7 software (GraphPad Software, Inc.) and SPSS software program, version 25 (IBM® SPSS®, Inc.). Continuous variables were expressed as mean and standard deviation (SD), whereas categorical variables were expressed as frequency, unless stated otherwise. Frequency comparison was done via the $\chi^2$ test or the Fisher exact test for the categorical variables and the Student *t*-test or the Mann–Whitney *U* test for the continuous variables.

Different regression logistic multivariate models were performed separately to predict each microbiological etiology as the dependent variable. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the model. A *P*-value <0.05 was considered significant for all analyses.

**Table 1** Demographics and clinical background of the 1901 hospitalized adult patients with community-acquired pneumonia.

| Characteristics | No. of patients (%)[a] |
|---|---|
| *Age (years), mean ± SD* | 72.0 ± 16.5 |
| 18–39 years | 100 (5.3) |
| 40–64 years | 449 (23.6) |
| 65–79 years | 581 (30.6) |
| ≥80 years | 771 (40.6) |
| *Male/female gender* | 1058 (55.7)/843 (44.3) |
| *Active smoker* | 338 (19.6)[b] |
| *Comorbid conditions* | |
| Alcohol abuse | 85 (4.5) |
| Diabetes mellitus | 418 (22) |
| Heart disease | 401 (21.1) |
| Chronic kidney disease | 211 (11.1) |
| Asthma | 28 (1.5) |
| COPD | 357 (18.8) |
| Structural lung disease[c] | 117 (6.2) |
| Immunosuppression[d] | 80 (4.2) |
| HIV infection | 121 (6.4) |
| Active malignancy | 133 (7.0) |
| Dementia | 199 (10.5) |
| **Antimicrobial treatments, *n* (%)** | |
| *Monotherapy* | |
| Penicillin G | 11 (0.6) |
| Amoxicillin/clavulanate | 289 (15.2) |
| Levofloxacin | 339 (17.8) |
| 3rd gen. cephalosporin | 68 (3.6) |
| Macrolide | 2 (0.1) |
| Piperacillin/tazobactam | 95 (5) |
| Carbapenem | 10 (0.5) |
| *Combination providing coverage of 'atypical' pathogens* | |
| Amox/clav + macrolide | 677 (35.6) |
| 3rd gen. CS + macrolide | 290 (15.3) |
| Pip/taz + macrolide | 58 (3.1) |
| Carbapenem + macrolide | 13 (0.7) |
| *Oseltamivir* | 11 (0.6) |
| *None/unknown* | 38 (2) |

[a] Data represent number (percentage) of patients for each variable, except patient age, which is presented as mean ± SD.
[b] Due to missingness, data concerning smoking habits reflect a proportion out of 1723 cases.
[c] Bronchiectasis, pleuritis or sequelae of prior tuberculosis conditioning alteration of the normal architecture of the lung.
[d] Immunosuppressive drugs were defined as any use of systemic steroids, azathioprine, mycophenolate mofetil, TNF-alpha inhibitor, Cyclosporine, Cyclophosphamide and/or Methotrexate within previous 3 months. COPD, chronic obstructive pulmonary disease. HIV, human immunodeficiency virus.

## Results

### Demographics and clinical background

After applying the selection criteria, the final study population consisted of 1901 patients. Clinico-demographic characteristics and initial antimicrobial treatments are presented in Table 1. Over half (55.7%) of the CAP patients were male, and mostly older people, 71.1% of the study population were ≥65 years old. Most patients (73.3%) had at least one comorbid condition and 30.2% had ≥2 comorbidities (data not shown). Previous respiratory disease was common (26.4%) with chronic obstructive pulmonary disease (COPD) accounting for the majority of cases (18.8%). Non-respiratory conditions were also considerably prevalent with diabetes mellitus (DM) and heart disease being present in 418 and 401 patients (22% and 21.1%, respectively).

## Microbiological etiology of CAP and diagnostic yield of different methods

Microbiological tests obtained included the following: blood cultures ($n = 1403$, 73.8%), sputum samples culture ($n = 1058$, 55.7%), urinary antigen assays ($n = 1066$, 56.1%), pleural fluid ($n = 41$, 2.2%), BAL ($n = 6$, 0.3%). In 266 cases (14%) no microbiology testing was performed. Out of the remaining patients, those with at least one sample collected, etiological diagnosis was obtained for 420 (25.7%) patients. *S. pneumoniae* was the most commonly detected agent (45.7%, $n = 192$), followed by *Haemophilus influenza* (19.8%, $n = 83$), GNB (10%, $n = 42$) – *Klebsiella pneumoniae* ($n = 13$), *Escherichia coli* ($n = 10$), *Pseudomonas aeruginosa* ($n = 8$), *Enterobacter* spp ($n = 3$), *Proteus mirabilis* ($n = 2$), *Serratia marcescens* ($n = 2$), *Acinetobacter baumannii* ($n = 2$), *Raoultella ornithinolytica* ($n = 1$), *Stenotrophomonas maltophilia* ($n = 1$) – *Influenza virus* (9.0%, $n = 38$), *L. pneumophila* (7.6%, $n = 32$), *S. aureus* (4.3%, $n = 18$), *Moraxella catarrhalis* (1.7%, $n = 7$) and to a lesser extent other bacteria and virus both representing 0.9% ($n = 4$), Table 2.

The overall diagnostic yield of blood or sputum cultures was low, with 7.4% (104 positive results in 1403 tests) and 16.4% (174 positive results in 1058 tests), respectively. However, the diagnostic performance increased significantly ($P < 0.0001$) to 21.6% when blood and sputum were both collected, and to 31.5% when urinary antigen tests for *S. pneumoniae* and *L. pneumophila* were added to blood and sputum cultures (Fig. 1). The most frequently isolated agent in respiratory samples was *H. influenzae* (21.4%), followed by *S. pneumoniae* (14.1%). In fact, there was a significant contribution of blood cultures in the etiological diagnosis of *S. pneumoniae*, as shown in Table 2, highlighting the importance of blood cultures to isolate the causative pathogen. A negative microbiological result was significantly associated to older patients, female gender, non-smokers, heart disease, chronic kidney disease (CKD), dementia and incomplete etiological diagnosis workup, and correlated negatively with HIV infection. Three independent predictors for unknown etiology were identified in multivariate analysis: increasing years of age ($P < 0.001$), non-smoking ($P = 0.025$) and lack of both blood/sputum cultures ($P < 0.001$) (Table 3).

### Seasonality

Winter and spring accounted for the majority of adult CAP cases, with highest prevalence of *S. pneumoniae*, *H. influenzae* and Influenza virus during the coldest half of the year. In all 3 years assessed, the peak month of hospitalization was January, to which the annual outbreaks of flu largely contributed. In fact, when compared to bacterial CAP cases, viral infections were almost exclusive to the winter and spring (Fig. 2). *S. pneumoniae* was the most frequently identified etiological agent in all months, except in August, when it was overtaken by GNB and *L. pneumophila*. In the multivariate analysis, winter and spring season was a positive predictor for *H. influenzae* (OR 2.23, 95% CI 1.22–4.08, $P = 0.01$) and Influenza virus (OR 14.01, 95% CI 1.91–102.99, $P = 0.001$), and a negative one for *L. pneumophila* (OR 0.14, 95% CI 0.06–0.34, $P = 0.001$) (Table 3).

## CAP etiology according to patients' characteristics

The distribution of causal microorganisms varied depending on age and comorbidities (Table 3). Multivariate logistic regression analyses were performed to determine the independent risk factors for each etiological agent. Increasing age was a negative predictor for *S. pneumoniae*, *Influenza* and *L. pneumophila*. Diabetes and heart disease were significantly less common in patients with CAP due to *S. pneumoniae* (OR 0.63, 95% CI 0.41–0.95, $P = 0.027$) and *H. influenzae* (OR 0.52, 95% CI 0.27–0.99, $P = 0.05$), respectively. Active smoking (OR 5.58, 95% CI 2.28–13.61, $P < 0.001$) and absence of any respiratory disease (OR 0.18, 95% CI 0.04–0.76, $P = 0.02$) were risks factors for legionellosis. Conversely, COPD was an important risk factor for *H. influenzae* cases (OR 2.12, 95% CI 1.31–3.43, $P = 0.002$). Dementia was associated with increased risk for GNB (OR 2.26, 95% CI 1.03–4.99, $P = 0.043$) and *S. aureus* (OR 3.01, 95% CI 0.98–9.46, $P = 0.054$). Blood/sputum cultures were used as a constant covariate across groups, to normalize data for those with most complete microbiological investigation. The exception to this rule was *L. pneumophila*, as this parameter had no significant impact, since almost all diagnoses were made using urinary antigen test.

## Mortality rates

The in-hospital mortality rate was 11.7%. Fifty of the 223 patients who died had etiological diagnosis and GNB were the most prevalent agents among the deceased. Within this group, this tendency was pushed by the 5 fatal cases out of 8 (62.5%) infected with *Pseudomonas aeruginosa* ($P < 0.001$). Bacteremia was also related with higher mortality, with 17 (16.3%) fatalities among 104 positive blood cultures, when compared to negative tests (135/1299, 10.4%; $P = 0.06$). Multiple logistic regression analysis confirmed *P. aeruginosa* infection as an independent mortality risk factor (OR 13.02, 95% CI 2.94–57.7, $P = 0.001$).

# Discussion

This study provides a comprehensive insight into the etiological and clinical profile of CAP hospitalized patients in Portugal and describes the real-life microbiological testing in this setting. Proper diagnostic testing improves clinical outcomes directly through individualization of antibiotic management, and indirectly by delivering relevant epidemiological data that influences initial empirical therapy. Although a fundamental exercise, establishing microbiological CAP diagnosis is challenging.[4] In a prospective study, when conventional methods (i.e., bacterial cultures, urinary antigen assays, serology) were combined with PCR-based methods, definitive or probable etiology was established in 63% of cases.[13] In our analysis, with complete standard microbiological testing (sputum, blood culture and urine antigen test), we attained a microbial confirmation in 31.5% of cases. While it represents a lower diagnostic rate than the described in prospective studies,[14–16] it is comparable to previous large real-life studies.[17,18] Due to the retrospective nature of this work, harvesting of all products was not possible in some cases, and 14% of the patients in the cohort did

**Table 2** Etiological findings and contribution of different methods to diagnostic yield in the study population.

| Pathogen | No. (%) of patients with positive findings[a] (*n* = 420) | Sputum or BAL samples for culture and/or *L. pneumophila or virus* PCR (*n* = 327) | Blood culture (*n* = 366) | Pleural fluid culture (*n* = 11) | Urinary antigen test (*n* = 301) | NP/OP swab (*n* = 34) |
|---|---|---|---|---|---|---|
| *S. pneumoniae* | 192 (45.7) | 46 (14.1) | 65 (17.8) | 2 (18.2) | 134 (44.5) | NA |
| *H. influenzae* | 83 (19.8) | 70 (21.4) | 15 (4.1) | – | NA | NA |
| GNB[b] | 42 (10) | 32 (9.8) | 16 (4.4) | 1 (9.1) | NA | NA |
| *Influenza virus* | 38[c] (9.0) | 4 (1.2) | – | NA | NA | 31 (91.2) |
| *L. pneumophila* | 32 (7.6) | 4 (1.2) | – | NA | 30 (10.0) | NA |
| *S. aureus* | 18 (4.3) | 16 (4.9) | 4 (1.1) | – | NA | NA |
| *M. catarrhalis* | 7 (1.7) | 7 (2.1) | – | – | NA | NA |
| Other bacteria[d] | 4 (0.9) | – | 4 (1.1) | – | NA | NA |
| Other virus[e] | 4 (0.9) | 1 (0.3) | – | – | NA | 3 (8.8) |

Data are number of patients and proportion (%) of cases whose infections were etiologically established by use of a particular method listed. BAL, bronchoalveolar lavage; GNB, gram-negative bacilli; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; NP, nasopharynx; OP, oropharynx; NA, not applicable.

[a] Represent frequency of positive finding by any microbiological method.

[b] Include either the following: *Klebsiella pneumoniae* (*n* = 13), *Escherichia coli* (*n* = 10), *Pseudomonas aeruginosa* (*n* = 8), *Enterobacter* spp (*n* = 3), *Proteus mirabilis* (*n* = 2), *Serratia marcescens* (*n* = 2), *Acinetobacter baumannii* (*n* = 2), *Raoultella ornithinolytica* (*n* = 1) or *Stenotrophomonas maltophilia* (*n* = 1).

[c] Three cases were diagnosed through serology, not described in the table.

[d] Include either the following: *Streptococcus agalactiae* or *Staphylococcus hominis* (*n* = 2 each).

[e] Include either the following: respiratory syncytial virus (RSV) or rhinovirus (*n* = 2 each).

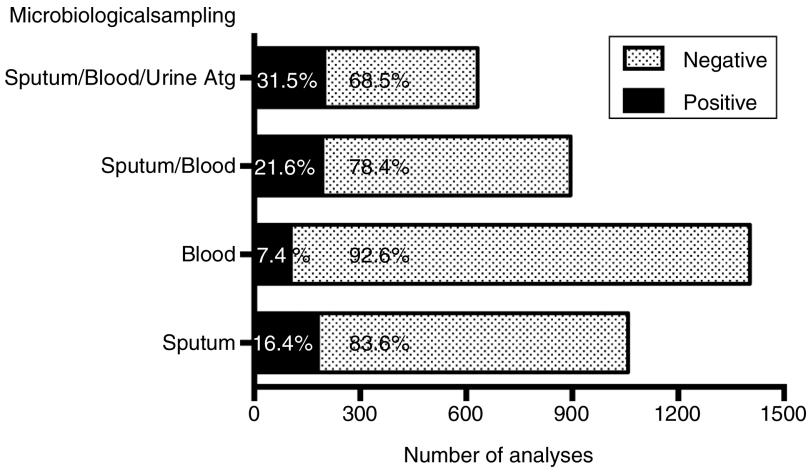


**Figure 1** Diagnostic performances of the different microbiological methods applied.

not undergo any microbiology test. We may speculate that clinicians are less prone to undergo invasive microbiological assessment in patients with the poorest performance status. Indeed, patients without microbiological studies were significantly older.

Additionally, our work confirms the low sensitivity of blood cultures described in other reports[18,19] with only 7.4% positive results. The low yield of blood cultures could be possibly explained by delay in sample collection and/or prior use of antibiotics, but these findings must also depend on bacterial infection biology, as there was a higher rate of bacteremia among pneumococcal disease. Microbial yield of sputum culture was also very modest. The poor quality of sputum accounted for several missing diagnoses (data not shown), further aggravated by ineffective cough or inappropriate sputum production, particularly at the older population fringe. Finally, once serologic assays are not routinely performed in our center, *Mycoplasma* and *Chlamydophila pneumoniae*, and supposedly several other cases of viral infections, could not be detected, which also affected importantly the overall diagnosis rate. Many studies conducted prospectively, performing serum IgM antibody measurement, combined or not with PCR detection, described atypical bacteria as major causes of CAP, with variable frequencies up to 18%, and the viruses involved in up to 30% of hospitalized CAP, only surpassed by *S. pneumoniae* as the most frequent agents.[20] In the present work, viral etiology was probably underestimated, having

**Table 3** Causal microorganisms depending on clinical background and independent risk factors for each etiological agent.

| | Unknown etiology ($n = 1481$) | *S. pneumoniae* ($n = 192$) | *H. influenzae* ($n = 83$) | GNB ($n = 42$) | *Influenza virus* ($n = 38$) | *L. pneumophila* ($n = 32$) | *S. aureus* ($n = 18$) | *M. catarrhalis* ($n = 7$) |
|---|---|---|---|---|---|---|---|---|
| **Univariate analysis** | | | | | | | | |
| *Age (years), mean ± SD* | 73.3 ± 16.0***H | 68.7 ± 16.4**L | 69.4 ± 17.3 | 74.1 ± 16.1 | 54.8 ± 14.9***L | 58.1 ± 16.5***L | 63.8 ± 20.3 | 79.6 ± 7.1 |
| *Male gender, n (%)* | 806 (54.4)*L | 104 (75.2) | 55 (66.3)*H | 24 (57.1) | 21 (55.3) | 25 (78.1)*H | 12 (66.7) | 4 (57.1) |
| *Winter & Spring, n (%)* | 1007 (68.0) | 136 (70.8) | 70 (84.3)**H | 25 (59.5) | 37 (97.4)***H | 8 (25)***L | 16 (88.9) | 7 (100) |
| *Active smoker, n (%)*[a] | 228 (15.4)***L | 45 (23.4)*H | 23 (27.7)*H | 6 (14.3) | 14 (36.8)*H | 19 (59.4)***H | 1 (5.6) | 0 |
| *Comorbid conditions, n (%)* | | | | | | | | |
| Alcohol abuse | 63 (4.3) | 13 (6.8) | 4 (4.8) | 2 (4.8) | 0 | 3 (9.4) | 0 | 0 |
| Diabetes mellitus | 337 (22.8) | 29 (15.1)*L | 18 (21.7) | 9 (21.4) | 11 (28.9) | 8 (25) | 4 (22.2) | 0 |
| Heart disease | 333 (22.5)**H | 35 (18.2) | 11 (13.3)*L | 7 (16.7) | 4 (10.5) | 4 (12.5) | 2 (11.1) | 3 (42.9) |
| Chronic kidney disease | 178 (12.0)*H | 12 (6.3)*L | 9 (10.8) | 7 (27.5) | 2 (5.3) | 1 (3.1) | 2 (11.1) | 0 |
| Asthma | 21 (1.4) | 5 (2.6) | 0 | 0 | 2 (5.3) | 0 | 0 | 0 |
| COPD | 268 (18.1) | 41 (21.4) | 28 (33.7)**H | 6 (14.3) | 8 (21.1) | 2 (6.3) | 0*L | 3 (42.9) |
| Structural lung disease[b] | 94 (6.3) | 11 (5.7) | 3 (3.6) | 2 (4.8) | 4 (10.5) | 0 | 2 (11.1) | 0 |
| Immunosuppression[c] | 64 (4.3) | 6 (3.1) | 2 (2.4) | 1 (2.4) | 4 (10.5) | 1 (3.1) | 1 (5.6) | 0 |
| HIV infection | 84 (5.7)*L | 19 (9.9) | 10 (12.0)*H | 2 (4.8) | 1 (2.6) | 2 (6.3) | 1 (5.6) | 0 |
| Active malignancy | 109 (7.4) | 14 (7.3) | 4 (4.8) | 3 (7.1) | 1 (2.6) | 1 (3.1) | 1 (5.6) | 0 |
| Dementia | 170 (11.5)**H | 13 (6.8) | 3 (3.6)*L | 8 (19.0) | 0*L | 1 (3.1) | 4 (22.2) | 0 |

Table 3 (*Continued*)

| | Unknown etiology (*n* = 1481) | *S. pneumoniae* (*n* = 192) | *H. influenzae* (*n* = 83) | GNB (*n* = 42) | *Influenza virus* (*n* = 38) | *L. pneumophila* (*n* = 32) | *S. aureus* (*n* = 18) | *M. catarrhalis* (*n* = 7) |
|---|---|---|---|---|---|---|---|---|
| *Both blood and sputum cultures, n (%)* | 609 (41.1)***L | 117 (60.9)***H | 62 (74.7)***H | 28 (66.7)**H | 32 (84.2)***H | 17 (53.1) | 16 (88.9)***H | 6 (85.7)*H |
| *Death, n (%)* | 173 (11.7) | 19 (9.9) | 5 (6.0) | 13 (31.0)***H | 5 (13.1) | 4 (12.5) | 3 (16.7) | 0 |
| **Multivariate regression analysis** | | | | | | | | |
| *Predictor, OR (95% CI), P-value* | *Age*, 1.01 (1.01–1.02), <0.001 *Active smoker*, 0.72 (0.53–0.96), 0.025 *Blood & Sputum culture*, 0.34 (0.26–0.43), <0.001 | *Age*, 0.99 (0.98–0.99), 0.025 *Diabetes mellitus*, 0.63 (0.41–0.95), 0.027 *Blood & Sputum culture*, 1.80 (1.32–2.45), <0.001 | *Winter & Spring*, 2.23 (1.22–4.08), 0.01 *Heart disease*, 0.52 (0.27–0.99), 0.05 *COPD*, 2.12 (1.31–3.43), 0.002 *Blood & Sputum culture*, 3.22 (1.94–5.34), <0.001 | *Dementia*, 2.26 (1.03–4.99), 0.043 *Blood & Sputum culture*, 2.39 (1.25–4.59), 0.009 | *Age*, 0.95 (0.93–0.97), <0.001 *Winter & Spring*, 14.01 (1.91–102.99), 0.009 *Blood & Sputum culture*, 4.71 (1.94–11.44), 0.001 | *Age*, 0.97 (0.95–0.99), 0.021 *Winter & Spring*, 0.14 (0.06–0.34), <0.001 *Active smoker*, 5.58 (2.28–13. 61), <0.001 Any respiratory disease, 0.18 (0.04–0.76), 0.020 | *Dementia*, 3.01 (0.98–9.46), 0.054 *Blood & Sputum culture*, 9.80 (2.24–42.93), 0.002 | |

Data represent number (percentage) of patients for each variable, except patient age, which is presented as mean ± SD. Each percentage was compared (Pearson's chi-square or Fisher's exact tests) to that of patients without the condition (data not shown). *L/*H Significantly lower/higher (respectively) than in patients without the condition (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

[a] Due to missingness, data concerning smoking habits reflect a proportion out of 1723 cases.

[b] Bronchiectasis, pleuritis or sequelae of prior tuberculosis conditioning alteration of the normal architecture of the lung.

[c] Immunosuppressive drugs were defined as any use of systemic steroids, azathioprine, mycophenolate mofetil, TNF-alpha inhibitor, Cyclosporine, Cyclophosphamide and/or Methotrexate within previous 3 months. CI, confidence interval. COPD, chronic obstructive pulmonary disease. HIV, human immunodeficiency virus. OR, odds ratio.

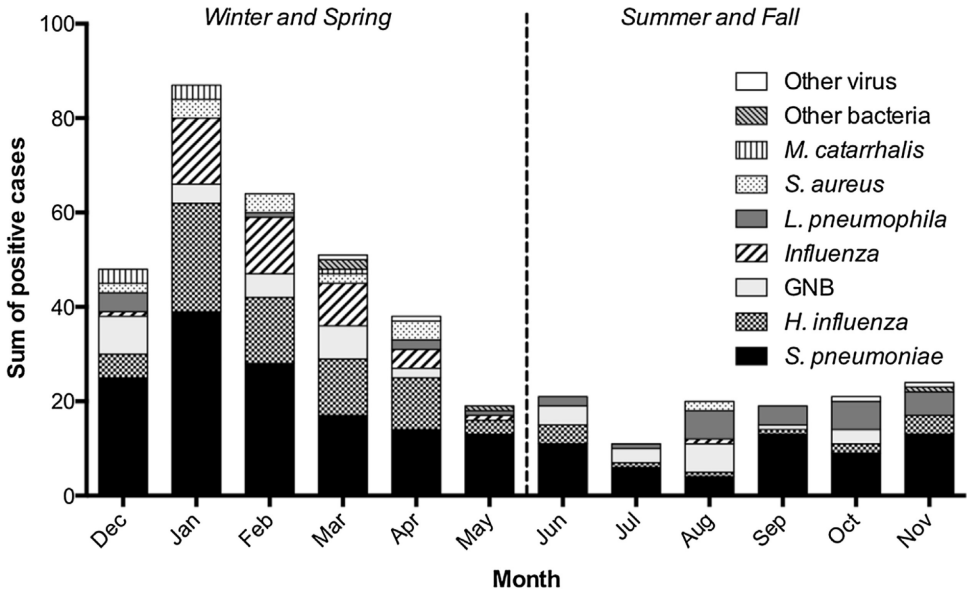


**Figure 2** Seasonal distribution of etiological agents.

been established by PCR of samples collected by pharyngeal swabs in selected patients, based on clinical judgement. Nevertheless, it is acknowledged that serology testing has little impact on the routine management of the individual patient.[20,21] Bearing this in mind and considering the high healthcare costs associated, there is a general notion that serologies are more useful in epidemiological studies than in clinical practice.

Considering the low microbial detection yield of various works, some authors have claimed that current empirical antimicrobial recommendations are based on weak evidence.[18] Knowing the importance of the early implementation of appropriate therapy, we derived etiological predictors from CAP patients' features, to better suit therapy to the most probable causative agent. Our data suggest that, in older people, *S. pneumoniae*, Influenza and *L. pneumophila* are less common, and a higher incidence of CAP is observed caused by GNB, *S. aureus* and *M. catarrhalis*, pathogens that more frequently present drug resistances. This is important, since CAP is a growing problem among the elderly.[1,22]

Globally, *S. pneumoniae* remains the most common detected cause of CAP[4] and our results confirm these data, with 45.7% of the identified cases. However, there was a large contribution of the urine antigen test for pneumococcal diagnoses, when a similar method is not routinely available to other microbial agents. In fact, if we consider etiological diagnosis based on respiratory samples alone, we find *H. influenza* as the most commonly isolated organism. It is known that *H. influenzae* is a common CAP pathogen in older patients and those with respiratory comorbidities, such as COPD, as is the case in our sample population. These patients usually present chronic bronchitis and are frequent sputum producers, which facilitates the noninvasive collection of appropriate sputum samples improving the diagnostic yield these cultures.

Both *S. pneumoniae* and *H. influenzae* may exist as commensal organisms of the upper respiratory tract, so quantitative multiplex nucleic acid amplification test (NAAT) would detect and differentiate the etiologic agent of CAP better. A study from the United Kingdom identified an etiologic agent by quantitative PCR in 87% of CAP patients, including *S. pneumoniae* in 36% and *H. influenzae* in 40%.[23]

Future studies are needed to unravel how demographic changes in European countries will impact current microbial epidemiology. Furthermore, it is expected that the incidence of CAP by *S. pneumoniae* will decrease due to the introduction of pneumococcal vaccines.[24] Thus, upcoming empirical antimicrobial treatment recommendations may have to take into special account the rise of beta-lactamase-producing agents in this setting, including *H. influenza*, *M. catarrhalis* and GNB. We report a significant proportion of CAP cases due to GNB (∼10%), with *Klebsiella pneumoniae* and *P. aeruginosa* comprising nearly half of these cases, which is only paralleled in a few other reports.[25,26] The highest incidence occurred in patients suffering from dementia and were associated with increased mortality of up to 30%. When controlling for age, dementia and other disabling comorbidities, *P. aeruginosa*, but not GNB as a whole, was an independent risk factor for mortality. These findings are identical to Spanish data,[25] where the authors reported 11% of GNB infections, associated with 32% mortality, much higher than observed with the non-GNB group (9%). In that publication, however, *P. aeruginosa* failed to be an independent predictor of death.[25] Similar effect on mortality related to GNB was found in Asian countries[27] and South America.[28] Unfortunately, there are no specific measures to prevent pneumonia caused by GNB in the community setting. Despite this, since dementia was an independent risk for GNB infections in our study, measures promoting good oral hygiene and minimizing the use of proton-pump inhibitors can help to reduce bacterial microaspiration among these patients. Additionally, hand feeding should be tried before considering tube feeding and a semi-recumbent position with the head of the bed at a 30–45° angle should be adopted in bedridden patients. Another well-recognized risk factor for GNB

infection or other drug-resistant bacteria is previous antibiotic treatment. In line with this, we believe that our results may contribute to antibiotic stewardship and decrease the prevalence of multidrug-resistant organisms.

Moreover, one of the highlights of the paper was the seasonal variability of microbiological agents. Seasonality was particularly important for *L. pneumophila* infections that occurred almost exclusively during summer and Fall. Given the potential severity of the disease, we propose that clinicians should have higher suspicion index and undergo more intensive diagnostic workup to exclude Legionellosis during that period. A similar approach has been already taken during Influenza season with active virus search during winter, with impact on treatment choices.

Some limitations of the study must be acknowledged. This was a retrospective observational study that could not evaluate all the clinical parameters that may affect etiology. Moreover, a complete microbiological evaluation was not performed in all patients and failure to perform serology cause potential bias in agent identification. Finally, this work was conducted in a particular setting, only including hospitalized patients in a tertiary northern Portuguese hospital. Therefore, these data may not reflect cases of less severity, diagnosed at small community hospitals or in other geographical regions.

In conclusion, besides promoting smoking cessation and encouraging flu and anti-pneumococcal vaccination, investing in the etiological diagnosis, taking into account the most probable agents in a given clinical context can lead to better antibiotic selection thus improving outcomes. Our data suggest that initial empirical coverage of GNB, including *P. aeruginosa*, should be considered in the elderly with dementia, since these patients usually have a worse prognosis and fail to provide appropriate sputum samples for culture.

Further studies on the epidemiology and prognostic risk factors for CAP caused by GNB and other resistance-prone agents are warranted to assess if early recognition of microbial etiology can modify the outcomes.

## Conflict of interests

The authors declare no conflict of interests.

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ORIGINAL ARTICLE

# Metronomic oral vinorelbine in a real-world population of advanced non-small cell lung cancer patients

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**KEYWORDS**
Non-small cell lung cancer;
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Elderly

**Abstract**
*Introduction:* An increasing body of evidence from clinical trials and real-world studies suggests that metronomic oral vinorelbine (VNR) is a promising treatment option for elderly and unfit advanced non-small cell lung cancer (NSCLC) patients. The aim of this multicenter study was to present real-world data about the experience in treatment of NSCLC with metronomic VNR in Portugal.
*Material and methods:* Retrospective data from NSCLC patients not eligible for conventional chemotherapy or tyrosine kinase inhibitors who received oral metronomic VNR irrespective of treatment line and dose was retrieved from 19 Portuguese Oncology Centers between 2016 and 2018.
*Results:* A total of 293 patients were included, with a median of 76 (39 – 94) years; 71% were ≥70 years old. Patients had a median of 3 comorbidities and predominantly (61%) ECOG PS 2. Most (42%) received metronomic oral VNR as first-line treatment. Overall response rate was 18%, with 42 (18%) partial and no (0%) complete responses. A total of 54% of patients experienced stable disease and 28% of patients, disease progression. Disease control rate was 72%. Patients were a median of 4 (1 – 40) months on treatment. Treatment discontinuation was observed in 90%, mostly (67%) due to disease progression, followed by death (16%). Adverse events leading to treatment discontinuation were only reported in 5% of patients. Female gender (HR 0.601, 95% CI 0.434 – 0.832; p = 0.002) and ECOG PS 1 (HR 0.625, 95% CI [0.443 – 0.881]; p = 0.007) were significantly associated with a lower risk of metronomic oral VNR discontinuation. Overall, 21% of patients experienced G3/4 toxicity.

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*Conclusion:* The present real-world results agree with what has been previously reported by other international Centers and support the concept that metronomic scheduling is a relevant and safe approach to treat advanced NSCLC patients.


## Introduction

Lung cancer remains one of the most commonly diagnosed cancer and a leading cause of mortality worldwide.[1] According to Globocan, the malignancy accounted for 11.6% of total cancer cases and 18.4% of total cancer deaths in 2018, representing a substantial health burden.[1] Non-small cell lung cancer (NSCLC), the dominant subtype, accounts for 80 – 90% of cases,[2,3] and a remarkable proportion of these patients (≈70%) presents with metastatic or locally advanced disease.[4,5]

Approximately half of lung cancers are diagnosed in people aged ≥70 years, and around 15% of cases in people aged ≥80 years.[6] With the aging of populations, this trend will predictably increase in upcoming years. Age is a relevant independent prognostic factor affecting patient survival.[6,7] Furthermore, the elderly are frequently frail, with poor performance status and multiple comorbidities, and often ineligible for conventional cytotoxic chemotherapy, associated with important toxicities.[8–11] For these reasons, treatment of elderly patients with advanced NSCLC can be challenging.

For advanced NSCLC patients without actionable oncogenic drivers (EGFR-sensitizing mutations, ALK rearrangements, ROS1 translocation, or BRAF V600 mutation), the updated 2019 guidelines of the European Society for Medical Oncology (ESMO) recommend platinum (preferably carboplatin)-based doublet chemotherapy for eligible elderly patients and for those with Eastern Cooperative Oncology Group [ECOG] performance status (PS) 0–2 and adequate organ function, and single-agent chemotherapy with gemcitabine, vinorelbine, docetaxel, or pemetrexed (in non-squamous NSCLC) for patients not eligible for doublet chemotherapy.[2,3] Regarding immune checkpoint inhibitors, ESMO guidelines consider that there is insufficient data but permit their use in ECOG PS 2 patients, but also advise on their use according to standard recommendations in elderly patients.[2,3]

Metronomic chemotherapy, the frequent or continuous administration of low-dose chemotherapy with no or short drug-free intervals between single administrations, allows for a prolonged treatment with potentially less toxicity.[12,13] The rationale behind metronomic administration is to improve the therapeutic index by balancing drug activity and treatment-associated toxicities, prolonging treatment duration and improving quality of life (QoL). This schedule was designed to overcome acquired tumour resistance to chemotherapy and has multiple mechanisms of action,[14] including antiangiogenic, cytostatic, and immunomodulating effects,[15–17] which allow the delay of cancer progression while reducing toxicity and decreasing the need for growth factor agents to recover from myelosuppression.[15] This profile makes this agent particularly suitable for elderly and/or fragile patients.

Vinorelbine (VNR), a semisynthetic vinca-alkaloid, was originally formulated as an intravenous (i.v.) agent, but later also as an oral treatment option. It was the first agent studied in mono-chemotherapy in elderly NSCLC patients: in the ELVIS study, the classical i.v. VNR schedule plus best supportive care (BSC) showed a survival benefit compared with BSC alone (median of 28 vs 21 weeks; HR 0.65; 95% confidence interval [CI] 0.45–0.93),[18] while in the study by Gridelli et al., oral VNR demonstrated good clinical outcomes with the classical administration in these patients.[19] Oral VNR has already shown significant activity in different NSCLC settings, either in combination or monotherapy, including concurrent chemoradiation for locally advanced disease, adjuvant treatment for resected disease, and palliative chemotherapy for recurrent/metastatic disease.[20]

Metronomic oral VNR has also been investigated among elderly NSCLC patients, both in clinical trial and real-life setting. The optimal dose for metronomic VNR administration was established as 50 mg given three times a week.[21,22] Metronomic oral VNR has demonstrated interesting activity and safety in elderly patients with advanced NSCLC in phase I/II trials.[22–26] In real-life setting, emerging retrospective data confirms the effectiveness and absence of relevant safety issues of metronomic oral VNR, and its applicability for patients unfit for standard chemotherapies.[27–32] More recently, metronomic oral VNR has also been evaluated as a switch maintenance regimen versus BSC in patients with advanced NSCLC who did not progress after first-line platinum-based chemotherapy in the phase II randomized MA.NI.LA study.[33] In this setting, the metronomic VNR schedule prolonged progression-free survival (PFS) compared to BSC, particularly in patients aged ≥70 years and in those with disease stabilization after induction chemotherapy. However, the dropout rate due to significant toxicity raises awareness of the need to further investigate the optimal metronomic oral VNR dose after induction chemotherapy.

According to the Spanish Working Group on Geriatric Oncology of the Spanish Society of Medical Oncology (SEOM), metronomic oral VNR is a suitable option for the treatment of elderly NSCLC patients.[34] And, overall, evidence is building on the benefit of metronomic oral VNR in the relevant proportion of frail/unfit NSCLC patients often excluded from clinical trials.

The aim of this multicenter study was to present real-world, retrospectively collected data about the experience in treatment of NSCLC with metronomic VNR in Portugal.

Effectiveness (overall response rate [ORR] and treatment duration) and safety data from Portuguese NSCLC patients treated with metronomic oral VNR is presented.

## Material and methods

This study was an observational, retrospective, real-world analysis of metronomic oral VNR in the treatment of advanced NSCLC patients. Data included NSCLC patients not eligible for conventional chemotherapy who received oral metronomic VNR irrespective of treatment line and dose, given three times a week for ≥1 complete treatment cycle. Information about disease progression, patient refusal, unacceptable toxicity, or death was collected from patients' clinical records in 19 Portuguese cancer-treating institutions in the mainland and islands from when VNR started to be routinely used in national clinical practice (2016) until December 2018. No formal ethical approval was required, given the study's retrospective and observational nature. All patient data was coded and secure.

Retrieved data included patients' (i) baseline clinical and demographic features (age, gender, tumour histological type), (ii) clinical characteristics at metronomic oral VNR start (number of comorbidities, Eastern Cooperative Oncology Group [ECOG] performance status [PS], prior treatment regimens), and (iii) metronomic oral VNR treatment data (VNR dose, best response according to RECIST criteria,[35,36] overall survival [OS], treatment duration, adverse events, and treatment discontinuations).

Outcome measures considered in the analysis included treatment duration, overall response rate (ORR), disease control rate (DCR), and toxicity. ORR was defined as the proportion of patients achieving complete or partial response as best overall response according to RECIST 1.1 criteria. DCR was defined as the percentage of patients presenting complete, partial, or stable disease.

Treatment was discontinued after disease progression or unacceptable toxicity, death, or patient preference. Treatment duration was defined as time since treatment start and discontinuation.

Some patients started treatment with the 50 mg dose and others with lower doses, which could be changed. Information of the lower delivered dose was also collected.

Adverse events were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.[37] Patients could receive palliative treatment as required according to local clinical practice but were excluded if concomitantly receiving other anticancer agents.

### Statistical analysis

Categorical variables were expressed as absolute and relative frequencies, and continuous variables as median and interquartile range (IQR).

Kaplan-Meier curve was estimated for treatment duration, and proportional hazard (or Cox) models were fitted to data to investigate whether patients' baseline demographic or clinical characteristics were associated with a higher risk of treatment discontinuation or death. The assumption of proportional hazards was tested, and presence of time-dependent covariates was assessed using Aalen models. The level of significance was set at $p < 0.05$.

**Table 1** Baseline characteristics of the study population.

| Characteristic | N = 293 |
|---|---|
| Age — years | |
| Median (range) | 76 (39 — 94) |
| Gender — n (%) | |
| Male | 221 (75) |
| Female | 72 (25) |
| Comorbidities — n (%) | |
| 0 | 18 (6) |
| 1 | 49 (17) |
| 2 | 70 (24) |
| 3 | 61 (21) |
| 4 | 47 (16) |
| 5 | 27 (9) |
| 6 | 14 (5) |
| 7 | 6 (2) |
| 8 | 0 (0) |
| 9 | 1 (0) |
| ECOG PS — n (%) | |
| 0 | 5 (2) |
| 1 | 60 (20) |
| 2 | 179 (61) |
| 3 | 49 (17) |
| Tumour histology — n (%) | |
| Squamous | 88 (30) |
| Non-squamous | 193 (66) |
| NOS | 12 (4) |

ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified.

## Results

A total of 293 patients, mostly male (75%), were enrolled in this study, with a median of 76 (range 39 — 94) years. Overall, 29% of patients were <70 and 71% were ≥70 years of age.

Baseline (i.e. at time of VNR start) characteristics of the study cohort are depicted in Table 1. Most patients (94%) had ≥1 comorbidities, mostly (45%) between 2 and 3. The median number of comorbidities was 3 (range 0 — 9). Patients with ECOG PS 2 were predominant (61%), with an also relevant proportion of patients with ECOG PS 3 (17%). Around 20% of patients with ECOG PS 1 were included. These were patients with important comorbidities contraindicating the use of other therapies or who had received prior treatments. Non-squamous histology was prevalent (66%), followed by squamous histology (30%), and few patients (4%) presented with not otherwise specified (NOS) carcinoma.

Most patients (42%) received metronomic oral VNR as first-line treatment, followed by 33% who received it as second line, 15% as third line, and a minority as fourth and subsequent lines of treatment (Table 2). Metronomic oral VNR initial treatment schedule was 40 mg *per* administration in 67% of patients, 50 mg *per* administration in 24% of patients, and 30 mg *per* administration in 9% of patients. Maximum delivered dose was 40 mg in 61% of patients and

**Table 2** Metronomic oral VNR effectiveness and safety data.

| Characteristic | | N = 293 |
|---|---|---|
| Previous treatment regimens — n (%) | | |
| 0 | | 123 (42) |
| 1 | | 97 (33) |
| 2 | | 45 (15) |
| 3 | | 17 (6) |
| 4 | | 6 (2) |
| 5 | | 2 (1) |
| 6 | | 3 (1) |
| VNR initial dose (mg/adm) — n (%) | | |
| 30 | | 26 (9) |
| 40 | | 197 (67) |
| 50 | | 70 (24) |
| VNR lowest dose (mg/adm) — n (%) | | |
| 30 | | 37 (13) |
| 40 | | 199 (68) |
| 50 | | 57 (19) |
| Best response — n (%) | | |
| CR | | 0 (0) |
| PR | | 42 (18) |
| SD | | 126 (54) |
| PD | | 66 (28) |
| Treatment duration — months | | |
| Median (range) | | 4 (1 — 40) |
| Treatment discontinuation — n (%) | | 264 (90) |
| Reasons for discontinuation — n (%)[a] | | |
| Disease progression | | 178 (68) |
| Adverse events | | 14 (5) |
| Death | | 43 (16) |
| Patient preference | | 10 (4) |
| Others | | 19 (7) |
| Adverse events — n (%) | Grade 1/2 | Grade 3/4 |
| Any event | | 62 (21) |
| Hematological events | | |
| Anemia | 90 (30.7) | 13 (4.4) |
| Neutropenia | 31 (10.6) | 30 (10.2) |
| Febrile neutropenia | 2 (0.7) | 15 (5.1) |
| Non-hematological events | | |
| Diarrhea | 36 (12.3) | 7 (2.4) |
| Fatigue | 91 (31.1) | 28 (9.6) |
| Nausea/vomiting | 44 (15.0) | 5 (1.7) |

VNR, vinorelbine; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
[a] Data available for 264 patients.

50 mg in 33% of patients. Minimum delivered dose is also presented, as some patients required initial dose reductions due to intolerance or toxicity. The most used schedule for first-, second-, and subsequent-line treatment was 40 mg *per* administration (27%, 24%, and 17%, respectively).

Overall response rate (ORR) with metronomic oral VNR was 18%, with 42 (18%) partial responses (PR) and no complete responses (CR). A total of 54% of patients experienced stable disease (SD) and 28% of patients experienced disease progression (PD). Disease control rate (DCR) was 72%. Patients were a median of 4 (range 1 — 40) months on treatment with metronomic oral VNR. Treatment discontinuation was observed in 90%, mostly (67%) due to disease progression, followed by death (16%). Adverse events leading to treatment discontinuation were observed in only 5% of patients.

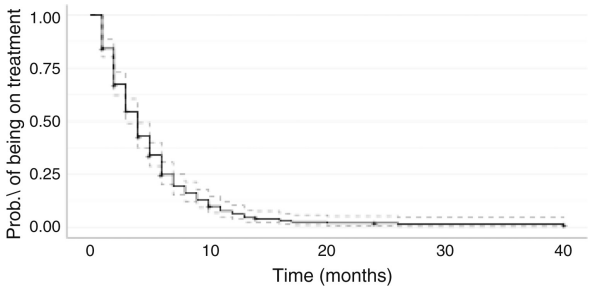


**Figure 1** Kaplan-Meier curve for metronomic oral VNR treatment duration.

The Kaplan-Meier curve for metronomic oral VNR treatment duration is shown in Fig. 1.

Females (median 5 months, 95% CI 4 — 6), patients with no comorbidities (median 5 months, 95% CI 3 — 10), with ECOG PS 1 (median 5 months, 95% CI 3 — 7), and with a VNR starting dose of 50 mg/administration (median 5 months, 95% CI 4 — 6 months) were a longer time on treatment with metronomic oral VNR (Table 3). Median treatment duration for ECOG PS 3 patients was 4 months (95% CI 3 — 6).

Features significantly associated with a lower risk of metronomic oral VNR treatment discontinuation were female gender (HR 0.601, 95% CI 0.434 — 0.832; p = 0.002) and ECOG PS 1 (HR 0.625, 95% CI [0.443 — 0.881]; p = 0.007; Table 4). Additionally, the number of comorbidities and prior lines of treatment were not associated with a change in metronomic oral VNR treatment time.

Concerning toxicities, among registered events most patients (46%) experienced grade 1/2 toxicity, including 31.1% of G1/2 fatigue, 30.7% of G1/2 anaemia, and 15.0% of G1/2 nausea or vomiting. A total of 21% of patients reported grade 3/4 toxicity, mostly G3/4 neutropenia (10.2%) and G3 fatigue (9.6%; Table 2), and 33% of patients experienced no toxicity with metronomic oral VNR.

Sixty-three patients required granulocyte colony-stimulating factors (GCSF) for neutropenia, accounting for 41% of all patients who developed neutropenia of any grade and for 9% of the overall study population.

## Discussion

The present study evaluated treatment outcomes of 293 advanced/metastatic NSCLC patients undergoing a metronomic oral VNR regimen, three times a week until progression, patient refusal, unacceptable toxicity, or death according to the approved indication.

The oral VNR formulation appears to have a similar effectiveness and better safety profile compared with its intravenous counterpart and enabled the use of a metronomic schedule, which has the advantages of being cost-sparing in terms of hospital expenditures, easier to prepare and administer (namely considering infusion-related procedures), and represents a more convenient approach for patients and for patient management.

**Table 3** Median time on treatment with metronomic oral VNR.

| Characteristic | N = 293 | Events | Time on VNR treatment | |
|---|---|---|---|---|
| | | | Median | 95% CI |
| Global | 293 | 264 | 4 | 3 — 4 |
| Gender | | | | |
| Male | 221 | 199 | 4 | 3 — 4 |
| Female | 72 | 65 | 5 | 4 — 6 |
| Nr. comorbidities | | | | |
| 0 | 18 | 15 | 5 | 3 — 10 |
| 1 | 49 | 45 | 4 | 3 — 5 |
| 2 | 70 | 64 | 4 | 3 — 5 |
| 3 | 61 | 58 | 4 | 3 — 6 |
| 4 | 47 | 41 | 4 | 2 — 5 |
| 5 | 27 | 24 | 3 | 2 — 5 |
| 6 | 14 | 12 | 3 | 1—NE |
| 7 | 6 | 4 | 5 | 4—NE |
| 8 | 1 | 1 | 5 | NE — NE |
| 9 | | | | |
| ECOG PS at VNR start | | | | |
| 0 | 5 | 5 | 3 | 1—NE |
| 1 | 60 | 46 | 5 | 3 — 7 |
| 2 | 179 | 165 | 4 | 3 — 4 |
| 3 | 49 | 48 | 4 | 3 — 6 |
| Histology | | | | |
| Squamous | 88 | 78 | 4 | 3 — 5 |
| Non-squamous | 193 | 175 | 4 | 4 — 5 |
| NOS | 12 | 11 | 2 | 1—NE |
| Previous regimens | | | | |
| 0 | 123 | 108 | 4 | 3 — 5 |
| 1 | 98 | 93 | 4 | 4 — 5 |
| 2 | 45 | 42 | 4 | 3 — 6 |
| >3 | 28 | 21 | 3 | 2—NE |
| VNR initial dose (mg/adm) | | | | |
| 30 | 26 | 22 | 3 | 2 — 4 |
| 40 | 197 | 182 | 4 | 3 — 4 |
| 50 | 70 | 60 | 5 | 4 — 6 |
| VNR minimum delivered dose (mg/adm) | | | | |
| 30 | 37 | 32 | 3 | 3 — 4 |
| 40 | 199 | 184 | 4 | 3 — 5 |
| 50 | 57 | 48 | 4 | 4 — 6 |

VNR, vinorelbine; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified; NE, not estimated.

The oral thrice weekly delivery results in a comparable delivery to weekly parenteral dosing, although leading to a more protracted exposure to lower drug concentrations.[26]

The NSCLC cohort included in this study had a high median age (76 years), several comorbidities (median of 3), and a high percentage of PS 2 patients (61%). Additionally, most patients (42%) received metronomic oral VNR as first-line treatment. Overall, this data is consistent with the profile of patients with advanced NSCLC unfit for polychemotherapy but still eligible for active treatment.

About 20% of patients with ECOG PS 1 were included. These were patients with important comorbidities or who had received prior treatments that contraindicated the use of other therapies.

Patients without comorbidities, good ECOG PS, and a VNR starting dose of 50 mg/administration reported longer time on treatment with the metronomic VNR schedule. The optimal monotherapy VNR dose can vary between 30 and 50 mg. Due to pre-existing comorbidities, the 40 mg dose was started in most patients and maintained, as patients displayed good tolerability and no adverse events. Indeed, most patients required no dose reductions.

Taking into account the specific characteristics of this population, it is noteworthy that most patients had their disease stabilized for a relevant period of time, with a DCR of 72% for the entire cohort.

Results here reported are consistent with those previously described by other authors. In the phase II MOVE trial, investigating metronomic oral VNR at the dose of 50 mg

**Table 4** Proportional hazard coefficients for metronomic oral VNR treatment discontinuation.

| Characteristic | $e^{\beta i}$ | | p |
|---|---|---|---|
| | Estimate | 95% CI | |
| Age | 0.991 | 0.974 – 1.007 | 0.272 |
| Gender[a] | | | |
| Female | 0.601 | 0.434 – 0.832 | 0.002 |
| Nr. comorbidities | 0.977 | 0.905 – 1.056 | 0.560 |
| ECOG PS[b] | | | |
| 0 | 1.973 | 0.773 – 5.033 | 0.155 |
| 1 | 0.625 | 0.443 – 0.881 | 0.007 |
| 3 | 0.852 | 0.594 – 1.222 | 0.384 |
| Histology[c] | | | |
| Non-squamous | 0.745 | 0.549 – 1.010 | 0.058 |
| NOS | 2.028 | 1.044 – 3.937 | 0.037 |
| Prior lines of treatment[d] | | | |
| 1 | 0.843 | 0.611 – 1.163 | 0.298 |
| 2 | 0.971 | 0.639 – 1.474 | 0.889 |
| >3 | 1.308 | 0.766 – 2.233 | 0.325 |
| VNR initial dose (mg/adm)[e] | | | |
| 30 | 1.315 | 0.511 – 3.384 | 0.570 |
| 50 | 0.893 | 0.535 – 1.489 | 0.664 |
| VNR minimum delivered dose (mg/adm) | | | |
| 30 | 1.064 | 0.544 – 2.083 | 0.855 |
| 50 | 0.971 | 0.578 – 1.630 | 0.910 |

[a] Taking male as reference.
[b] Taking ECOG PS 2 as reference.
[c] Taking squamous histology as reference.
[d] Taking no prior treatment as reference.
[e] Taking 40 mg/adm dose as reference.

as first-line treatment for elderly patients with advanced NSCLC, median age was 80 years, 62.8% of patients had ECOG PS 2, and median time to disease progression was 5 months.[22]

Also similarly to the present study, the most frequent all-grade non-hematological toxicity in that trial was fatigue (32.4%), with 0.1% of G3/4 fatigue.

In a phase II study of the Hellenic Oncology Research Group, metronomic oral VNR at the dose of 50 mg was administered to advanced NSCLC patients in second line and beyond.[25] Patients' median age (65 years) was lower than in the present study (76 years) and most patients (76.1%) had ECOG PS 1 (versus only 20% in this study). Despite the clinical trial setting, safety outcomes reported in the Hellenic Group study were similar to those reported in the present real-world study, with fatigue and neutropenia being the most frequent non-hematological and hematological G3/4 toxicities reported. In the Hellenic Group study, median time to tumour progression (TTP) was 2.2 months, but the study only included patients treated in second and subsequent lines, while the present study included 42% of patients treated upfront. In a recent retrospective study by Camerini et al., 270 patients with advanced NSCLC were enrolled, with a similar median age to this study's cohort (76 years).[28] Forty-nine percent of patients had PS $\geq$ 2, compared with 78% of patients in the present study, and 67% were treated in first line versus 42% in this study. Median overall TTP was 5 (range 1 – 21) months, in accordance with the present study. In the study by Camerini, G3/4 toxicity mainly consisted in G3 fatigue and anemia and occurred in 2% of patients.

In this cohort retrieved from daily clinical practice of NSCLC treatment, the main cause of treatment discontinuation was disease progression (67%), with only 5% of patients discontinuing treatment due to adverse events. Additionally, more than 30% of patients experienced no treatment-related toxicities and most reported adverse events were G1/2.

Toxicity is a relevant issue in the palliative setting of NSCLC treatment, and efforts should be made to achieve an optimal balance between the desired treatment benefit (quality of life improvement and/or survival extension) and drug-related toxicity. As here evidenced, the toxicity of metronomic oral VNR was generally well tolerated and easily manageable. Results obtained are clinically relevant, as toxicity-related discontinuation rates were low, and suggest that single-agent metronomic oral VNR has an acceptable clinical effectiveness and safety when used in first and subsequent lines of treatment of advanced NSCLC patients.

As study limitations, it should be acknowledged that this retrospective analysis did not include a control group and that patients enrolled had different numbers of previous lines of treatment. No information was retrieved regarding tumour molecular characteristics, PD-L1 expression, stage, or previous lines of therapy. Due to the number of observed deaths and short follow-up, it was not possible to estimate median OS. Time to progression and PFS data were not collected.

Regarding comorbidities, only the number was registered and no Charlson index or similar was applied. Smoking status was not presented and there is no data in the literature on pharmacokinetics or pharmacodynamics, response, or toxicity changes by smoking status.

Intrinsic to the study's retrospective nature, the risk of registration bias should also be considered, especially regarding adverse events.

Lastly, study design precluded subgroup analyses by treatment line or performance status, which were not performed.

## Conclusions

The present study reports the experience of 19 Portuguese Centers with the use of metronomic oral VNR in advanced NSCLC patients. Overall, results agree with what has been previously reported by other international Centers and add support to the concept that metronomic scheduling is a relevant and safe approach to treat these patients. Furthermore, it seems to be a legitimate option for ECOG PS 2 and 3 patients with various comorbidities, enabling disease stability for a considerable period of time with good tolerability, low toxicity, and a favorable disease control. Importantly, the main cause of treatment discontinuation with this regimen was disease progression, with only a few patients discontinuing treatment due to safety issues. The number of observed deaths and short follow-up time precluded estimations of median OS or PFS in this study.

The Portuguese experience with metronomic oral VNR here reported, together with the experience of other international Centers, is important to build up evidence on this promising new treatment option.

Future real-world prospective studies are desirable, focusing on the evaluation of predictive factors, use of geriatric assessment tools, and assessment of quality of life and cost-effectiveness associated with this treatment. Also, it would be relevant to investigate the subgroup of patients receiving second-line immunotherapy following first-line metronomic oral VNR, as several studies report a synergistic effect between the two therapies.[15,38]

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## Conflicts of interest

The authors have no conflicts of interest to declare.

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REVIEW

# Issue 1 - "Update on adverse respiratory effects of outdoor air pollution" Part 2): Outdoor air pollution and respiratory diseases: Perspectives from Angola, Brazil, Canada, Iran, Mozambique and Portugal

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**KEYWORDS**
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GARD;
Portugal

**Abstract**
*Objective:* To analyse the GARD perspective on the health effects of outdoor air pollution, and to synthesise the Portuguese epidemiological contribution to knowledge on its respiratory impact.
*Results:* Ambient air pollution has deleterious respiratory effects which are more apparent in larger, densely populated and industrialised countries, such as Canada, Iran, Brazil and Portugal, but it also affects people living in low-level exposure areas. While low- and middle-income countries (LMICs), are particularly affected, evidence based on epidemiological studies from LMICs is both limited and heterogeneous. While nationally, Portugal has a relatively low level of air pollution, many major cities face with substantial air pollution problems. Time series and cross-sectional epidemiological studies have suggested increased respiratory hospital admissions, and increased risk of respiratory diseases in people who live in urban areas and are exposed to even a relatively low level of air pollution.
*Conclusions:* Adverse respiratory effects due to air pollution, even at low levels, have been confirmed by epidemiological studies. However, evidence from LMICs is heterogeneous and relatively limited. Furthermore, longitudinal cohort studies designed to study and quantify the link between exposure to air pollutants and respiratory diseases are needed. Worldwide, an integrated approach must involve multi-level stakeholders including governments (in Portugal, the Portuguese Ministry of Health, which hosts GARD-Portugal), academia, health professionals, scientific societies, patient associations and the community at large. Such an approach not only will garner a robust commitment, establish strong advocacy and clear objectives, and raise greater awareness, it will also support a strategy with adequate measures to be implemented to achieve better air quality and reduce the burden of chronic respiratory diseases (CRDs).


## Introduction

Worldwide, chronic respiratory diseases (CRDs) are one of the five leading causes of morbidity and mortality of non-communicable diseases (NCD), according to the World Health Organization (WHO).[1] Furthermore, the Forum of International Respiratory Societies (FIRS) considers chronic obstructive pulmonary disease (COPD) and asthma, pneumonia, tuberculosis and lung cancer as the five most prevalent pulmonary diseases.[2] Together, they contribute significantly to the increasing global burden of NCD.[3—7]

To better elucidate various aspects of CRDs and to support countries and organizations globally dealing with CRDs, the Global Alliance against chronic Respiratory Diseases (GARD) was established in 2006 as a voluntary alliance of medical and scientific societies, patients' associations, and governmental institutions with WHO.[8] The main objective of GARD is to reduce the global burden of CRDs so that the world will be a place where all people breathe freely. In particular, GARD focuses on the needs of people suffering from CRDs in low- and middle-income countries (LMIC).[9] This is especially relevant since LMICs have a disproportionately high burden of the CRD-associated morbidity and mortality.[10]

Air pollution is a significant risk factor for CRDs, and with well documented adverse health impacts on human,[11—16] especially in GARD countries.[17—20] Health effects range from minor irritation of the upper respiratory system to serious chronic respiratory and cardiac disorders, as well as worsening of cardiac and pulmonary diseases, premature mortality and decreased life expectancy.[21,22] Short-term exposure to air pollution may contribute to worsening of respiratory symptoms in people with asthma or COPD,[23,24] while continuing or long-term exposures seem to increase the risk of development of COPD in those with asthma, therefore acquiring features of asthma COPD overlap (ACO).[25] Furthermore, air pollution has a substantial impact on quality of life in those who are living with CRDs,[12,13] and novel, non-respiratory, health effects have been described in a joint document of the American Thoracic Society/European Respiratory Society (ATS/ERS).[11,26]

Regarding mortality, the WHO 2016 Report[21] on ambient air pollution suggested that 4.2 million deaths every year occur as a result of exposure to ambient air pollution. According to the estimates of the Global Burden of Disease (GBD), air pollution was the fifth major risk factor of death in the world, accounting for 7.6% of all deaths globally in 2015.[16,27—29] A more recent GBD study in 2020 showed that approximately 12% of all deaths in 2019 were due to the combined effects of indoor and outdoor pollution.[30]

Despite successful attempts to reduce air pollution in advanced industrial countries, mortality resulting from air pollution exposure has not decreased across GARD countries.[34] On the contrary, with the increasing level of air pollution, a rise in the number of deaths resulting from NCD has been noted in LMICs[16] and GARD countries,[31] especially in the more vulnerable population (e.g., people of lower socioeconomic status), compounding a disproportional risk.[32,33]

In Portugal, in spite of a global reduction in pollutant emission, air quality has not improved accordingly for all pollutants. The annual emission and air quality trends in Portugal in 2009—2015 have been studied.[35] Although the emissions of carbon monoxide (CO), nitrogen dioxide ($NO_2$), sulphur oxides (Sox), and particulate matter ($PM_{10}$) showed

a general decreased trend in the study period, there was also a notable increasing trend towards in the last two years studied. Based on a comparative analysis of the spatial distribution of emissions available for 2009 and 2015,[36] several points were highlighted: higher emissions, mainly of $NO_2$ and $PM_{10}$, were verified in industrial areas and urban centres; Lisbon Metropolitan Area was the most problematic region in terms of emissions of all pollutants; the North region had a reduction of $PM_{10}$ emissions, compared with the other regions; $NO_2$ emissions showed an increase in most of the country.[35]

The 2020 Report of the European Environment Agency (https://www.eea.europa.eu/publications/air-quality-in-europe-2020-report) showed that years of life lost attributable to air pollutants in Portugal, in 2018 per $10^5$ inhabitants were 541 for $PM_{2.5}$, 84 for $NO_2$, and 42 for $O_3$, whereas the number of premature deaths were 4900 for $PM_{2.5}$, 750 for $NO_2$, and 370 for $O_3$. Although these levels are lower than those in most other European countries, they represent an average value for the country and are less representative of the situation in more urbanized and industrialized cities such as Lisbon and Porto. Thus, it is paramount to more accurately depict the impact of outdoor air pollution in Portugal by reporting or stratifying findings by a more refined geographical unit (such as by region).

## Methods

This narrative review is divided into two main topics: a *perspective from some GARD countries,* and the *Portuguese perspective*. The GARD view includes some general comments on the societal burden of CRDs as well a brief analysis of the role of various ambient air pollutants on CRD-related outcomes. This is further exemplified by the experience of some GARD countries: Iran, Canada, Brazil, Angola and Mozambique. The Portuguese perspective aims to summarise the main findings of epidemiological studies on the relationship between estimates of global and specific outdoor air pollutants and some of the most relevant CRD-related outcomes.

### The perspective from some GARD countries (Angola, Brazil, Canada, Iran, and Mozambique)

A view on the problem of ambient air pollution and its impact on respiratory health was elaborated by country level GARD coordinators and this was complemented by country-specific literature searches on the topic. The analysis included Medline searches on PubMed and Embase databases from inception (of records in each database) to 30 October 2021, using the following search terms "outdoor air pollution" and "respiratory health" AND "Iran" or "Canada" or "Brazil" or "Angola" or "Mozambique". Only studies on the relationship between ambient air pollution and respiratory outcomes were included in this narrative review.[37,76]

### The Portuguese perspective

The Portuguese perspective aimed to summarise evidence collected by studies on ambient air pollution and CRDs carried out in Portugal only, and was based on a non-systematic review of the literature. Searches were carried out in PubMed, Embase, and SciELO, as primary sources, from inception to 30 October 2021, using the following search terms "outdoor air pollution", AND "respiratory health", or "asthma", or "wheezing", or "chronic bronchitis", or "COPD" and "Portugal". As secondary sources, additional references found by authors' review were also included. All observational and analytical epidemiological studies, including cohort, case-control and cross-sectional studies, using traditional epidemiological approaches and/or statistical modelling, written in any language, were accepted. A total of 81 articles was retrieved. All articles were screened by two independent authors. After screening of titles, abstracts and full text, 29 articles were selected.[77–105] Studies not including respiratory outcomes were excluded.

## Results

### Some examples from GARD countries from around the world (Table 1)

#### Iran

Some studies on air pollution in Iran have shown that CO and particulate matter were the most important air pollutants at concentrations higher than standard values, especially in Tehran, with association with respiratory signs and symptoms.[37] Research on the association between ambient air pollution and CRDs such as asthma and COPD showed a relationship between hospital admissions due to exacerbations of these diseases and levels of various air pollutants in major populated cities,[38–40] namely in terms of interaction with weather variables.[41,42] A positive relationship between asthma and air pollutants was also more significant in more "urban" (and polluted) than in more "rural" control sites.[43] Finally, studies fully based on statistical modelling of the distribution of diverse air pollutants and various CRDs (with a focus on asthma) have also shown a positive association.[44–47] However, the Iranian society had not received any appropriate or efficient training and awareness regarding air pollution, in spite of the deleterious effects of air pollution on respiratory health in populated cities being alarming.[48]

#### Canada

Canada is one of few countries (9%) where air quality is within the WHO recommended limits. Nevertheless, several cohort studies were carried out in the country and yielded relevant results. A first cohort study found that early life exposure to oxidant air pollutants ($O_3$ and $NO_2$) was associated with an increased risk of incident asthma and eczema in children.[49] In addition, other cohort studies, performed in major Canadian cities, have also shown various positive associations: between various air pollutants (namely $PM_{2.5}$, $NO_2$, $O_3$ and $O_x$) and the incidence of COPD in adults[50]; between exposure to ultrafine particles (UFP) and COPD (although this association was lost when exposure was adjusted for $NO_2$)[51]; and between long-term exposure to iron (Fe), copper (Cu), and reactive oxygen species (ROS) and the incidence of asthma and COPD, COPD mortality, pneumonia mortality and overall respiratory mortality. The associations were more robust for COPD, and mortality from overall

**Table 1** Main studies that evaluated the effects of external pollution on respiratory health in some GARD countries.

| Author and year of publication | Country and locality or region | Exposure | Population group | Health outcome | Type of study, year and analysis | Main conclusions |
|---|---|---|---|---|---|---|
| Namvar et al, 2020[37] | Tehran, Iran | $PM_{2.5}$, $PM_{10}$, $SO_2$, CO | Children < 7 years-old attending day care centres | Cough, phlegm, wheezing, chest pain, current or past asthma, "bronchitis" | Cross-sectional (2015); analysis using crude and adjusted logistic regression analyses | Long-term exposure to air pollutants near the home:<br>(a) CO - associated with increased risk of persistent phlegm (OR = 1.40; 95% CI = 1.09-1.81);<br>(b) $NO_2$, and $SO_2$ associated with increased risk of current asthma. |
| Masjedi et al, 2003[38] | Tehran, Iran | $PM_{10}$, $SO_2$, CO, $O_3$, $NO_2$, THC (mean 3-, 7- and 10-day levels) | Adult patients residing in Tehran for at least 2 years, with acute asthma or COPD exacerbations, admitted to hospitals | Number of emergency admissions due to acute asthma or COPD exacerbations | Time series (5 months; 1997-1998); analysis using multiple stepwise regression; time-series analysis | Positive correlation between ER admissions for acute asthma and:<br>(a) exposure to $SO_2$ — mean 3-day levels ($r$ = 0.24; p = 0.049), and mean 10-day levels ($r$ = 0.56; p = 0.019);<br>(b) exposure to $NO_2$ — mean 7-day levels ($r$ = 0.28; p = 0.049). |
| Khalilzadeh et al, 2009[39] | Tehran, Iran | $PM_{10}$, $SO_2$, CO, $O_3$, $NO_2$ | Patients admitted to Emergency units due to acute asthma or cardiovascular complaint | Number of emergency admissions due to acute asthma or cardiovascular conditions | Time series (12 months; 2004-2005); analysis using non-adjusted Pearson correlation | Significant positive correlation (r) between number of admissions for cardiopulmonary complaints and levels of: (a) CO ($r$ = 0.731; p = 0.016); (b) $PM_{10}$ ($r$ = 0.752; p = 0.012). |
| Raji et al, 2020[40] | Ahvaz, Iran | $PM_{2.5}$, $PM_{10}$, $SO_2$, CO, $O_3$, $NO_2$, NO | Adults (elderly and non-elderly) admitted to hospitals due to asthma, COPD or bronchiectasis exacerbations | Number of hospital admissions due to acute asthma, COPD or bronchiectasis exacerbations | Time series (2008-2018); analysis using adjusted Quasi-Poisson regression | Increased ER admissions for asthma were significantly associated with (a) $PM_{2.5}$ levels (RR = 1.004; 95% CI = 1.002-1.007); (b) $NO_2$ levels (RR = 1.040; 95% CI = 1.008-1.074); (c) $SO_2$ levels (RR = 1.069; 95% CI = 1.017-1.124).<br>Increased ER admissions for COPD were significantly associated with (a) $PM_{2.5}$ levels (RR = 1.003; 95% CI = 1.002-1.005); (b) $NO_2$ levels (RR = 1.049; 95% CI = 1.010-1.090); (c) CO levels (RR = 1.641; 95% CI = 1.233-2.191).<br>Significant associations also seen with $PM_{10}$ levels and bronchiectasis. |
| Masoumi et al, 2017[41] | Ahvaz, Iran | $PM_{10}$, $SO_2$, CO, $O_3$, $NO_2$, $NO_x$ | Adults admitted to hospitals due to acute respiratory complaints (rainfall associated bronchospasm epidemic period versus non-epidemic period) | Number of emergency admissions due to acute respiratory complaints (shortness of breath, wheezing, coughing and phlegm) | Case-control (2011-2015); analysis using binomial regression | Significant positive relationship between ER respiratory admissions and each unit of increase in NO (adjRR = 1.008; 95% CI = 1.001-1.016; p = 0.037) and $SO_2$ (adjRR =1.014; 95% CI = 1.000-1.028; p = 0.044) levels during the epidemic periods, and $NO_2$ (adjRR =1.010; 95% CI = 1.001-1.019; p = 0.023) levels during the nonepidemic periods. |
| Geravandi et al, 2017[42] | Ahvaz, Iran | $PM_{10}$ | Adults admitted to hospitals due to asthma attacks, acute bronchitis and COPD (dusty days versus non-dusty days) | Number of emergency hospitaladmissions due to acute respiratory complaints (HARD) — asthma, acute bronchitis, COPD | Case-control (2010-2012); analysis using correlation analysis (dust events and $PM_{10}$-related hospital admissions) | Number of HARD admissions was associated with the highest daily $PM_{10}$ concentrations, in 2010-2012, and this was more significant on dusty days (correlations varying between 0.53 and 0.62). |
| Shakerkhatibi et al, 2021[43] | 3 villages (1 in industrial area; 1 with potential urban air pollution; 1 with no potential air pollution) in northwest Iran | $PM_{10}$, $SO_2$, $NO_2$, Volatile Organic Compounds (VOC), benzene, toluene, xylenes | Children and adolescentes from the 3 villages | Prevalence of asthma | Cross-sectional (2016); analysis using two-step hierarchical logistic regression modeling and latent class analysis (LCA) | Higher probability of severe asthma (6.8%) in the "industrial area" village than in the other two villages (2.6% and 1.8%). Adjusted odds of moderate and severe asthma were lower in the control villages than in the "industrial area" village (ORs 0.135 - 0.697). |

**Table 1** (*Continued*)

| Author and year of publication | Country and locality or region | Exposure | Population group | Health outcome | Type of study, year and analysis | Main conclusions |
|---|---|---|---|---|---|---|
| Shakerkhatibi et al, 2021[44] | Urmia, Iran | $PM_{2.5}$, $PM_{10}$ | Adults admitted to hospitals for asthma, chronic bronchitis, emphysema and COPD | Number of daily hospital admissions for asthma, chronic bronchitis, emphysema and COPD | Case crossover; analysis using conditional logistic regression | In the adjusted model, an increment of $PM_{10}$ and $PM_{2.5}$ increased the risk of admissions for asthma by 1.124 (95% CI =1.062-1.191), and 1.117 (95% CI = 1.055-1.184), respectively. Also for $PM_{2.5}$, the estimated OR was 1.5-fold higher in women (OR = 1.078 (95% CI = 1.037-1.121) than in men (OR = 1.032 (95% CI = 0.996-1.069). |
| Razavi-Termeh et al, 2021[46] | Tehran, Iran | $PM_{2.5}$, $PM_{10}$, $SO_2$, CO, $O_3$, $NO_2$ (and distance to parks and streets) | Clinical records of asthmatic children (Hospital Information System) | Children with asthma living in Tehran | (2019); analysis using geostatistical methods including spatial autocorrelation and Random Forest machine learning model | Distribution of asthma was not random, and occurrence of the disease was affected by environmental conditions. $PM_{2.5}$, $PM_{10}$, distance to park, distance to street had a stronger spatial correlation. |
| To et al, 2020[49] | Toronto, Canada | $PM_{2.5}$, $O_3$, $NO_2$ (and greeness) | Children of the T-CHEQ study | Incident asthma, rhinits and eczema | Cohort (average of 17 years − up to 2016); analysis using Cox proportional hazards regression models (single, multipollutant, and oxidants models); Moran's I was to measure spatial autocorrelation and clustering | At birth and / or first 3 years of life exposures to $NO_2$ and $O_3$ were associated with an increased risk of incident asthma - adjusted Hazard ratios (adHR) between 1.14 and 1.23) or eczema (adHR between 1.05 and 1.07) in children, particularly in those $\leq$ 4 years-old. |
| Shin et al, 2021[50] | Ontario, Canada | $PM_{2.5}$, $O_3$, $O_x$, $NO_2$ | Adults from the Ontario Population Health and Environment Cohort (ONPHEC), without respiratory diseases | Incident asthma and COPD | Cohort; analysis using Cox proportional hazards model; stratified analysis; sensitivity analyses | Every interquartile range increase in $PM_{2.5}$, $NO_2$, $O_3$ and $O_x$ was consistently associated with 3-7% higher incidences of COPD, but not asthma, in adults. |
| Weichenthal et al, 2017[51] | Toronto, Canada | Ultra-fine particles (UFP), $NO_2$ | 30-100 year old adults from ONPHEC, without respiratory diseases | Incident asthma, COPD and lung cancer | Cohort (1996-2012); analysis using random-effect Cox proportional hazard models | No clear evidence of positive association between long-term exposure to UFP and respiratory disease independently of other pollutants. |
| Zhang et al, 2021[52] | Toronto, Canada | Iron (Fe) and copper (Cu) in $PM_{2.5}$ | 40-85 year-old adults from (ONPHEC), without respiratory diseases | Incident asthma, COPD, COPD mortality, pneumonia mortality, respiratory mortality; generation of reactive oxygen species (ROS) | (2001-2016); analysis using land-use regression model; estimation of ROS levels; mixed-effects Cox proportional hazard regression models; sensitivity analyses; Shape Constrained Health Impact Function | Positive association between long-term exposure to Fe, Cu and ROS and risks for all respiratory outcomes. |
| Stieb et al, 2009[54] | 7 cities, Canada | $PM_{2.5}$, $PM_{10}$, $SO_2$, CO, $O_3$, $NO_2$, | Records of children and adults visting ER due to acute cardiovascular or respiratory reasons, | ER visits for asthma, COPD, respiratory infections (or cardiovascular reasons) | Time-series (1990s-early 2000s); analysis using generalized linear models adjusted for meteorological conditions and city-specific conditions | $O_3$ had the most consistent associations with ER visits for asthma (3.2%; 95% CI = 0.3−6.2% per 18.4 pp(b), and COPD (3.7%; 95% CI = 0.5−7.9% per 18.4 pp(b). $PM_{10}$ and $PM_{2.5}$ were strongly associated with asthma visits in the warm season: 14.4% increase in visits (95% CI = 0.2−30.7) per 20.6 $\mu g/m^3$ $PM_{10}$, and 7.6% increase in visits (95% CI = 5.1−10.1), per 8.2 $\mu g/m^3$ $PM_{2.5}$). |
| Stieb et al 2000[55] | St. John, Canada | $PM_{2.5}$, $PM_{10}$, $SO_2$, $O_3$, $SO_4^{(2-)}$, Coefficient of | Records of individuals visting ER due to acute cardiovascular or respiratory reasons | ER visits for asthma, COPD (or cardio vascular reasons) | Time series (1992-1996); analysis using single and multiple pollutant models with | In single-pollutant models, positive association between all pollutants (except for $NO_2$ and COH) and asthma visits, and positive effects on all respiratory diagnosis groups were observed for $O_3$, |

**Table 1** (*Continued*)

| Author and year of publication | Country and locality or region | Exposure | Population group | Health outcome | Type of study, year and analysis | Main conclusions |
|---|---|---|---|---|---|---|
| | | Haze (COH), aeroallergens | | | stepwise procedures and sensitivity analyses | $SO_2$, $PM_{2.5}$, $PM_{10}$, and $SO_4^{(2-)}$. In multipollutant models, pollutant gases, particularly $O_3$ and $SO_2$ exhibited more consistent effects. |
| Weichenthal et al, 2016[56] | 15 cities across Ontario, Canada | $PM_{2.5}$, influence of oxidative potential of $PM_{2.5}$ | Children and adults with asthma or COPD, residing in the studied cities, who attended ER due to exacerbations of their respiratory illness | Risk of ER visits due to asthma, COPD and all respiratory outcomes (ICD 10th revision: codes J00-J99) | Time-stratified case crossover (2004-2011); analysis using conditional logistic regression, adjusted for time-varying covariates | $PM_{2.5}$ levels were associated with ER visits for all respiratory illnesses. Glutathione-related oxidative potential modified the impact of low concentrations of $PM_{2.5}$. |
| Moraes et al, 2019[59] | São Paulo, Brazil | Air temperature, relative humidity, precipitation, $PM_{10}$ | Children (0-9 years-old) | Hospitalizations for respiratory diseases | Longitudinal study (2003-2013); analysis using generalised linear models with negative binomial distribution, and distributed lag non-linear model | Significant high risk association between air temperature, relative humidity, rainfall and $PM_{10}$ and hospitalizations for respiratory diseases.<br>For $PM_{10}$ ($> 35 \mu g/m^3$) for total sample and for female sex, the highest RR were 1.299 (95% CI = 1.045 − 1.614), and 1.512 (95% CI = 1.914 -2.067), respectively. |
| Carvalho et al, 2018[60] | Porto Alegre, Brazil | $NO_2$, $O_3$ (measured in individual filters given to the two studied groups) | Healthy, male, professional bikers (index group), and office workers (control group) | Oxidative stress and genetic damage | Cross-sectional study (2016); analysis using Mann-Whitney U test or Chi-square test, and multiple linear regression analysis | $NO_2$ and $O_3$ levels in filters were significantly higher in bikers than in office workers:<br>(a) $NO_2$: 106.77 ± 20.17 $\mu g/m^3$/h versus 14.18 ± 3.69 $\mu g/m^3$/h, respectively;<br>(b) $O_3$: 225.03 ± 45.47 $\mu g/m^3$/8 h versus 12.14 ± 3.85 $\mu g/m^3$/8 h.<br>$NO_2$ and $O_3$ levels and showed a strong positive correlation with plasma lipid peroxidation in bikers. |
| Santos et al, 2016[61] | São Paulo, Brazil | $PM_{2.5}$ | Non-smoking workers (taxi drivers, traffic controllers, forest rangers) | Lung function | Longitudinal study (2008-2012); workers attended 4 weekly visits, for 1 month | Compared to workers in the lowest exposed group (forest rangers), those with the highest level of exposure had significantly reduced predicted FVC and increased predicted $FEF_{25-75\%}$/FVC. |
| Ribeiro et al, 2019[62] | São Paulo, Brazil | Traffic density, $NO_2$ | Adults living in two city zones with diferente socioeconomic status (richer and poorer areas) | Incident respiratory cancer; Respiratory cancer mortality | Longitudinal study (2002-2013); analysis using age-adjusted binomial negative regression models | Increased rate of respiratory cancer incidence and mortality in association with increased traffic density and $NO_2$ levels, and this was stronger in the poorer areas. For<br>$NO_2$ in poorest regions, the incidence rate ratio (IRR) for mortality in the highest exposed group was 1.44 (95% CI = 1.10 - 1.88) while in the least deprived area, the IRR for the highest exposed group was 1.11 (95% CI = 1.01 - 1.23). |
| Agudelo-Castañeda et al, 2019[63] | 5 cities in south Brazil | $PM_{10}$, $PM_{2.5}$, $NO_2$, $O_3$ | Hospital admissions data for children, adults and elderly individuals | Respiratory hospitalizations | Ecological time-series (2013-2016); analysis using adjusted multivariable Poisson regression models | An increase of 10 $\mu g/m^3$ in the monthly average concentration of $PM_{10}$ was associated with an increase of respiratory hospitalizations in all age groups; for $NO_2$ and $SO_2$, stronger intermediate-term effects were found in 6-15 year-old children; for $O_3$, higher effects were found in children < 1 year. |
| Bravo et al, 2016[64] | São Paulo, Brazil | $PM_{10}$, $NO_2$, CO, $SO_2$, $O_3$ | Adults ≥ 35 years-old | Non-accidental, cardiovascular and respiratory mortality (number of daily deaths) | Case cross-over, longitudinal study (1996-2010); analysis using fitted conditional logistic regression models | Increased risk of respiratory mortality were significantly associated with all pollutants, in both sexes, and 35-64 and 65-74 age ranges, OR associated with an IQR increase in air pollutant concentrations between 1.16 and 3.81, mostly with 1-day lag. |
| Costa et al., 2017[65] | São Paulo, Brazil | $PM_{10}$, $NO_2$, CO | Elderly (deaths registered at the Mortality Information Improvement Program) | Non-accidental and cause-specific mortality | Daily time series (2000-2011); analysis using Poisson generalized additive models | $PM_{10}$, $NO_2$, and CO exposures were associated with short-term mortality displacement for nonaccidental and circulatory, but not respiratory, deaths. |

**Table 1** (*Continued*)

| Author and year of publication | Country and locality or region | Exposure | Population group | Health outcome | Type of study, year and analysis | Main conclusions |
|---|---|---|---|---|---|---|
| Nawaz & Henze, 2020[68] | Amazonia, Brazil | $PM_{2.5}$ from biomass burning (forest fires) | Various age groups | Premature deaths due to COPD, lung cancer, acute lower respiratory illness (ALRI) (and ischemic heart disease, and stroke) | (2018; 2019); analysis using computational GEOS-Chem adjoint modeling, with sensitivity analysis, and risk assessment | Premature deaths contributed by biomass burning emissions between July and September made up 10% of total annual $PM_{2.5}$-related premature deaths. |
| Andrade Filho et al., 2013[73] | Manaus, Brazil | $PM_{2.5}$ (from burning biomass), meteorological conditions | Children | Hospital admissions for respiratory diseases | Ecological study of time series (2002-2009); analysis using Pearson correlation and multiple linear regression | Hospital admissions for respiratory diseases in children were significantly correlated with humidity in the rainy season and the association with $PM_{2.5}$ was negative ($R = -0.168$; $p = 0.003$). |
| Ignotti et al., 2010[76] | Tangará da Serra and Alta Floresta, Brazil | $PM_{2.5}$ (from burning of biomass) | Children and elderly | Hospital admissions for respiratory diseases | Ecological study of time series (2005); analysis using generalized additive models with Poisson errors | In Alta Floresta, increased $PM_{2.5}$ levels were associated with hospital admissions for respiratory diseases in children and the elderly. The % increases in relative risk (%RR) of hospitalization for respiratory diseases in children were significant for the whole year and for the dry season (6%; 95% CI = 1.4-10.8) with 3-4 day lags. The %RR for the elderly was significant for the current day of the drought, with a 6.8% increase (95% CI = 0.5-13.5) for each additional 10 $\mu g/m^3$ of $PM_{2.5}$. |

respiratory causes or from pneumonia.[52] Finally, a study using population data from Ontario (the largest province in Canada), found that adult individuals exposed to higher levels of air pollution (namely $PM_{2.5}$ and $O_3$) had nearly threefold greater odds of developing ACO.[25]

Furthermore, various studies using statistical modelling have also shown positive associations: between overall pollution indices (including "floating" particles and $SO_2$) and acute respiratory illnesses[53]; between $O_3$ (even at low levels) and asthma- and/or COPD-related hospital visits[54-57]; and between $PM_{2.5}$ and asthma as well as COPD emergency room (ER) visits.[56] Interestingly, two of the previous studies also showed that concomitant factors may influence these relationships: warmer seasons may promote a stronger association between ambient air $PM_{2.5}$ and $PM_{10}$ levels and asthma hospital visits[54]; in addition, between-city differences in glutathione-related oxidative potential may modulate the impact of low levels of $PM_{2.5}$ on asthma and COPD hospital visits[56].

These studies suggest that there is no safe level of air pollution and that improving air quality will contribute to the prevention of asthma and other allergic disease in childhood and adolescence, and possibly COPD and ACO, in adults.

**Brazil**

Brazil ranks sixth among the largest greenhouse gases emitters, representing 3.2% of the world total. Per capita emissions are also higher than the world average. In 2019, the average $CO_2$ emission per Brazilian was 10.4 gross tons, against 7.1% of the world average.[58] Urban climate change, excessive air pollution and increased social inequalities have become determining factors for the high risk of hospitalizations for respiratory diseases.[59] One study showed that professional motorcyclists who suffer prolonged exposure to air pollution have worsening of pre-existing respiratory diseases.[60] Furthermore, exposure to different levels of traffic-related $PM_{2.5}$ was significantly associated with a reduction in forced vital capacity (FVC) of workers in the city of São Paulo.[61] Traffic density and $NO_2$ were also associated with an increased rate of incidence and mortality from cancer in the respiratory system in residents of poor regions in the city of São Paulo.[62] In addition, a study carried out in southern Brazil reported an increase in hospital admissions for respiratory causes in all age groups with every 10 $\mu g/m^3$ increase in the average monthly concentration of $PM_{10}$.[63] An increased risk of non-accidental mortality from cardiovascular and respiratory diseases was shown in a study to be significantly associated with exposure to $NO_2$, $SO_2$ and CO, but not to $O_3$.[64] In addition, a significant association between exposure to $PM_{10}$, $NO_2$ and CO and non-accidental deaths and circulatory diseases in elderly residents in São Paulo has been documented.[65]

Besides urban pollution, forest fire-related air pollution is also a problem in Brazil.[66] During the 2019 fire season, premature deaths were attributed to fire emissions and accounted for 10% of all $PM_{2.5}$-related premature deaths in the country.[67,68] During periods of active fire, $PM_{2.5}$ was significantly associated with inflammatory respiratory effects,[69,70] and respiratory morbidity including asthma, COPD, bronchitis and pneumonia.[71–73] Furthermore, poor socioeconomic conditions increase the association between

exposure to $PM_{2.5}$ due to forest fire and ER visits and hospitalizations for asthma and heart failure.[74–77]

Thus, public policies are needed in Brazil, to enhance the communication by public health professionals to the exposed populations, so that actionable information and guidelines are more effectively shared such that health and quality of life can be improved.

**Angola and Mozambique**

In Angola, although there is no nationwide air quality monitoring network, there are examples of some monitoring projects, such as in Luanda.[106] The General State of the Environment Report, produced by the Ministry of Urbanism and Environment (MINUA), in 2006, showed a worrying picture of indoor and outdoor air quality which was dominated by gas emissions from traffic, electric generators, industry, burning of solid waste in streets, and biomass combustion in poorly aerated sites, all of which can induce serious respiratory problems.[107] This is further compounded by the fact that, although there are studies on the prevalence and clinical features of asthma in children and adolescents from Luanda, which showed high levels,[108,109] there are currently no epidemiological data on the prevalence of asthma or COPD in adults. Furthermore, no studies have been carried out in Angola, on the relationship between outdoor air pollution and respiratory diseases.

In Mozambique, the Environmental Law, the assessment of the Environmental and Regulatory Impact of Health and Safety, and other laws which include Industrial and Environmental Emission Patterns, the Regulations for Environmental Auditing and Inspection, among others, constitute the main legislation which regulates air pollution issues.[110,111] Just like in Angola, the degree of industrialization in Mozambique is still low in general, but high in and around the bigger cities such as Maputo, Beira and Matola. In these locations, pollution may result, among other reasons, from the combined effect of obsolete equipments and lack of significant protection regulations for the population against dangerous pollution sources,[112] and also from waste management problems and automobile traffic-related emissions ($CO_2$, CO, $NO_x$).[113] In addition, uncontrolled bush burning in rural zones, mainly in the north and centre of the country, is one of the main sources of pollutants.[114,115] In fact, measurements of pollutants, which began in 1996, showed that burning of biomass was the main source of particulate matter pollution, followed by industrial activities.[115] There is also significant emission of $CO_2$, methane ($CH_4$) and $NO_2$ in production, transportation and utilisation of vegetable coal in certain areas of the country.[116] Finally, there is intense exploitation of coal in open pit mines in the province of Tete, and this type of mining is associated with air pollution and a high rate of respiratory diseases in those areas, particularly in children.[117] However, there are no published studies on the effects of outdoor air pollution on respiratory diseases in Mozambique.

Thus, it is crucial that research studies on such relationship are carried out both in Angola and in Mozambique, and also that a broad effort to raise awareness is implemented, involving multiple stakeholders as well as the community, in integrated research – societal effort[118] so that environmental research may result in prevention, mitigation and minimization measures, reducing the associated burden and costs,[119] aligned with the "Declaration of Libreville on Health and Environment in Africa"[120] and the related "2010 Luanda Compromise".[121]

## Portuguese perspective

Most studies performed in Portugal have used statistical models to assess and predict the relationship and impact of various air contaminants, meteorological conditions and CRDs, and have mostly used data on hospital admissions of adults and children, as a possible effect of exposure to outdoor air pollution. Fewer analytical epidemiological studies were conducted to study the relationship between outdoor pollution and CRDs (mostly asthma) and they were mainly focused on urban children. Finally, there were a few studies focused on exposure to volcanic air pollution and its impact on lung diseases.

(a) Analytical epidemiological surveys

Various analytical epidemiological studies were carried out in Portugal to study the relationship between exposure to ambient air pollutants and epidemiological indices of respiratory diseases. These studies are summarized in Table 2. Most studies were carried out in urban settings (Lisbon,[77–79] Viseu,[80,81] Estarreja[82,83] or Setúbal[84]) and involved children.[77–81] These studies normally used validated questionnaires such as the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, to analyse the presence of asthma and/or rhinitis in urban or rural schools. Most frequently studied ambient air pollutants were $PM_{2.5}$, $PM_{10}$, CO, $NO_2$, although other parameters were assessed in some of the reports, namely elements associated with resuspension or vehicle motors,[77–79] or BTEX – benzene, toluene, ethylbenzene and xylenes.[80,81]

Most studies showed that pollutant concentrations were higher than advised by the World Health Organization and U. S. Environmental Protection Agency, but below the current European Union value, although in some areas, such as Lisbon, concentrations were even higher. However, most studies were cross-sectional and this is a main limitation which should be addressed in future projects.

Some representative studies carried out in urban or rural settings and on the relationship between volcanic activity and respiratory diseases will be analysed next.

In a 2006–2007 study, the ISAAC questionnaire was distributed to 806 children attending four primary schools in the small, low-industrial city of Viseu, to identify children who reported wheezing in the previous 12 months.[80,81] Six hundred and forty-five questionnaires were returned, and 77 of the children reported wheezing in the previous 12 months. Of these, 54 were allowed to be included in the study and a total of 51 participants completed the protocol: record of clinical symptoms, pH analysis in exhaled breath condensate (EBC), measurement of exhaled nitric oxide fraction (FeNO), and spirometry, in four separate visits. Outdoor and indoor levels of air pollutants ($O_3$, NO, $NO_2$, CO, BTEX – benzene, toluene, ethylbenzene and xylenes, $PM_{10}$ and $PM_{2.5}$) were measured. Lung function parameters, as

**Table 2** Air pollution effects in Portugal: (1) Main epidemiological studies that evaluated the effects of external pollution on respiratory health in Portugal.

| Author and year of publication | Locality or region | Exposure | Population group | Health outcome | Type of study, year and analysis | Health outcome results |
|---|---|---|---|---|---|---|
| Urban studies on relationship between exposure to air pollutants and respiratory outcomes | | | | | | |
| Freitas et al, 2009[77] Freitas et al, 2009b[78] Almeida et al, 2009[79] | Lisbon | $PM_{2.5}$, $PM_{10}$, various elements associated with soil resuspension or vehicle motors, and water soluble ions | Children (5-10 years-old) attending pre-primary and primary schools | Rhinitis, asthma / wheezing (ISAAC questionnaire definition) | Cross-sectional (2006-2007); analysis using non-parametric Spearman R test, and Principal Component Analysis | There is a mixture of contributions of tested pollutants (namely $PM_{2.5}$ and its speciation for (i) chemical elements - Na, K, Sc, Cr, Fe, Co, Zn, As, Se, Br, Sb, Cs, La, Ce, Hg; (ii) the water-soluble cations $Ca^{2+}$, $K^{+}$, $Mg^{2+}$, $Na^{+}$, $NH_4^{+}$; and (iii) water-soluble anions $Cl^{-}$, $NO_3^{-}$, $SO_4^{2-}$ (which are soil resuspension- or vehicle motor-associated) to rhinitis in children, and this may vary according to season. |
| Borrego et al, 2007[80] Martins et al, 2012[81] | Viseu | Outdoor $PM_{2.5}$, $PM_{10}$, CO, $O_3$, NO, $NO_2$, BTEX (also indoor air pollutants) | Saud'Ar study (Wheezing children - ISAAC questionnaire definition; also studied at city hospital) | Respiratory functional and inflammatory outcomes ($FEV_1$, $FEV_1$/FVC, FEF25-75%, $\Delta FEV_1$; FeNO, pH of EBC); Clinical outcomes (wheezing, need of rescue medication; ER visits) | Prospective (4 study points in 2006-2007); analysis using mesoscale modelling system; adjusted Generalised estimating equation (GEE) two pollutant modelling with exchangeable working correlation; Spearman's rank correlation | Significant relationship between: a) $PM_{10}$ and wheezing [-0,70 (-1.14 to -0.25; p = 0.002)]; (b) $NO_2$ and wheezing [-2.08 (-3.59 to -0.58; p = 0.007)]. (b) toluene and need of rescue medication [0.21 (0.01 to 0.42; p = 0.041)], and ER visits [0.26 (0.06 to 0.46; p = 0.010)]; (c) ethylbenzene and need of rescue medication [0.45 (0.02 to 0.87; p = 0.039)]. (d) $PM_{10}$, $NO_2$, benzene, toluene, and ethylbenzene and various parameters of lung function; (e) $PM_{10}$, $NO_2$, benzene, and ethylbenzene on phEBC. No significant effects were seen on FeNO. |
| Neuparth et al, 2012[82] Valente et al, 2014[83] | Estarreja | Indoor and outdoor $PM_{10}$, $NO_2$ smoking, dusty workplace | Adults - exposed workers of Estarreja chemical complex (ECC) and general population controls from the same geographical area | Physician-diagnosed asthma, and symptoms of chronic bronchitis; $FEV_1$/FVC (Neuparth,2012) | Case-control (2 periods in 2011 and 2012); analysis using a second-generation Gaussian model (URBAIR model); also an individual exposure model (DoseAR); also CHIMERE exposure model | All individuals spent > 90% of their time indoors; there was high $PM_{10}$ and $NO_2$ exposure variability. No significant differences in exposure were observed between the two studied groups. Analysis of the relationship between asthma or chronic bronchitis did not directly involve $PM_{10}$ or $NO_2$. |
| Farinha et al, 2021[84] | Setúbal | $PM_{10}$, $O_3$, CO, $SO_2$, $NO_2$, measured at two stations | Asthma patients seen at an Allergy outpatient hospital clinic | Intensity of asthma symptoms (0-5 visual analogue scale) — Sum of the Scores of Asthma Symptoms (SSAS) | Longitudinal (March-April 2018); analysis using a temporal causal model — autoregressive time series model. | All pollutants influenced intensity of asthma symptoms. $O_3$ level was the best predictive factor of symptom variability (particularly with a lag 5; $p<0.05$), and $PM_{10}$ (lag 4), CO (lag 5) and $NO_2$ (lag 4) were secondary markers. |
| Rural studies on relationship between exposure to air pollutants and respiratory outcomes | | | | | | |
| Alvim-Ferraz et al, 1988 (2002 data)[85] Sousa et al, 2009 (Phase 1)[86] Sousa et al, 2011 (Phase 2)[87] | Torre de Moncorvo, Mogadouro, and Espiunca | $O_3$ | Children from local schools from two areas with high $O_3$ exposure (Torre de Moncorvo and Mogadouro) and from an area with low $O_3$ exposure (Espiunca) | Prevalence of asthma (Phase 1: ISAAC questionnaire-based (data from Espiunca had been collected in 2002); Phase 2: spirometry-based | Cross-sectional (2007); analysis using univariate analysis as well as logistic regression models to calculate risks and odds ratios | Stage 1: Questionnaire-based: the lifetime prevalence of asthma (wheezing) was significantly higher in the areas with high $O_3$ exposure (7.1%) than in those with low exposure (3.2%). Stage 2: Children living in the former areas had a 3-fold higher risk of having asthma than children living in the latter areas [RR = 2.84 (95% CI = 1.82 — 4.43) and OR = 3.02 (95% CI = 1.88 — 4.86]. |

**Table 2** (*Continued*)

| Author and year of publication | Locality or region | Exposure | Population group | Health outcome | Type of study, year and analysis | Health outcome results |
|---|---|---|---|---|---|---|
| Relationship between exposure to volcanic activity and respiratory outcomes | | | | | | |
| Amaral and Rodrigues, 2007[88] | S. Jorge (Furnas) and Santa Maria, Azores islands | No parameters were measured (exposure to $SO_2$ and $H_2S$ was inferred) | Clinical records of children and adults registered at each healthcare centre of each region: Furnas (high volcanic activity) and Santa Maria (without volcanic activity) | Incident chronic bronchitis stratifed by age groups | Restrospective (1991-2001); analysis using relative risk estimates and Chi-square tests | The estimated age-standardised incidence rates for chronic bronchitis were higher in Furnas (224.8 for males and 196.7 for females) than in Santa Maria (56.3 for males and 18.3 for females), for both sexes. Living in Furnas was associated with significant risk ratios of chronic bronchitis in relation to living in Santa Maria [RR males=3.99 (95% CI = 2.98-5.35); RR females =10.74 (95% CI = 6.55 − 17.34)], for both sexes. |
| Linhares et al, 2015[89] | Ponta Delgada and Ribeira Quente, Azores islands | Soil $CO_2$ flux | Children and adults living in Ribeira Quente (high volcanic activity as active fumarolic fields and degassing soils − hydrothermal area) and Ponta Delgada (no volcanic activity) | Prevalence of COPD and restrictive defects (questionnaire-and spirometry-based) | Cross-sectional (2013); analysis using Mann-Whitney U test, Pearson Chi-square test, adjusted binary logistic regression model; odds ratios adjusted for age, gender, tafigue, astma and smoking | The hydrothermal area in comparison with the non-hydrothermal are showed significant differences: (a) higher prevalence of restrictions (10.2% versus 3.0%; $P = 0.001$); (b) higher prevalence of COPD (33.6% versus 11.9%; $p<0.001$); (c) higher prevalence of more severe obstructions (mild, 15.7 versus 4.4, moderate, 6.8 versus 2.2, and severe, 4.7 versus 0, respectively). (d) higher OR for restrictive defects and COPD - 4.4 (95% CI 1.78−10.69) and 3.2 (95% CI 1.82−5.58), respectively. |

well as wheezing symptoms, use of rescue medication (bronchodilators) and emergency department visits in the previous 6 months were used as clinical outcomes. A generalized estimating equation (GEE) approach with an exchangeable working correlation showed that exposure to $PM_{10}$, $NO_2$, benzene, toluene and ethylbenzene was associated with a decrease in $FEV_1$ and an increase in $\Delta FEV_1$, (change in $FEV_1$ 15 minutes after inhalation of 200 $\mu$g of salbutamol) while increased exposure to $NO_2$ and benzene was also associated with a decrease of $FEV_1/FVC$ and $FEF_{25-75\%}$, the same was found with ethylbenzene for the latter. Acidity of EBC was associated with increased exposure to $PM_{10}$, $NO_2$, benzene and ethylbenzene. Ethylbenzene and toluene were the only pollutants with a significant positive association with FeNO and with symptoms in the previous months, respectively.

Another study performed in the city of Setúbal assessed the association between the intensity of asthma symptoms in adult patients seen at an outpatient clinic and the variation of $PM_{10}$, $O_3$, $NO_2$, $SO_2$, and CO levels in the city.[84] Patients were instructed to record the intensity of their respiratory symptoms daily, in March and April 2018, and such symptom scores were added together to obtain a daily score. Daily levels of pollutants were obtained from the website of the Portuguese Environment Agency (APA). Data were analysed using a temporal causal model (autoregressive time series models based on the concept of Granger causality). Detected daily air pollutant levels were below internationally regulated values for background / traffic-related components− 26.85 / 35.11 $\mu g/m^3$ for $NO_2$, 232.13 / 255.80 $\mu g/m^3$ for CO, and 21.63 / 19.73 $\mu g/m^3$ for $PM_{10}$− indicating low level of air pollution. $O_3$ was significantly associated with asthma symptoms, particularly with a 5-day lag, whereas $PM_{10}$, CO and $NO_2$ also had a significant but less robust impact, with a 4-5 daylag.

Three related studies on rural pollution were performed in three places in northern Portugal, aiming to compare the prevalence of childhood asthma between two rural areas with high $O_3$ concentrations (Torre de Moncorvo and Mogadouro), and an area with low $O_3$ concentrations (Espiunca), and to determine potential risk.[85−87] The presence of asthma was determined by self-report using the ISAAC questionnaire and a subgroup of children with positive questionnaires was further studied by spirometry. Logistic regression models were used to calculate odds ratios. Globally, this project showed that children living in the exposed areas had a 3-fold higher risk of having asthma than those living in the unexposed area, a difference which the authors attributed to $O_3$ pollution.

The association between chronic exposure to indirect volcanic (namely hydrothermal) activity and respiratory diseases was investigated in two studies carried out in the Azores islands.[88,89] In one of the studies,[88] incidence rates of chronic bronchitis were much higher in the volcanically active (risk attributed to $H_2S$ and $SO_2$, although no measurements of these gases were carried out) area for both sexes, especially in the younger groups. In addition, the risk of chronic bronchitis for the population of the active area was significant in relation to those living in inactive areas (males RR = 3.99; females RR = 10.74). In the other study,[89] the prevalence of restrictive and obstructive respiratory morbidities in the study group was significantly higher than in the reference group. Further, the prevalence of more severe

bronchial obstructions was higher in the study group. Multivariable analyses showed that exposure to volcanogenic pollution significantly predicted the presence of spirometric restrictive and obstructive patterns, and worsening of COPD.

Overall, epidemiological analytical studies carried out in Portugal have shown that chronic exposure to outdoor air pollution (namely $PM_{2.5}$, $PM_{10}$, $O_3$, $NO_2$) may be associated with a higher prevalence of asthma, higher prevalence of symptoms and/or changes in respiratory function. Furthermore, this may occur even at low levels of pollution. Further studies are needed, particularly involving cohorts and with longitudinal monitoring data.

(b) Routine statistics studies

Most studies on the relationship between outdoor air pollution and respiratory diseases performed in Portugal have been based on statistical modelling of data collected from different databases. "All respiratory causes", asthma and/or COPD were the most studied respiratory problems. In addition, parameters under study have included ER admissions due to disease exacerbations and these were analysed in relation to different time lags regarding increases in air pollutant levels.

There are twelve key studies in Portugal that examined the relationship between outdoor air pollutant levels and ER admissions for various respiratory causes. Most were carried out in large, industrial cities such as Lisbon (n=6) and Porto (n=2), and three were multicenter. These studies are summarized in Table 3.

Regarding outdoor air pollutants that were assessed and incorporated into analysis, $PM_{10}$ (studied in isolation in 1 report), $O_3$ (analysed in isolation in 1 study), $SO_2$ and $NO_2$ were the most frequently studied, while NO was the least frequently assessed pollutant. Most studies analysed various pollutants ($PM_{10}$, $SO_2$, $NO_2$, CO, $O_3$), with data most frequently obtained from local stations belonging to APA and made available daily at the QualAR online database (https://qualar.apambiente.pt/). Various meteorological factors (e.g., temperature, rain, humidity, wind) included either as main environmental determinants or as covariates in analytical models of outdoor air pollutants have also been analysed.

ER admissions or hospitalizations, as well as mortality due to exacerbations of asthma, "all respiratory causes", and COPD were the most frequently studied respiratory outcomes. Of these, asthma was the most commonly studied (single focus in two studies), and COPD the least frequently studied, with asthma, COPD and "all respiratory causes" being simultaneously analysed only in three studies. Most hospital admission data were obtained from the Central Administration of the Health Service (ACSS), with mortality data being retrieved from the National Institute of Statistics. Patient records mostly included adults and children, with two studies focused only on children.[93,94]

The methods used in analysing the association between exposure to air pollutants and clinical outcomes varied significantly across studies but most frequently involved various statistical models such as General Additive Poisson Regression Models (GAM-type), Quasi-Poisson GAM combined with distributed lag non-linear model (DLNM), Ordinary Least Squares Linear Regression, and Cross-correlation method models. Two studies from the same group used Principal Component Analysis.[97,98] Most models adjusted the effects of pollutants by incorporating meteorological and other factors (e.g., seasonality, age ranges, etc).

Globally, results have shown that $PM_{10}$[91–97,99,100] and $SO_2$[90–92,97,99,100] were most frequently positively associated with respiratory disease-related outcomes (however, $PM_{10}$ levels were inversely correlated with hospital admissions for COPD, in one study[99]). With a slightly lower frequency, $PM_{2.5}$,[92,93,96,97,101] CO,[90,92,95,97,98,100] and $NO_2$[91,92,95,97,100,102] have also been shown to be positively correlated with respiratory disease outcomes. $O_3$ was a special situation since it showed positive correlations with respiratory outcomes in four studies: with all respiratory causes, asthma, and COPD,[91] acute upper respiratory infections (AURI) and chronic lower respiratory diseases (CLRD),[95] and COPD and "allied conditions",[98] and respiratory mortality in those $>$ 65 years-old, as well as ER visits in those $<$ 14 years-old and those $>$ 65 years-old[100]; however, in contrast, it showed negative correlations in two studies: with asthma[97] and with all respiratory causes.[101]

The concern about forest fires is growing as not only do they impact on respiratory health, the incidence is on the rise due to climate change. One study examined the ambient levels of $PM_{10}$ and $PM_{2.5}$ associated with large fires in 2017 in the centre region of Portugal and the incidence of asthma symptoms in asthmatic children.[103] Data were collected daily at five local rural monitoring stations belonging to the APA network. The $PM_{10}$ and $PM_{2.5}$ concentrations increased during the fires, with daily concentrations exceeding the European and Portuguese guidelines for various days in 2017 (up to 704 $\mu g/m^3$ for $PM_{10}$ and 46 $\mu g/m^3$ for $PM_{2.5}$, respectively). An estimated incidence of 3524 episodes of asthma symptoms per 100,000 individuals at risk was attributable to exposure to these fires. This study quantified the effect of forest fires on the incidence of asthma symptoms in children living at affected areas and suggested that rural stations should measure pollutants associated with respiratory health.

**Pollution reduction benefits**

Reducing air pollution may have various respiratory health benefits.[122] Some studies used an Impact Pathway Approach to estimate the potential health impacts and benefits (or avoided external costs) from improvements in air quality in Portugal.[104,105] Various emission reduction scenarios, based on individual and combined abatement measures (e.g., replacing 10% of light vehicles below Euro 3 with hybrid vehicles, or implementing reduction technologies for $PM_{10}$ from industrial combustion and production processes), were tested for the main activity sectors (traffic, residential and industrial combustion and production processes) of a Portuguese urban area (Porto Metropolitan Area). Implementation of all measures would result in a significant reduction in $PM_{10}$ and $SO_2$ emissions, thereby improving air quality and contributing to saving almost 9 million €/year, an amount which includes direct costs (health care and non-health care costs associated with treatment and caring) and indirect costs

**Table 3** Air pollution effects in Portugal: 2) Main studies using routine statistics to analyse the effects of external pollution on respiratory health in Portugal.

| Study | Study area | Exposure | Population group | Health outcome | Type of study, year and analysis | Health outcome results |
|---|---|---|---|---|---|---|
| Relationship between exposure to outdoor air pollutants and admissions to hospitals for acute respiratory diseases | | | | | | |
| Alves et al, 2010[90] | Lisbon | $PM_{10}$, $SO_2$, CO, $O_3$, NO, $NO_2$ | Clinical records of patients (children and adults; age groups 0-14, 15-64, > 64 years old) admitted to 12 hospitals because of all respiratory causes, asthma, and COPD; also cardiovascular causes (data from IGIF) | Daily counts of hospital admissions due to all respiratory causes, asthma, and COPD (also cardiocirculatory causes) | Time-series (1999-2004); analysis using General Additive Poisson Regression Models (GAM-type) with linear and quadratic tendency terms to control for confounding temperature, humidity and seasonal effects; 1, 2 and 3-day lags | Significant association (1-day lagged) between levels of $SO_2$ and increased childhood ER admissions for all respiratory causes, with an increased risk (*RR* = 1.139) for an increase of 10 $\mu g/m^3$ of $SO_2$ daily concentrations. CO was also significantly associated, with a 2-day lag, with ER admissions for all respiratory causes in patients > 64 years-old |
| Freitas et al, 2010[91] | Lisbon | $PM_{10}$, $SO_2$, CO, $O_3$, NO, $NO_2$, temperature, humidity | Clinical records of patients (children and adults; age groups 0-14, 15-64, > 64 years old) admitted to 12 hospitals due to respiratory causes; also cardiovascular causes (data from IGIF) | Daily counts of hospital admissions due to all respiratory causes, asthma and COPD (also cardiocirculatory causes) | Time-series (1999-2004); analysis using t tests, F tests, parametric (Pearson) correlations, with a time lag of zero | Multiple, significant, correlations between temperature, humidity, $PM_{10}$, $SO_2$, $O_3$ and $NO_2$ and hospital admissions for all respiratory diseases, asthma and COPD. |
| Cruz et al, 2015[92] | Lisbon | $PM_{2.5}$, $PM_{10}$, $SO_2$, CO, $O_3$, NO, $NO_2$ | Clinical records of patients (children and adults; age groups 0-14, 15-64, > 64 years old) admitted to 13 hospitals due to respiratory causes; also cardiovascular causes (data from ACSS) | Daily counts of hospital admissions due to all respiratory causes, and asthma (and due to all circulatory and various cardiovascular diseases) | Time series (2006-2008); analysis using Ordinary Least Squares Linear Regression | Significant positive associations between:<br>(a) CO, NO, $NO_2$, $SO_2$, $PM_{10}$ and $PM_{2.5}$ and respiratory diseases for ages 0-14 years (up to 1.9 % hospital admissions increase with 10 $\mu g/m^3$ pollutant increase); and<br>(b) NO, $NO_2$ and $SO_2$ and respiratory diseases for ages above 64 years (1.3% hospital admissions increase with 10 $\mu g/m^3$ CO increase). |
| Moreira et al, 2008[93] | Lisbon | $PM_{2.5}$, $PM_{10}$ | Children (0-14 years-old) admitted to a hospital ER as well as being seen at outpatient clinic, due to respiratory conditions (direct data from the hospital) | Daily counts of hospital admissions due to respiratory causes: acute infection, chronic infection, rhinits, influenza, pneumonia, chronic bronchitis, emphysema, COPD, asthma, bronchiectasis and other | Time series; (January-December 2004); analysis using models of multiple linear regression; 3- and 5-day lags | Significant association between the zone where children with respiratory problems were seen at a healthcare unit and the city areas with the highest PM levels. |
| Rodrigues et al, 2021[94] | Lisbon | $PM_{10}$, temperature, relative humidity | Records of children (age groups: 0-4, 5-9 and 10-14 years, and disaggregated by sex) admitted to Hospitals of the Lisbon Metropolitan area, due to asthma (data from ACSS) | Daily counts of hospital admissions due to asthma | Time series (2009-2015); analysis using a Quasi_Poisson generalized additive model combined with a distributed lag non-linear model (DLNM); different lags (up to 3 month-lag) | An increased risk of asthma-related hospital admissions was observed with $PM_{10}$ with a 2% (RR = 1.02; CI 95% 1.01−1.03) in the general sample, and in male children; also in age group 5-9 years, with an increased risk at lag 0 of RR =1.03; 95% CI (1.01−1.05). Temperature and relative humidity also had significant effects. |
| Franco et al, 2020[95] | Lisbon Metropolitan área (Lisbon, Odivelas, Amadora) | $PM_{10}$, $NO_2$, NO, CO, $O_3$ | Records of patients (children and adults; age groups 0-14, 15-64, > 64 years old) admitted to Hospitals, due to respiratory and circulatory causes (data fromACSS) | Number of daily hospital admissions due to all repisratory diseases (ARD), chronic lower respiratory diseases (CLRD), or acute upper respiratory infections (AURI) | Time series (January-December 2015); analysis using various models and time lags Ordinary Least Squares linear regression; best models selected by statistical significance | Association was seen between air pollution and AURI (2.93% increased ER admissions per 10$\mu g/m^3$ increase in air pollution); significant between ARD and air pollution (2.2% increased ER admissions per 10$\mu g/m^3$ increase in air pollution).<br>CO was the pollutant most frequently associated with ER admissions due to ARD, AURI and CLRD. $O_3$ also showed a substantial association in the older age groups, increasing ER admissions due to AURI and CLRD (4.1% and 4.8% per 10$\mu g/m^3$ increase in $O_3$ levels, respectively). |

**Table 3** (*Continued*)

| Study | Study area | Exposure | Population group | Health outcome | Type of study, year and analysis | Health outcome results |
|---|---|---|---|---|---|---|
| | | | | | | $NO_2$ had the largest average effect on ER admissions across all models and age groups (4.4% increase in ER admissions per 10$\mu g/m^3$ increase in $NO_2$), with the strongest associations being with CLRD and AURI. NO and $PM_{10}$ had the fewest associations with ER admissions but $PM_{10}$ still had a significant impact on respiratory diseases (4.52% increase in ER admissions per 10$\mu g/m^3$ increase in $PM_{10}$ levels). |
| Almeida et al, 2014[96] | Setúbal | $PM_{2.5}$, $PM_{10}$, $O_3$ | Records of patients (children and adults; age groups 0-14, 15-64, $>$ 64 years old) admitted to Setúbal Central Hospital because of circulatory and respiratory causes (data from ACSS) | Daily counts of hospital admissions due to all respiratory causes, and asthma (and circulatory and various cardiovascular diseases and cerebrovascular disease), | Time series (January-December 2009); analysis using various models (DAY, WEEK, O&MA, MA&MA) of Ordinary Least Squares Linear Regression | An increase of 10 $\mu g/m^3$ in $PM_{10}$ was associated with a rise of 1.6% in hospital admissions for respiratory causes in individuals $<$ 14 years; an increase of 10 $\mu g/m^3$ in $PM_{10}$ was associated with a rise of 0.8 $-$ 0.9% in hospital admissions for respiratory causes in individuals $>$ 64 years; an increase of 10 $\mu g/m^3$ in $PM_{2.5}$ was associated with a rise of 0.8-1.1% in hospital admissions for respiratory diseases in individuals $>$ 64 years. |
| Azevedo et al, 2011 (data from 2005)[97] | Porto | $PM_{10}$, $SO_2$, CO, $O_3$ (collected at 11 stations); $PM_{2.5}$ (collected only at 1 station) | Records of patients (no information on age ranges) admitted to 4 major Hospitals due to asthma / bronchitis (direct data from the hospitals) | Number of daily hospital admissions due to asthma /, bronchitis | Time series (June-August 2005); analysis using Principal Component Analysis (PCA) and Pearson correlation coefficient; adjustemnt for temperature and wind; 1- and 2-day lags | Pearson correlation showed that: (a) for 1-day lag: only CO and NO had significant, positive correlations with asthma / bronchitis: for CO (Pearson=0.209; p = 0.024); for NO (Pearson=0.234; p = 0.024); $O_3$ had a significant, negative correlation (Pearson= -0.233; p = 0.024); (b) for 2-day lag; $O_3$ was also negatively correlated with asthma / bronchitis (Pearson= -0.213; p = 0.041); $PM_{2.5}$ and CO had a significant, positive correlation: for $PM_{2.5}$ (Pearson=0.241; p = 0.02), for CO (Pearson=0.219; p = 0.035). PCA also showed negative association between $O_3$ and asthma / bronchitis, and positive associations between $PM_{10}$, $PM_{2.5}$, NO and CO and asthma / bronchitis (in the Winter), and between $SO_2$ and $NO_2$ and asthma / bronchitis (in the Summer). |
| Azevedo et al, 2011[98] | Porto | $O_3$ | Records of patients (no information on age ranges) admitted to 3 major Hospitals due to various circulatory or respiratory causes (direct data from the hospitals) | Number of daily hospital admissions due to COPD, bronchitis, asthma, pneumoconioses and other lung diseaes due to external agents; also due to various cardiocirculatory causes | Time series (June-August 2005); analysis using Principal Component Analysis (PCA) and ANOVA; 0- to 4-day lags | PCA analysis did not show an association between $O_3$ concentrations (studied with a 4-day lag) and hospital admissions due to respiratory causes. In specific periods results showed that increased incidence of admissions due to COPD and "allied conditions" (including bronchitis and asthma) was associated with exposure to $O_3$, NO and CO. |
| Alves et al, 2005[99] | Porto | $PM_{10}$, $SO_2$, assessed at 3 different places in the city, with varying influences of industry and traffic | Records of patients (children and adults) admitted to Gaia Hospital, due to COPD exacerbations (direct data from the hospital) | Number of daily emergency admissions (ER) due to COPD | Time series (1 January 31 December), analysis using cross-correlation method models; up to 12-day lags | Positive relation between $SO_2$ and ER admissions was found using some models, with stronger association for lag 0 than with 1- or 2-day lags. A negative relation between $PM_{10}$ and ER admissions, with stronger association for 1- or 2-day lags. |
| Nicolau et al, 2010[100] | Matosinhos, Maia, Valongo and Lisbon (GeoFASES | $PM_{10}$, CO, $O_3$, $NO_2$, $SO_2$ | Records of patients admitted to Hospitals due to all causes, respiratory causes and circulatory causes (data ACSS); | Daily mortality counts (2000-2004) and ER visits (2000-2007) due to respiratory causes | Time series (2000-2004); analysis using Poisson regressions developed from Generalized Additive Models (final model | Only $O_3$ showed an increased risk (RR = 1.071 for each 10 $\mu g/m^3$ increase in $O_3$) of respiratory mortality and only in people $\geq$ 65 years old. $PM_{10}$, $NO_2$, $SO_2$ and CO showed a significantly |

**Table 3** (*Continued*)

| Study | Study area | Exposure | Population group | Health outcome | Type of study, year and analysis | Health outcome results |
|---|---|---|---|---|---|---|
| | multicentre project) | | mortality data obtained from the National Institute of Statistics; data from total sample of patients and also stratified into ≤14 years old and ≥ 65 years old | | used only single pollutants) and Pearson correlation; 0- to 8-day lags | increased risk of ER visits (RR between 1.001 and 1.089), with different lags and mostly in the total sample, in ≤ 14 yrs old and in ≥65 yrs old). |
| Martins et al, 2021[101] | 58 monitoring stations in mainland Portugal (data on QualAr website) | $PM_{2.5}$, $PM_{10}$, $NO_2$, CO, $O_3$, $SO_2$ | Records of patients (children and adults) admitted to Hospitals due to respiratory causes (data from ACSS) | Daily hospital admissions due to respiratory causes | Multicentre time series (2005-2017); statistical modelling analysis using the INGARCH approach incorporating relevant covariates; cluster analysis; 1- to 7-day lags | PM and NO covariates had, in general, positive coefficients indicating that an increase in their concentrations is associated with an increase in hospital admissions. In contrast, lower levels of $O_3$ were associated with increased hospital admissions. |
| Ayres-Sampaio et al, 2014[102] | Various locations in Portugal (stratified into % urban coverage: low, moderate, high) | $PM_{10}$, $NO_2$, temperature, relative humidity, Normalized Difference Vegetation Index (NDVI) | Records of patients (no information is given on age ranges) admitted to Hospital, due to asthma exacerbations (data fromACSS) | Number of daily hospital admissions due to asthma; asthma admission rates / 1000 inhabitants in each municipality | Multicentre time series (2003-2008); analysis using linear regression analysis | In the most urban group, high temperatures, low NDVI, and high $NO_2$ levels had consistent relationships with asthma in all seasons (Pearson correlation coefficients ranging from 0.351 - 0.600; 0.376 - 0.498; and 0.405 - 0.513, respectively). No significant effect was seen with $PM_{10}$. |
| Relationship between exposure to forest fire-related outdoor air pollutants and admissions to hospitals due to asthma | | | | | | |
| Oliveira et al, 2020[103] | 5 rural locations | $PM_{2.5}$ (levels could only be determined in 2 locations), $PM_{10}$ | Children living in rural area | Estimation of incident asthma symptoms in children / 100,000 individuals at risk | Statistical modelling using data from 2017 forest fires; analysis using WHO AIRQ+ model application | $PM_{10}$ and $PM_{2.5}$ levels were increased during large fires, with daily concentrations exceeding the European/national guidelines in various periods of 2017 (up to 704 $\mu g/m^3$ for $PM_{10}$ and 46 $\mu g/m^3$ for $PM_{2.5}$), respectively. Potential incidence of 3524 cases of asthma symptoms / 100,000 children at risk, during such periods. For $PM_{10}$, RR (median; 95% CI)= 1.03 (1.01-1.05), with attributable proportion of cases varying between 1.99 and 3.62%, depending on locality. |
| Studies addressing health benefits of outdoor air pollution reduction | | | | | | |
| Silveira et al, 2016[104] | Porto | $PM_{10}$ (MAPLIA project) | Children and adults | Parameters used to calculate benefits: asthma in children, chronic bronchitis in children and adults, and related relative risk, baseline annual rate and health costs | Impact pathway approach involving 4 abatement measures; analysis using 7 abatement scenarios; health impacts analysed using Equation (MAPLIA system) | Implementation of all measures would result in a reduction in $PM_{10}$ emissions by almost 8%, improving air quality by about 1% and contributing to a benefit of 8.8 million €/year for the entire study domain, due to reduction of health-related costs. |
| Miranda et al, 2016[105] | Porto | $PM_{10}$, $NO_x$ (MAPLIA project) | Children and adults | Some parameters used to calculate benefits: (a) $PM_{10}$: short-term (asthma in 5-9 yr-old children; respiratory hospital admissions, all ages); long-term (incidence chronic bronchitis children and adults); (b) $NO_2$: short-term (respiratory hospital admissions, all ages); | Impact pathway approach involving 4 abatement measures; analysis using 15 scenarios; health impacts analysed using MAPLIA system; comparison of implementation costs and avoided external costs (based on health benefits) | Implementation of all measures would result in a reduction of 4.5% at most for $PM_{10}$ and $NO_2$ concentrations. This corresponds to reductions of up to 2.8 $\mu g/m^3$ for $PM_{10}$ and up to 1.2 $\mu g/m^3$ for $NO_2$, improving air quality and contributing to a benefit of 8.9 million €/year for the entire study domain, due to reduction of health-related costs. |

(associated with loss of productivity due to morbidity as well as loss of production due to morbidity or mortality) as well as intangible costs (non-market costs associated with pain and suffering).[104]

## Discussion

### Perspective from some GARD countries

Although there is evidence showing the negative effects of air pollution on the respiratory system,[123,124] such evidence is limited in various GARD countries, due to the lack of epidemiological studies. Nevertheless, current information shows that the level of exposure to pollutants in some GARD countries is higher than the current level in industrial regions from high-income countries and has exceeded the standards recommended by the WHO. China and India have the highest concentration of air pollutants,[123,125] and in other countries, air pollution does not seem to have reached such high levels.

Given the many gaps in our knowledge about the dominant ambient air pollution in some GARD countries, we have a limited knowledge about the real impact of such pollution on respiratory diseases and mortality of the population in these countries. However, if one assumes that poverty increases the vulnerability resulting from ambient air pollution (and vice versa), then air pollution should be specifically damaging for the poorest GARD countries.

Furthermore, the methods of assessment of results with regard to air pollution exposure in some GARD countries are very discrepant, and studies are generally cross-sectional and therefore have a weaker standard compared to methods adopted by others. Exposures data were often measured by questionnaires without representative individual measurements nor analysed using GIS-based models. Therefore, with these design limitations, the current general evidence generated was not robust enough to estimate the real impact of ambient air pollution on respiratory health in the populations in these GARD countries. Unfortunately, currently there was a lack of studies with reliable statistics on mortality at regional or national scales in some GARD countries.

The WHO estimate of 91%[21] of the world's population living in places where air quality levels exceed the WHO guideline limits, is concerning. This calls for urgent need for building public understanding of associations of air pollution and health. Thus, the following recommendations are proposed for a better and more precise assessment of the impact of air pollution on the respiratory health of populations in some GARD countries:

(1) In order to assess a sound relationship between air pollution and respiratory diseases or respiratory disabilities in locations where research is carried out, 5—10-year studies should be designed and performed with large samples;
(2) More than one year of follow-up is required to estimate the incidence of disease based on pulmonary function testings;
(3) The time-points of such studies and the number of participants should be large enough to ensure the ability to study effects of heterogeneous environmental conditions and health backgrounds;
(4) There is a need to improve study quality and respiratory health of individuals living in the studied sites: it implies socio political support and allocating more budget and specialists for conducting wide cohort studies, especially in countries where air pollution and respiratory dysfunction are more severe. Such studies will have essential social advantages in terms of protecting public health.
(5) Further attempts are needed to promote efficiency of preventive measures and empowerment of citizens in some GARD countries.

### Portuguese perspective

Although air pollution levels are not among the highest in Europe, the most urbanized cities in Portugal, namely Lisbon and Porto, have significant elevations in the main pollutants. Exposure to these pollutants is associated with a higher risk of respiratory disease. Furthermore, with climate change, the effects of air pollution are likely to worsen. Since air pollution exerts a substantial health and economic strain on societies, it is imperative that a broad and integrated approach is implemented, targetting reducing emissions of air pollutants, as well as reducing exposure by other means. Thus, policy makers should consider reducing air pollutants in order to achieve better air quality management and reduce pollution-worsened respiratory diseases such as asthma and COPD. The implementation of the National Emission Ceilings Directive is important, since it requires the definition of emission reduction measures in an Air Pollution Control Program. The FUTURAR[126] research project has addressed this topic, following an integrated assessment modelling approach, to estimate health impacts, costs and benefits associated with air quality in the future,[127,128] and one of its conclusions is that the expected reduction of $PM_{10}$ and $NO_2$ levels in the future will reduce the number of premature deaths.

## Conclusions

Worldwide, ambient air pollution increasingly adversely impacts respiratory health at all ages, and has amounted to substantial high economic and societal costs. This situation may be further compounded by climate change. It is paramount to establish strong research teams to conduct further interdisciplinary studies on air pollution and health effects (such as effects on the respiratory system health).

An integrated approach must involve governments (in Portugal, namely the National Programme against Respiratory Diseases (PNDR), of the Directorate General of Health, Portuguese Ministry of Health, which hosts GARD-Portugal, but also other governmental institutions), academia, health professionals and health institutions, scientific societies, patient associations and the community at large. Such an approach not only will garner a robust commitment, establish strong advocacy and clear objectives, and raise greater awareness, it will also support a strategy with adequate measures to be implemented to achieve better air quality and reduce the burden of CRDs.

## Conflict of interest

None

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LETTER TO THE EDITOR

# Correlations between radiological and histological findings in patients with pulmonary vein stenosis after radiofrequency ablation: A case series

*To the Editor,*

Worldwide, atrial fibrillation (AF) affects 1-2% of the population, and left atrium (LA) transcatheter linear radiofrequency (RF) ablation is an established therapeutic option in this subset of patients.[1,2] The rationale behind this technique is consequent to the fact that premature atrial ectopic beats in AF originate predominantly from the atrial myocardial sleeves and extend into the pulmonary veins. RF energy at the junctions between the pulmonary venous ostia and the LA can electrically isolate the arrhythmogenic sources of ectopias, eliminating the AF trigger.[3] However, transcatheter RF ablation has been associated with rare but life-threatening complications, such as pulmonary vein stenosis (PVS).[4,5] The clinical profile and computer tomography (CT) features of this complication have been previously described,[6] but data on radiological-pathological correlations are still limited. Here we present two cases of PSV after transcatheter RF ablation in which histopathological features were obtained. Patients signed a consent form for publishing their clinical data anonymously.

**Clinical data**. Patient N 1. A 48-year-old non-smoker female nurse, presented with a history of waxing and waning left lower lobe consolidations, recurrent fever, moderate dyspnea on exertion and left chest pain. She had been treated with RF ablation 14 months earlier for a paroxysmal AF. Pulmonary function tests (PFT) showed only a slight decrease of DLCO (62% of predicted). Laboratory tests revealed mild leukopenia, moderate anemia with normal CRP.

Patient N 2. A 50-year-old non-smoker tradesman sought medical consultation for hemoptysis. He had been submitted to RF ablation 10 months earlier for an uncontrolled paroxysmal AF. PFT were unremarkable and laboratory tests documented only a mild anemia.

Both patients underwent a CT scan and a transbronchial cryobiopsy.[7] In case N 2 a pleural biopsy was also carried out.

**Imaging features**. In both cases CT scan showed multiple parenchymal ill-defined rounded opacities in the subpleural regions and smooth peripheral thickening of the interlobular septa. The mediastinal window of the CT scan showed a stenotic aspect of pulmonary veins. Furthermore, in case N 2 a significant pleural thickening associated with loculated effusion was documented (Fig. 1).

**Histopathologic findings.** In both cases visceral pleura was detected in biopsy samples. It appeared thickened and fibrotic and hyperplastic mesothelial cells were detected. The interlobular septa were thickened because of edema and fibrosis. The pulmonary veins embedded in the fibrotic interlobular septa presented partial or complete obliteration of the lumen by organized thrombi. The alveolar spaces, mainly around interlobular septa were occupied by hemosiderin-laden macrophages and the alveolar walls were expanded by dilated alveolar capillaries superimposed in rows (capillary hemangiomatosis-like aspects). Areas of parenchymal ischemic necrosis were also evident (alveolar walls identified as "ghost of the normal structures"; alveolar spaces containing proteinaceous edema and hemosiderin laden macrophages) (Fig. 2).

**Pathologic-radiologic correlations**. The histological background here reported allows clear interpretation of the imaging findings. Alveolar consolidation and tiny cavitation are due to the necrosis together with alveolar hemorrhagic and intra-alveolar proteinaceous edema, while alveolar hemorrhage outside the areas of necrosis is mainly the cause of the ground glass attenuation. The capillary hemangiomatosis-like aspects are the morphological basis of the "*crazy paving pattern*". Finally, the thickening of the interlobular septa visible in CT scans are the radiological manifestation of chronic venous thrombosis and septal edema and fibrosis.

Like previous reports, in our case series the clinical features of this dramatic complication also became manifest at around 12 months from the RF ablation.[8] In conclusion the histopathologic findings detected in pulmonary and pleural biopsies explain the CT aspects of PVS as a complication of transcatheter RF ablation. These imaging features are similar to those observed in idiopathic veno-occlusive disease or pulmonary capillary hemangiomatosis. However, the presence of ischemic areas and infarction necrosis on biopsy samples are not observed in the above mentioned primary vascular disorders. The parenchymal venous infarcts are,

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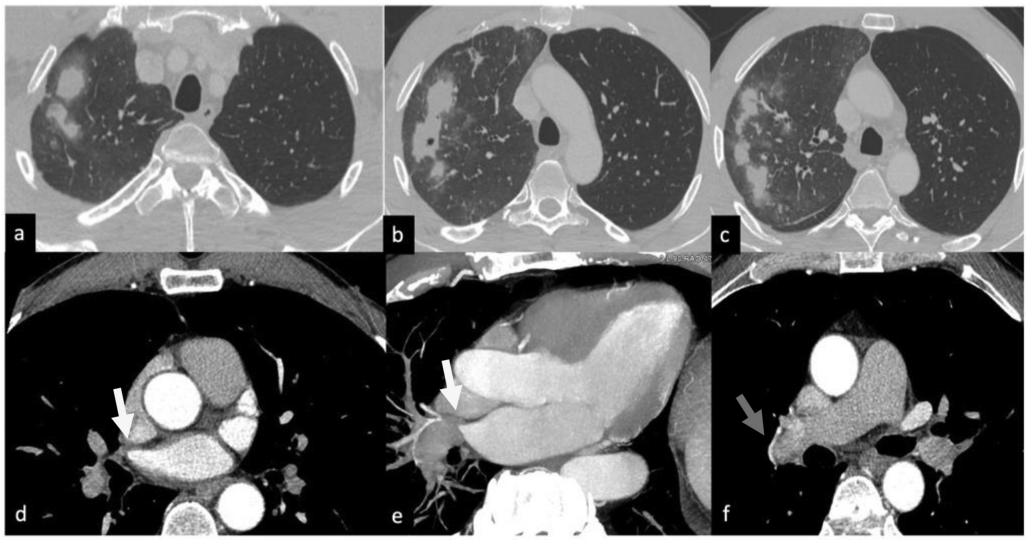


**Figure 1** Ill-defined, rounded and partially confluent consolidations with halo sign are present in the right upper lobe. Mild alveolar ground glass attenuation is present in the surrounding parenchyma (a-c). Tiny cavitation is visible in one of the consolidated lesions (b). Axial images with mediastinal window and MIP reconstructions show right upper pulmonary vein stenosis (d, e - yellow arrows) associated with hypertrophy of bronchial arteries (f - red arrow).

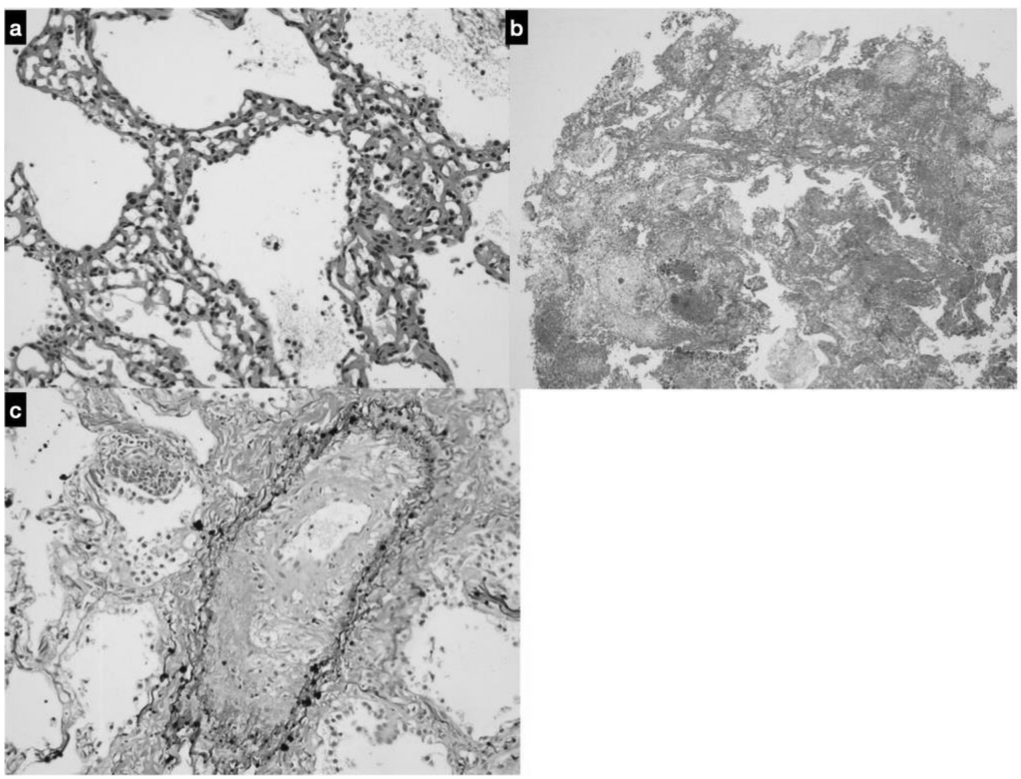


**Figure 2** (a) Alveolar walls thickened containing dilated capillary superimposed in rows (H&E, mid power, x10); (b) A sample containing necrotic lung parenchyma. Lung structures are still identifiable as «ghosts», a typical effect of ischemia; intra-alveolar hemorrhage and proteinaceous edema are also evident (H&E, low power, x4); (c) in interlobular pulmonary vein the lumen is partially obliterated by an organizing thrombus (Van Gieson-elastic fibers, high power, x20).

along with the lobar or sub-lobar distribution of the lesions, the most relevant cue for hypothesizing the diagnosis. The presence of organized thrombi in the peripheral pulmonary veins confirm that the intravascular damage starts in the larger veins and subsequently extends to the peripheral venules and this could explain why in some cases an irreversible pulmonary hypertension may complicate the disorder when not treated early.[4-6]

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LETTER TO THE EDITOR

## Images. Thoracic NUT carcinoma: an exceptionally rare entity with a challenging approach

*Dear Editor,*

Nuclear protein in testis (NUT) carcinomas are exceptionally rare and aggressive, with unknown incidence. Although these carcinomas were initially recognized as occurring almost exclusively in young patients, recent literature suggests that NUT carcinomas (NCs) may affect both sexes equally, with an extensive age range.[1—3]

NC is a rare and poorly differentiated carcinoma. In nearly 70% of cases, the *NUT* gene (15q14) is fused to the *BRD4* gene (19p13.1), resulting in a *BRD4-NUT* fusion gene that leads to global hypoacetylation and transcriptional repression of differentiation genes.[1,3,4] Hereditary or environmental factors are not related.[5] Almost 51% of NCs originate from thorax, 41% from head and neck, 6% from bone or soft tissue, and 2% from other organs.[1] The "midline" term is no longer included in the "WHO classification of tumours".[6] Regardless of NC predisposition to involve midline structures, were described cases of carcinomas arising from the bladder, pancreas, salivary glands, and bones.[4,7]

We report a case of a 25-year-old male with no relevant medical history or smoking habits who sought medical care for a subacute cough lasting four weeks. Clinical examination was unremarkable. Chest X-ray showed right mediastinal enlargement, and chest CT evidenced a 64 × 50 mm infracarinal mediastinal mass and a right middle lobe consolidation (Fig. 1A—C). Videobronchofibroscopy revealed small nodular lesions on the left main bronchus entrance and middle lobe bronchus narrowing due to a "cauliflower" lesion (Fig. 2A-B). Bronchial biopsies, endobronchial ultrasound, and transbronchial needle aspiration of station 7 lymph nodes were performed. Bronchial and lymph node samples showed solid to trabecular pattern neoplasia with keratin pearls and abrupt keratinization. Immunohistochemistry was positive for NUT protein (C52B1; 1:40; Cell Signaling Technology, Inc., USA), p40, p63, CK5, CK34B12 and CD56 (Fig. 2C—E), and negative for TTF-1, Napsin-A, synaptophysin, chromogranin and CD34. FISH and RT-PCR were not performed.

Subsequent evaluation, including PET/CT, revealed an extensive middle lobe infiltrative lesion (94 × 69 mm); right broncho-hilar, infracarinal (with left main bronchus projection), oesophageal, and diaphragmatic adenopathies; a hepatic lesion; a right supra-renal nodule; and osteomedullary lesions. An IV-B stage thoracic NC (TNC) was assumed, and the patient is presently enrolled in a clinical trial of a bromodomain and extraterminal (BET) inhibitor.

The clinical signs of TNCs are nonspecific, including dyspnoea, haemoptysis, chronic cough, nausea, and pain from bone metastasis.[5] In a review of seven TNCs, all patients complained of cough lasting for more than a month.[2] Usually, symptoms relate to tumour location and mass effect. Because of the tumour's rapid development, constitutional symptoms are not frequent.[7] Usually, TNCs are accompanied by distant metastases at the time of diagnosis.[5] Bones are the most common site of extrathoracic involvement, and it is thought that the majority of these patients do not live long enough to develop brain metastases.[2,7] A recurrent question has been whether NCs arise primarily in the lung, or secondarily involve the lungs due to aggressive growth within the mediastinum[5]. In WHO 5$^{th}$ edition, were reclassified as thoracic NUT carcinomas.[6]

The histologic features are unspecific; it is poorly differentiated, with or without squamous differentiation with a monomorphic appearance. Abrupt keratinization is suggestive but not pathognomonic of this entity.[8] NCs can mimic other undifferentiated neoplasms, such as germ cell tumours, Ewing's sarcoma or lymphoma.[7] In the reported case, one of the evaluated neuroendocrine

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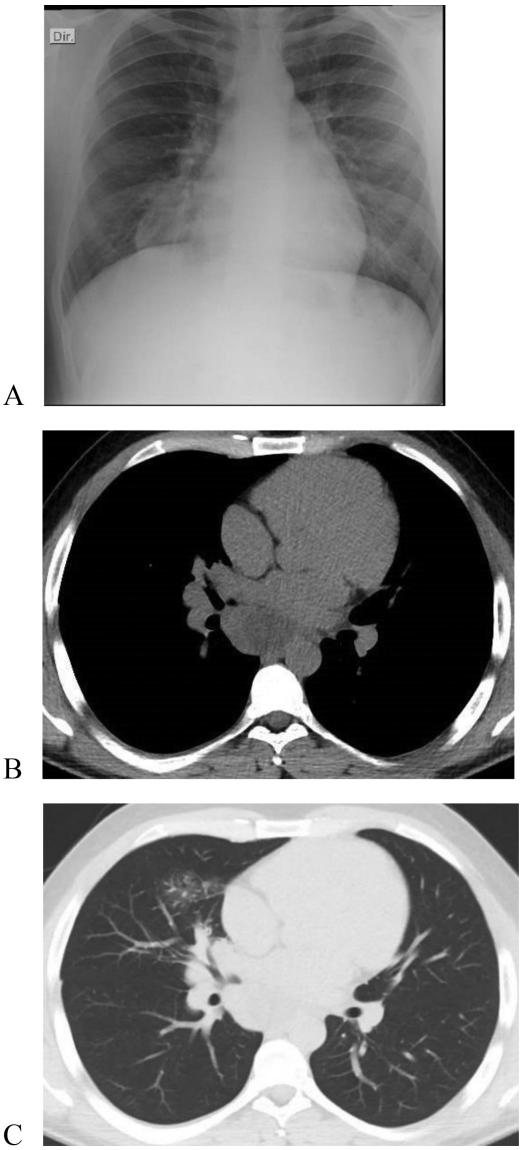


**Fig. 1** (Original images) (A) Chest x-ray with right mediastinal enlargement. (B-C) Chest computed tomography, depicting an infracarinal mediastinal mass and a right middle lobe consolidation. (Original images).

(NE) markers (CD56) was positive, highlighting an unusual finding and the nonspecific character of NE marker expression, underlining the need to maintain a broad differential diagnosis when approaching high-grade carcinomas.[9] Thoracic tumours with aggressive expression and pleomorphic/undifferentiated carcinomas should warrant prompt evaluation for NUT translocation.[1] Diagnosis is based on the demonstration of the *NUT* genetic rearrangement, either by NUT immunohistochemical analysis, FISH or RT-PCR.[1,7,8] In imaging descriptions of TNCs, they usually present as large masses with lymphadenopathy and pleural involvement, with no side/lobar predilection[1] — relatively nonspecific but consistent features. In seven assumed pulmonary NCs, the most constant imaging finding was a large unilateral lesion involving the lung, pleura and mediastinal lymph nodes.[2]

The diagnosis is frequently overlooked. Several factors contribute to underdiagnosis, namely insufficient reporting, age bias and nonspecific morphology.[7]

Currently, there are no standardized guidelines aimed at treating NC.[1,2] Surgical options are limited by its fast growth. Radiotherapy frequently has a palliative role, and NC usually does not respond to chemotherapy or immunotherapy regimens.[7]

Further possible therapeutic options include histone deacetylase inhibitors and BET inhibitors.[5] BET inhibitors bind to the BRD4-NUT chromatin binding site, inhibiting gene activation, and at least three studies have reported improved survival in NC patients.[1] However, the outcome has been invariably fatal, and the average survival rate is six to seven months after diagnosis.[7]

Regardless of the patients' age and the absence of risk factors, NC should be included in the differential diagnosis of thoracic masses with a rapidly progressive clinical course.[2] The outcome is poor, as NCs are refractory to conventional therapy, and promising targeted therapies are currently under testing. Both clinicians and pathologists should be aware of this rare entity to make the proper diagnosis and establish effective treatment algorithms.

## Author contributions

Study conception and design: Ana Alfaiate, Vera Clérigo.

Data acquisition: Ana Alfaiate, Carolina Padrão, Vera Clérigo, Ivone Fernandes.

Data analysis and interpretation: Ana Alfaiate, Carolina Padrão, Vera Clérigo, Ivone Fernandes.

Drafting of the manuscript: Ana Alfaiate, Vera Clérigo.

Critical revision of the manuscript for important intellectual content: Carolina Padrão, Ivone Fernandes.

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

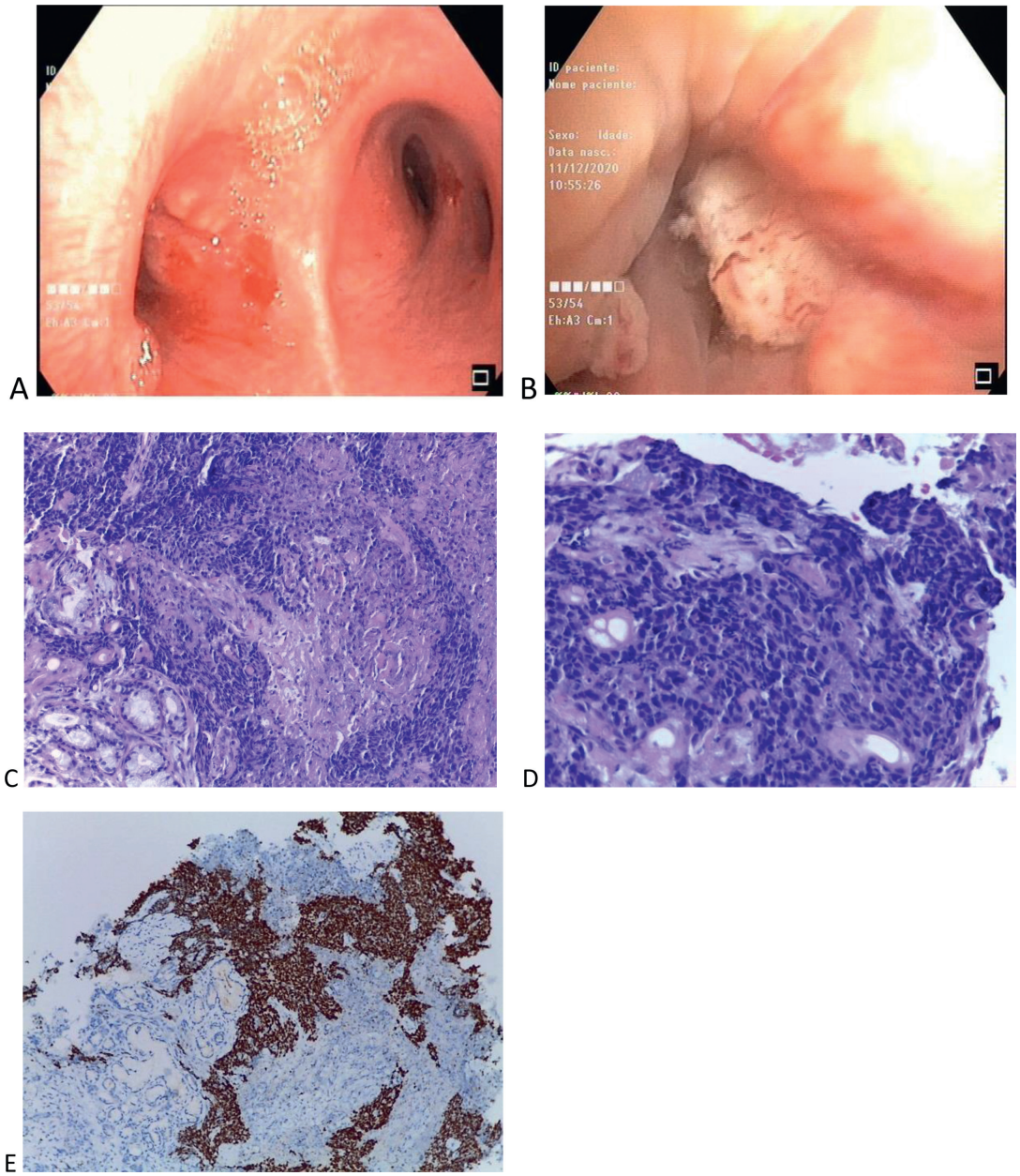


**Fig. 2** (Original images) (A-B) Videobronchofibroscopy images: (A) Small nodular lesions on the left main bronchus entrance (B) Middle lobe bronchus narrowing due to a "cauliflower" lesion. (C) Respiratory mucosa fragments, documenting infiltration by solid to trabecular pattern neoplasia of small, cuboidal cells with granular chromatin and generally absent nucleoli, with scant eosinophilic cytoplasm. Foci of necrosis and abrupt keratinization and keratin pearls formation are identified (C-HE 10x, D-HE 20x). (E) Immunohistochemical study positive, strong and diffuse for NUT (HE 10x). (Original images).

## Conflicts of interest

None declared.

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LETTER TO THE EDITOR

# Osimertinib-induced lymphocytopenia and pneumocystis jirovecii pneumonia

*Dear Editor*

Osimertinib is recommended as first-line therapy for patients with advanced lung adenocarcinoma harboring epidermal growth factor receptor (EGFR) mutations.[1] Compared with other EGFR-tyrosine kinase inhibitors (TKIs), treatment with osimertinib causes a high incidence of leukopenia, particularly lymphocytopenia. We report a case of pneumocystis jirovecii pneumonia (PjP), which seemed to occur after osimertinib-induced lymphocytopenia and resultant immunosuppression.

An 86-year-old man with a past smoking history (3 pack-years) was diagnosed with stage IA3 right upper lung adenocarcinoma (cT1cN0N0) in March 2021 (Fig. 1A—C). Instead of

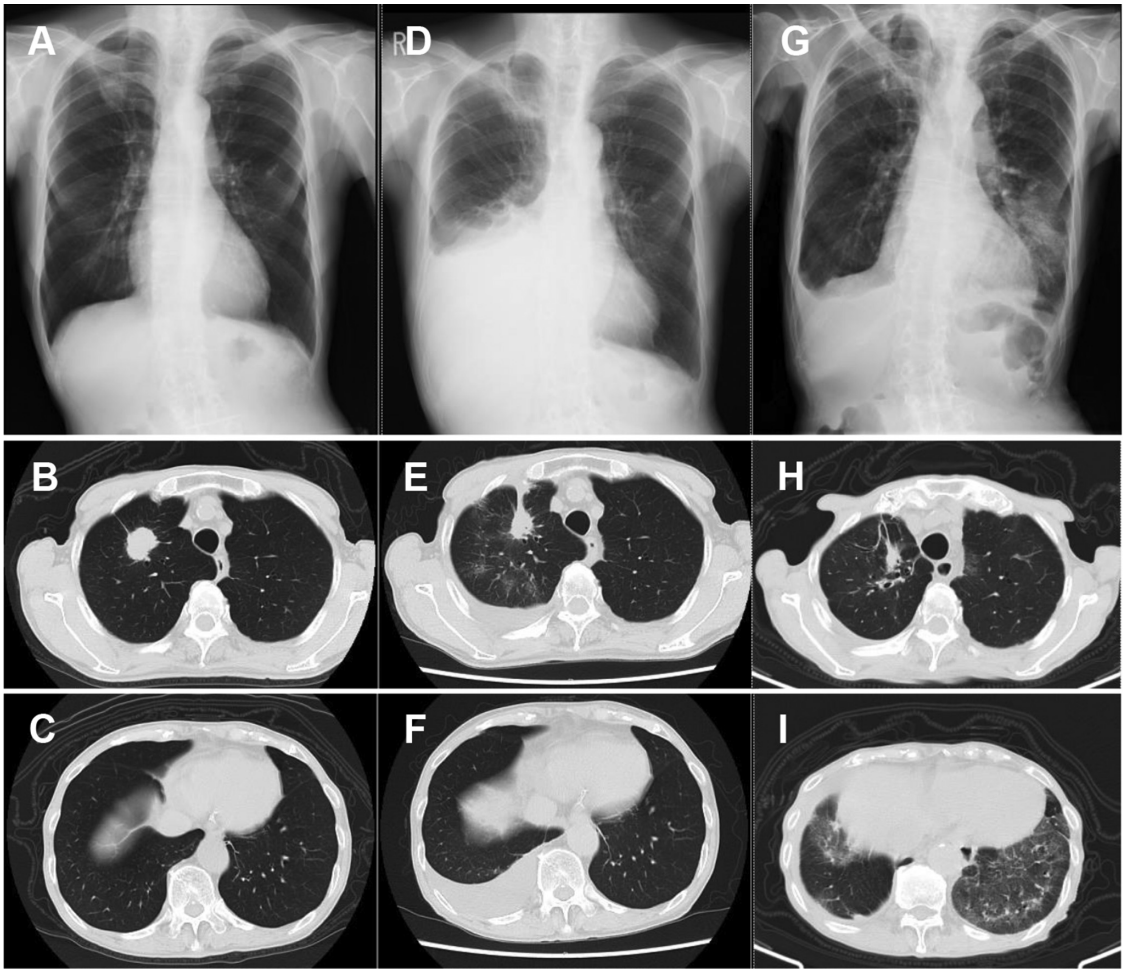


**Fig. 1** Chest X-ray (CXR) and computed tomography (CT) findings of an 86-year-old man on referral (A-C in March), relapse (D-F in August), and admission (G-I, in December). Both CXR and CT show bilateral ground-glass opacities on admission (G and I).

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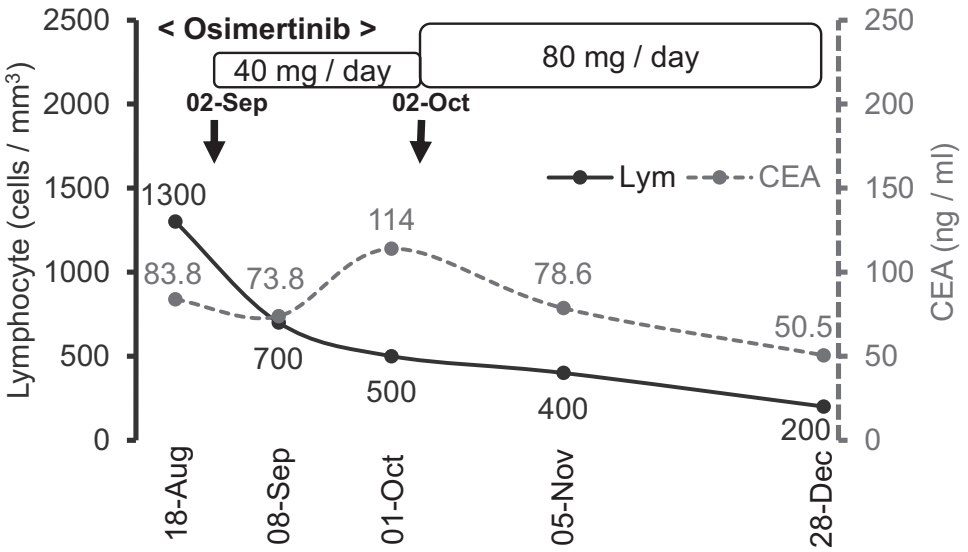


**Fig. 2** The clinical course of the patient, including laboratory data and treatment.
CEA; carcinoembryonic antigen, Lym: lymphocyte.

curative surgical resection, he opted for heavy ion radiotherapy in May 2021, with significant shrinkage of the nodule. However, his disease recurred in August 2021, and he presented with right carcinomatous pleuritis (Fig. 1D–F). Based on the cytological detection of an adenocarcinoma harboring the L858R EGFR mutation, osimertinib 40 mg daily was initiated as first-line therapy in September 2021 [peripheral blood lymphocyte (PBL): 1700 cells / $mm^3$]. Beginning in November 2021 (PBL: 700 cells / $mm^3$), the drug dose was increased to 80 mg daily. Although he had a good performance status with grade 2 dermatitis, his PBL further decreased in November 2021 (400 cells / $mm^3$). Thereafter, he noticed gradual worsening dyspnea on exertion and was eventually admitted to our hospital in December 2021 (on day 118 from the onset of osimertinib treatment). The chest-computed tomography revealed remission of the right pleural effusion, although new bilateral ground-glass opacities were noted (Fig. 1G–I). Further diagnostic studies, such as bronchoscopic examination, could not be conducted because the patient was hypoxemic. We suspected that the lesions were consistent with osimertinib-induced interstitial lung disease (ILD), thus we discontinued osimertinib and started intravenous prednisolone (40 mg daily). The laboratory data on admission showed decreased PBL (200 cells / $mm^3$), and HIV serology was negative. His serum $\beta$-D-glucan was elevated (174 pg/ml), serum aspergillus galactomannan *antigen* was negative, and sputum PCR for Pneumocystis jirovecii DNA was positive on day 4 of hospitalization; all of which supported the diagnosis of PjP. He was treated with sulfamethoxazole-trimethoprim, which improved his symptoms and lung shadow dramatically. We are now planning to re-start osimertinib at a lower dose, which would not cause severe PBL reduction.

Osimertinib is a third-generation EGFR-TKI and a good treatment option in patients with EGFR-mutated advanced lung adenocarcinoma.[1] Other than the rare but sometimes lethal ILD, EGFR-TKIs are widely considered as relatively safe and well tolerated drugs compared with previous cytotoxic drugs.[1,2] Among various EGFR-TKIs, osimertinib has a unique adverse effect of early reductions in leukocyte and platelet counts; most of which usually stabilize over time and remain above the lower limit of normal thereafter. Lymphocytopenia is more common and was found in 62% of the included patients, although most were mild or moderate in severity and usually did not lead to dose interruption or discontinuation (grade 3 or higher lymphocytopenia is reported to be 6.1%).[3] In this case, the gradual increase in drug dose was inversely correlated with the severity of the lymphocytopenia (Fig. 2). Compared with the absolute peripheral blood neutrophil counts, the PBL count usually remains low in priority when assessing for adverse events; therefore, it might be necessary to pay attention to sustained lymphocytopenia.

Pneumocystis jirovecii infections are typically seen in patients on steroid treatment and in immunocompromised hosts with impaired cell-mediated immunity, such as patients with human immunodeficiency virus infection and hematologic neoplasms. PjP has also been reported to develop among patients with lung cancer, and an analysis by Lee et al. reported radiotherapy and lymphopenia ($<$ 1,000 cells / $mm^3$) as significant risk factors for PjP development.[4] Several TKIs such as idelalisib cause higher incidence of PjP.[5] However, there have only been a few reports concerning the relationship between PjP and EGFR-TKIs such as gefitinib,[6] erlotinib,[7] and afatinib.[8] Considering that the medical history of the patients in these reports suggested the presence of the above-mentioned risk factors for PjP, such as corticosteroid use [6,7] or post-chemoradiation therapy status,[8] it is unclear whether EGFR-TKIs are directly associated with the occurrence of PjP or if the prior immunocompromised status was more important. In 2021, Emilie et al. reported two cases of PjP during treatment with osimertinib [9]; neither of the subjects had any risk factors, and the author suggested the necessity of PjP prophylaxis. Since lymphocytopenia is a unique adverse event of osimertinib, it might be possible that the PjP

occurred as an opportunistic infection secondary to the osimertinib treatment

In conclusion, this is a rare but important report of PjP, due to osimertinib-induced lymphocytopenia. Since the discontinuation of EGFR-TKIs can sometimes cause "flares" of the disease (accelerated disease progression) and result in poor prognosis,[10] physicians must be careful in differentiating drug-induced ILD and other opportunistic infections such as PjP during osimertinib-induced lymphocytopenia.

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## Ethics approval

This study was exempt from ethics review board approval by the Institutional Ethic Committee.

## Informed consent

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

## Conflicts of Interest

The authors have reported that no potential conflicts of interest exist with any companies/ organizations whose products or services may be discussed in this article.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.04.005.

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LETTER TO THE EDITOR

## A rare but potentially fatal cause of hemoptysis

*Dear Editor*

The Swan-Ganz catheterization provides valuable hemodynamic information but presents current specific indications. Its routine use in critically ill patients and in patients with severe cardiopulmonary disease and high risk of intraoperative hemodynamic compromise undergoing surgery was abandoned due to lack of prognostic improvement and risk of complications.[1] However, it remains an important diagnostic procedure in patients with suspected or previous history of pulmonary arterial hypertension (PH).[1] Pulmonary artery (PA) injury is a rare but most feared complication with an estimated incidence of 0.031% to 0.05% and a mortality that ranges from 50 to 70 percent.[2]

We describe the case of a 67-year-old non-smoker female patient, with a personal history of systemic sclerosis, PH, systemic arterial hypertension, aortic stenosis submitted to biological valve prosthesis placement, epilepsy, and osteoporosis, usually medicated with enalapril, amlodipine, bosentan, pentoxifylline, acetylsalicylic acid, sodium valproate and inhaled fluticasone and salmeterol. The patient was admitted to the ICU due to the development of massive hemoptysis during right cardiac catheterization to measure pulmonary capillary wedge pressure, experiencing cardiorespiratory arrest in asystole treated with advanced life support maneuvers, orotracheal intubation with a large bore single lumen endotracheal tube (ETT), bilateral lung invasive mechanical ventilation and blood transfusion. Bronchoscopy at admission, 48h after the critical episode and on the day of extubation revealed no active bleeding. Chest computed tomography (CT) angiography showed a nodular lesion with contrast enhancement at the level of the posterior segment of the left inferior lobe, suggestive of a pseudoaneurysm with a mural thrombus (Fig. 1A). Given the spontaneous bleeding control after the first episode, and the lack of prompt access to embolic therapy, requiring inter-hospital transportation, priority was given to clinical stabilization and supportive care, with improvement. After extubation, arterial embolization was proposed to prevent recurrence, which the patient refused. A conservative attitude was adopted, according to the patient's wishes, with favorable outcome. Chest CT-angiography on the 7$^{th}$ day (Fig. 1B and 1C) and chest CT, without contrast administration at patient's request, two weeks later, showed PA pseudoaneurysm stability. Six-year follow-up revealed clinical stability with no bleeding recurrence.

Hemoptysis due to PA injury during Swan-Ganz catheterization presents high mortality and morbidity rates[2,3] PA injury occurs more frequently in women with >60 years old, PH, mitral valve disease, hypothermia, and under anticoagulants.[1,2] Right pulmonary arterial circulation involvement predominates, and hemoptysis is the main manifestation which develops on the day of the procedure in half the cases.[2] PA injury may result in intrapulmonary hemorrhage, pseudoaneurysm, or re-endothelization.[2] Pseudoaneurysms, usually diagnosed on contrast enhanced CT,[1] may be manifested by massive life-threatening hemoptysis, but there is a broad spectrum of manifestations with asymptomatic cases and findings from imaging studies. These are at risk of subsequent hemorrhage that can be fatal.[1,2,4]

The therapeutic approach to this complication involves two main concerns: first, the immediate protection of the airway and, secondly, the prevention of a new bleeding episode originating from the injured PA. Intubation with a large bore ETT is recommended in life-threatening hemoptysis to facilitate blood and thrombus extraction as well as early interventional and diagnostic bronchoscopy, but its passing should not delay intubation.[5] In most patients, both lungs are ventilated but single lung or double lumen ventilation can be considered for patients who continue to bleed.[5] In single lung ventilation, tidal volumes should be reduced accordingly.[5] There is still no consensus on the most effective endobronchial method for preventing asphyxia from airway bleeding.[2,5,6,7] However, several authors have suggested that, when performed by experienced professionals, the simultaneous use of a dual lumen ETT and a balloon catheter may offer the best protection, preventing flooding of the contralateral lung and the ipsilateral non-bleeding bronchial segments.[2,6] The role of inhaled tranexamic acid in life-threatening hemoptysis needs further investigation.[5] In patients with pseudoaneurysms, the favorite treatment option to prevent bleeding recurrence seems to be arterial embolization,[1,4] which has shown a high success rate (~89%).[2,3] Complications associated with this procedure include contrast-associated nephrotoxicity, rare erroneous

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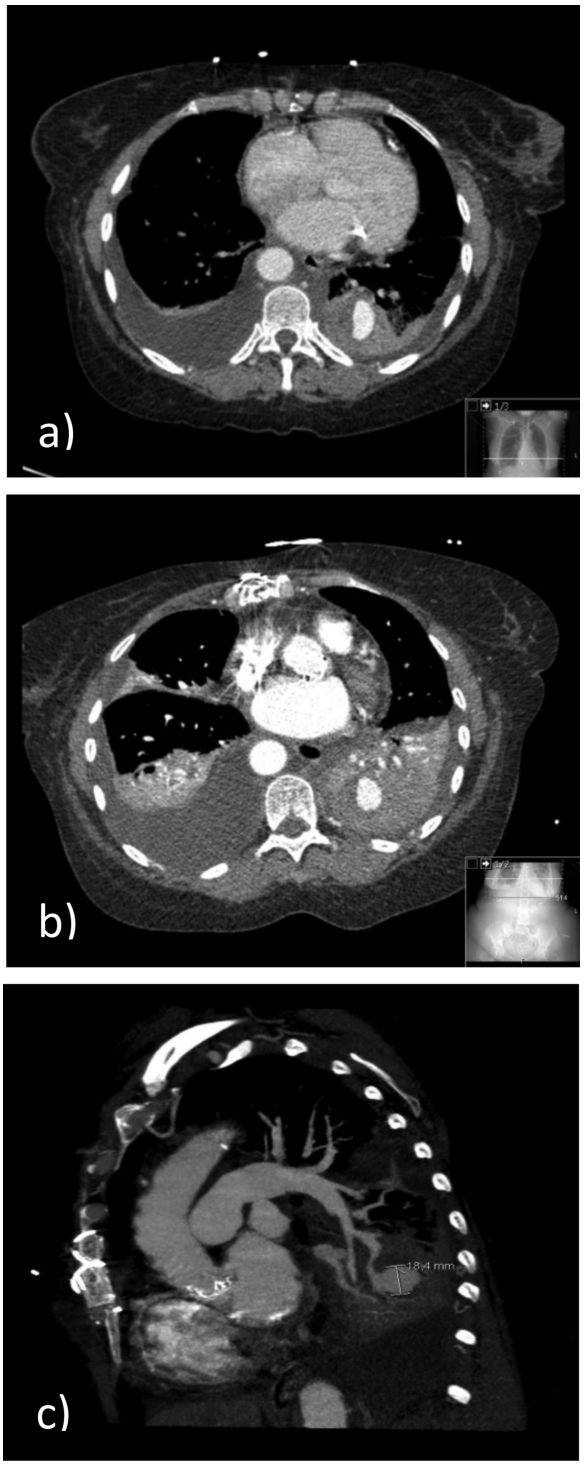


**Fig. 1** (A) Chest CT-angiography at ICU admission. consolidation at the left inferior lobe (LIL) with areas of spontaneous hyperdensity and "ground glass" opacities; Nodular lesion with contrast enhancement, at the posterior segment of the LIL, in continuity with a pulmonary artery tree branch, suggestive of a pseudoaneurysm with a mural thrombus. (B) and (C) Chest CT-angiography (7th day of hospitalization). Pseudoaneurysm arising from the posterior basal branch of the left inferior lobar pulmonary artery; bilateral pleural effusion with passive atelectasis; and consolidation due to hemorrhagic alveolar filling at the LIL.

migration of the embolization material to other arterial beds with risk of pulmonary infarction or paraplegia, and pseudoaneurysm recurrence.[2,5,7] Other therapeutic procedures include surgical resection and local injection of thrombin. However, there is currently insufficient data on the most appropriate and effective therapeutic strategy.[2] The incidence of bleeding recurrence in patients with the development of pseudoaneurysms in whom a conservative "watch and wait" strategy is adopted is of 30-40%, with a mortality rate of 40-70%.[2]

In the case described, there were several risk factors for the occurrence of this complication: age over 60 years, female gender, and the main diagnosis of PH. Although involvement of the right pulmonary arterial circulation is more frequent, the pseudoaneurysmal lesion was located at the left inferior lobar PA, providing an atypical presentation of this unusual adverse event. This complication, though rare, is potentially fatal and raises questions about the procedures to be followed. Unfortunately, it can occur even to a highly experienced practitioner who had already successfully performed thousands of exams.

## Conflicts of interest

None declared.

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CORRESPONDENCE

## Alpha-1 antitrypsin deficiency, asthma and pregnancy. Is there a place for augmentative therapy?

Dear editor,

We have read with interest the article entitled pregnancy in alpha 1 antitrypsin (AAT) deficiency and the role of intravenous AAT therapy [1] and we would like to make some considerations in this regard. The first is it attracts attention that substitution therapy is used in a patient who has no indications for it (diagnosis of bronchial asthma, *Pi*SZ* genotype and AAT levels of 80 mg/dL), if we review the indications according to the latest European Guide for the Diagnosis and Treatment of AATD, the *Pi*SZ* genotypes are excluded for it, because there is no evidence to support efficacy of AAT augmentation therapy in *Pi*SZ*, *Pi*MZ* or current smokers of any protein phenotype,[2] and currently there are no indications for diseases other than chronic obstructive pulmonary disease (COPD).

Up to date, we know that patients with the *Pi*SZ* genotype appear to be at risk of developing respiratory disease (in the form of emphysema) and liver disease (in the form of fibrosis and/or cirrhosis), and because of this, we sometimes choose for starting augmentative treatment (even knowing that it is not indicated by the guidelines) in those who have been diagnosed with emphysema-type COPD due to the poor evolution of patients with usual treatment.[3] However, in the case presented, we did not observe data on pulmonary emphysema that would support the use of this treatment.

We also know that bronchial asthma is defined as a chronic inflammatory disease of the airways, it is well known in which different cells and inflammatory mediators participate, and that cells such as eosinophils as a cell mainly that produce inflammation of the airways and that main function of the AAT in the body is to be the major inhibitor of elastase produced by neutrophils. It behaves as an acute phase reactant, increasing its levels to deal with inflammatory or infectious phenomena, so it theoretically seems to be a good candidate to counter the effects produced by bronchial asthma at the cellular level. However, nowadays the use of augmentative therapy in patients with AATD and bronchial asthma is highly controversial and no guidelines support its use in this type of patient due to lack of evidence.

One thing that has become clear in this case is that during pregnancy, patients affected by AATD can worsen the symptoms of their respiratory disease and appear other types of complications,[4] which is why it is necessary to closely monitor them. Nevertheless, the effect of AATD and augmentation in pregnancy has not been studied and thus guidance is relevant on expert opinion and clinical experience. Existing case reports of AATD and pregnancy have focused primarily on whether pregnancy can be tolerated in individual patients.[5]

This case is very complex and should be based on expert opinions, since although AATD presents a great clinical variability, the guidelines can help make decisions, but it would be necessary to carry out studies with a large sample size to verify that the theory and real cases such as the current one, and the replacement therapy can be extended to for diseases other than COPD and the other genotypes.

### Declaration of Competing Interest

The author declares have no conflicts of interest related directly or indirectly to the contents of the manuscript.

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### Supplementary materials

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CORRESPONDENCE

# Pregnancy in patients with Alpha 1 Antitrypsin (AAT) deficiency and the role of intravenous AAT therapy. Authors' reply

We would like to thank Dr. Hernandez Perez and colleagues for their comments on our article concerning pregnancy in patients with Alpha 1 Antitrypsin Deficiency (AATD),[1] and for engaging in an interesting discussion surrounding the critical issue of Alpha 1 Antitrypsin (AAT) replacement therapy in non-standard indications, such as individuals with *Pi**SZ genotype and/or diseases other than pulmonary emphysema.[2] We certainly agree that the case presented is very complex; therefore, we will attempt to clarify some points.

The first point by Hernandez Perez and colleagues is that we prescribed augmentation therapy to a patient with *Pi**SZ genotype, despite the ERS statement not supporting this indication.[3] When making this decision, we nevertheless considered that an unknown proportion of *Pi**SZ individuals may have an increased risk for lung and liver diseases, especially if they suffer from frequent inflammatory respiratory exacerbations, which is the case for our patient.[4] As an indirect confirmation of this, approximately 8% of patients carrying the *Pi*SZ* genotype receive AAT therapy in Italy and Spain.[5] In support of our decision, it is important to note that at the time augmentation therapy was initiated (week 18 of pregnancy), our patient had serum AAT levels largely below the theoretical "protective threshold" (38 mg•dL$^{-1}$).

A second point notes that we treated a patient suffering from severe asthma, despite the fact that AAT therapy is only approved for subjects with pulmonary emphysema. The effective contribution of AATD to asthma severity is unclear; however, the potential pathophysiological implications of low levels of AAT suggest an association with an increased risk of bronchial remodelling and fixed obstruction. Recently, we retrospectively investigated a group of 143 patients with severe asthma, showing that AATD was present in 10 out of 143 patients (6.99%). At the 12-month follow-up, forced expiratory volume in 1 second ($FEV_1$; litres), $FEV_1$ % predicted, and forced vital capacity (FVC) decline expressed as variation vs. baseline were significantly greater in individuals with abnormal AAT levels compared to those with normal values ($>$110 mg•dL$^{-1}$).[6] Considering this and the significant drop in $FEV_1$ recorded at week 18 of pregnancy, we considered that AAT therapy might be effective in reducing the rate of lung volume decline and improving asthma control in our patient.

Finally, Hernandez Perez and colleagues note that we treated a pregnant woman despite a lack of studies on the effect of augmentation therapy in pregnancy. However, when making this choice we believed that our patient was at increased risk of pregnancy-related complications, due to the combined effect of low AAT levels and recurrent asthma exacerbations,[7] and concluded that AAT therapy might reduce both the maternal and foetal risk.

In summary, although we agree that AAT augmentation therapy for non-standard indications requires further study to investigate its safety and efficacy, we believe that it is probably time to move on from its original prescriptive placing to broader scenarios.

## Conflicts of interest

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PHOTO

# Human pulmonary dirofilariasis: A pitfall in solitary pulmonary nodule

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Human heartworm is a zoonotic disease caused by the parasite *Dirofilaria* spp., a helminth of the Nematoda class which was first reported in 1961 in a case of human pulmonary dirofilariasis (HPD).[1]

We report the case of a 38-year-old man, engineer, former smoker (4 pack-per-year) who presented to the emergency department with face edema. No pathological background. No animals at home.

Physical examination revealed a slight face edema. Except for eosinophilia (2000/uL) other routine tests were unremarkable and on chest X-ray a small peripheral solitary lung nodule on the right lung was visible.

Chest computed tomography, demonstrated a $4 \times 3 \times 2{,}3$ cm, irregular justa-pleural solid mass of the right middle lobe (Fig. 1-A). A CT-Guided transthoracic lung biopsy was performed but revealed extensive necrosis, histiocytes, lymphocytes and myofibroblasts suggestive of a benign, granulation-like tissue, few eosinophilic cells, Charcot Leyden crystals and was negative for malignancy. A 18F-FDG PET-CT showed low 18F-FDG uptake by the nodule with maximum standardized uptake (SUV) of 1.3 (Fig. 1-B). Since diagnosis could not be obtained from histological examination and malignancy could not be excluded, a video-assisted thoracoscopic surgery (VATS) with wedge resection was performed.

In the anatomical sample, a white well-delimited area was observed and when sliced a yellow nodule with increased consistency measuring $2{,}3 \times 1{,}9 \times 1{,}2$ cm was identified. The intraoperative histopathological diagnosis was granuloma without malignant cells.

The postoperative histopathological diagnosis was consistent with a central zone of necrosis surrounded by granulomatous inflammation and a fibrous wall. A worm was found in the lumen of an artery within the area of necrosis containing remnants of *Dirofilaria immitis* (Fig. 1- C).

The final pathologic review of the resected lesions suggested a diagnosis of HPD.

Human pulmonary dirofilariasis is rare in Europe, with less than 40 cases reported. However, true incidence is limited since data is derived from isolated case reports.[2]

Dirofilaria is endemic in the Mediterranean region. Nevertheless distribution is changing due to environmental questions like temperature increase.[3]

Human dirofilariasis is transmitted by the bite of an infected mosquito from an infected dog or cat, which acts as a vector, and transmits *Dirofilaria immitis* larva to the skin.[4]

In accidental hosts, like humans the surviving larvae migrate to the small vessels of the pulmonary artery and generate vasculite, formation of granulomas and obstruction, inflammation and pulmonary infarction after death of parasite.[2]

Most cases reported are in middle-aged adults between 40 and 50 years of age.[4]

More than half of Dirofilaria infections patients are asymptomatic and symptomatic forms include fever, hemoptysis, dyspnea and chest pain.[2]

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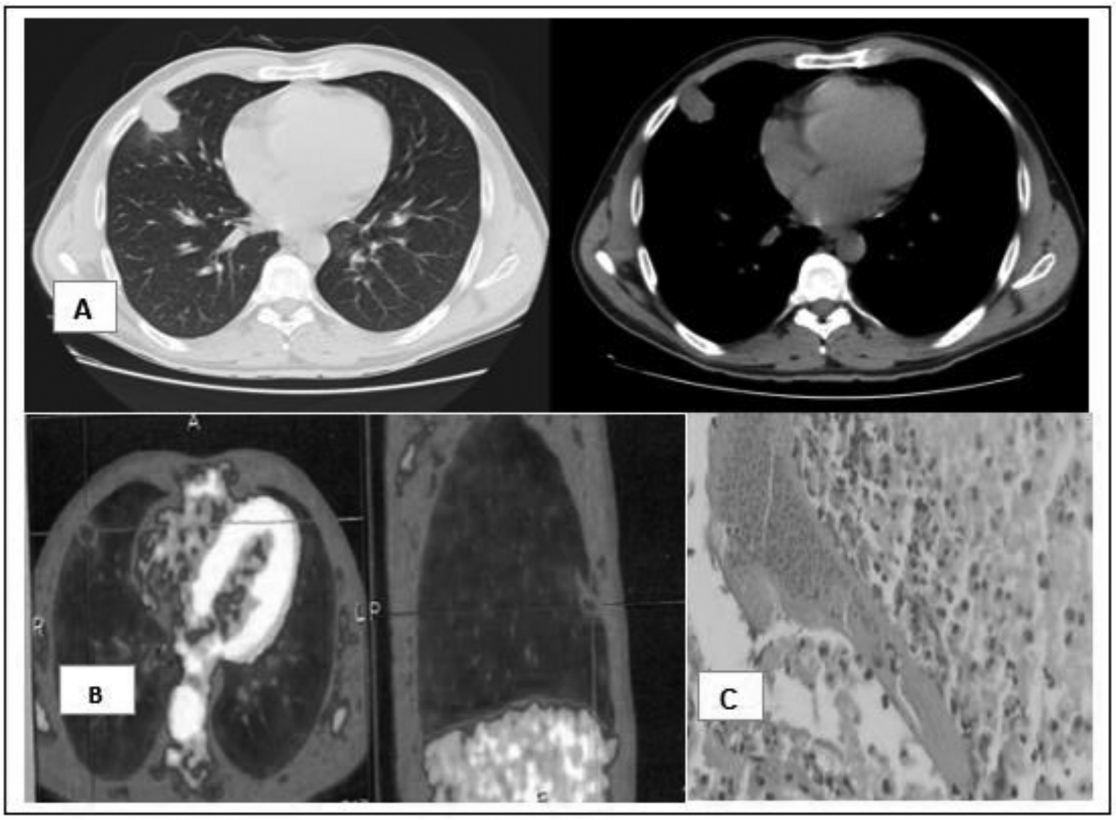


**Fig. 1** A- Chest computed tomography with an irregular justa-pleural mass. In the anatomical piece, a white well-delimited area was observed and when sliced a yellow justa-pleural nodule with increased consistency measuring 2,3 × 1,9 × 1,2 cm was identified; B- PET-CT with low 18F-FDG uptake (1.3); C- The intraoperative histopathological diagnosis was granuloma without malignant cells. Postoperative histopathological diagnosis was consistent with a central zone of necrosis surrounded by granulomatous inflammation and a fibrous wall. A worm was found in the lumen of an artery within the area of necrosis containing remnants of *Dirofilaria immitis*.

Systemic eosinophilia is relatively uncommon with 11—17% in most Japanese series.[5]

It usually presents as a solitary spherical, non-calcified, wedge-shaped, often spiculated or cavitated subpleural pulmonary nodule, ranging from 1 to 3 cm, with predilection to the right lower lobe of the lung.[5]

Serological studies have poor sensitivity (50%) in detecting antibodies because of cross reactivity with other nonfilarial parasites and their presence may only indicate exposure to larval antigens.[6]

Because there is no reliable noninvasive test for *Dirofilaria* infection, nearly all cases require biopsy to establish the diagnosis and permit treatment.[6]

In summary, the authors draw attention to this case for its extreme rarity.

The pathological analysis is fundamental in a case where the most frequent diagnostic hypotheses were ruled out by the other complementary diagnostic tests and where careful anamnesis continues to play a fundamental role.

Although considered a clinically benign disease, an excisional lung biopsy is nearly always needed for diagnosis and treatment and minimally invasive surgery with VATS should be performed whenever possible.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

## IMAGES: Nocardia pneumonia — A surprising and rare pulmonary infection mimicking lung cancer

Nocardiosis is a rare bacterial infection caused by *Nocardia spp*. Lung is one of the most affected organs, but it may involve other tissues, such as central nervous system and skin.[1] It is usually associated with immunosuppression but it might occur in immunocompetent patients.[2]

Radiological appearance is widely variable. It might present as pulmonary nodules, consolidations, cavitated masses or pleural effusions,[3,4] which is why it can be confused with other infectious pathologies or malignancy.

We report the case of a 73-years-old man, former smoker (45 packs/year), with known history of hypertension, cerebrovascular disease and anxiety. He was referred to our department due to persistent cough and hemoptoic sputum for 6 months, without any others symptoms, and treatment failure after 2 empiric antibiotic courses with persistent heterogeneous mass on radiology imaging. Physical examination revealed decreased breath sounds in the lower third of the right hemithorax and chest-X-ray showed the reported heterogeneous hypotransparency in the right base. Blood analysis was unremarkable apart from an elevated c-reactive protein (82.7 mg/L). Chest CT scan (Fig. 1 (a) and (b)) confirmed an irregular lung mass in the right lower lobe, measuring $6.04 \times 5.21 \times 3.82$ cm, heterogeneous, with spiculated borders and small cavitations inside, along with some mediastinal adenopathies, characteristics suggestive of malignant lesions. Given the known risk factor of smoking, the lasting clinical condition without treatment response and the suspected characteristics of the lung mass on CT imaging, a lung cancer diagnosis was hypothesized and transthoracic biopsy was performed. Histology analysis on routine haematoxylin-eosin (H&E) stain revealed a chronic inflammatory infiltrate, with no cytological atypia observed, and with higher amplification evidence of numerous thin, filamentous, tree-like branching rods (Fig. 1 (c) and (d)). The use of modified Gomori's and Grocott-Gomori's methenamine silver stains allowed identification of these colonies of branching hyphae-like appearance microorganisms, periodic acid-schiff negative, compatible with infection by *Nocardia spp* (Fig. 1 (e), (f) and (g)).

The sputum study was not successful for microbiological identification. The patient refused other invasive procedures, namely bronchoscopy.

He was admitted for empirical intravenous treatment with Trimethoprim/Sulfamethoxazole (TMP/SMX) 15 mg/kg per day.[5] Four weeks later, given good clinical response and radiological improvement, he was discharged with maintenance oral TMP/SMX to meet at least six months of treatment. CT scan reassessment 6 months after shown near-complete resolution of the mass and fundamental sequelae alterations at the level of the right lung base (Fig. 1 (h) and (i)). At the time this report was written, the patient was asymptomatic and there was no radiological evidence of relapse.

In summary, we presented a rare case of pulmonary nocardiosis in an immunocompetent patient, without relevant medical conditions impairing his immune system, and who was first evaluated due to neoplastic suspicion.

Since the symptoms are nonspecific the diagnosis of Nocardia pneumonia is challenging.[1—4] In this case, as microbiological identification was not possible, the diagnosis relied on histologic examination and was supported by remarkable clinical and radiological improvement after proper antibiotherapy. When sensitivity testing is not possible, a first course of intravenous therapy with TMP/SMX for at least 2—3 weeks, followed by oral therapy is recommended.[5] Depending on the clinical evolution, the total duration of treatment can last up to 12 months in severe cases.[5,6] Keeping a close follow up is crucial.

The prognosis depends on the extent of the disease and comorbidities, but an early diagnosis and timely treatment are associated with a decrease in mortality and a lower risk of relapse.[1,5,6]

Although there are some reported cases in immunosuppressed patients, the information about clinical features and outcome of pulmonary nocardiosis in immunocompetent patients is still sparse.

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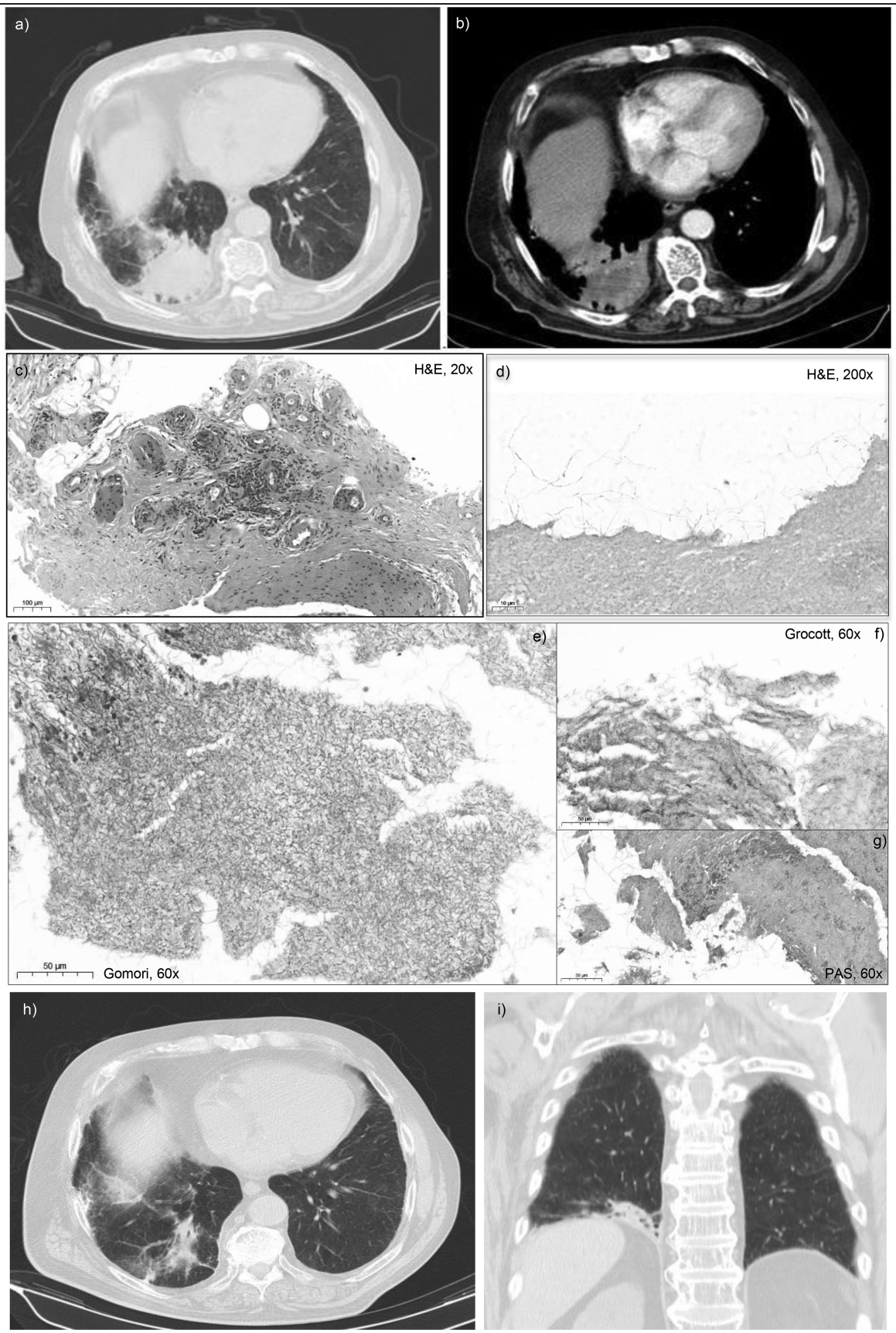


**Fig. 1** **(a)** and (**b)** Chest CT scan showing a heterogeneous lung mass, with irregular and spiculated borders and small cavitations inside, measuring 6.04 × 5.21 × 3.82 cm and located in the right lower lobe; (**c)** Trans-thoracic biopsy core at 20x routine haematoxylin-eosin stain (H&E) showing moderated perivascular chronic inflammatory infiltrate of the fibrous parenchyma, almost devoided of

## Conflicts of Interest

The authors have no conflicts of interest to declare.

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epithelial component and without evidence of malignant neoplasia; (**d)** High power field (H&E, 200x) showing the bacterial colony where the tree-like branching filamentous rods of *Nocardia spp*. are evident; (**e)** Modified Gomori's method for reticulum stain (60x) also highlights the fungi-like morphology of *Nocardia spp*. (**f)** Grocott-Gomori's methenamine silver stain (60x) reveals in black the branching hyphae appearance of the bacteria. (**g)** The periodic acid-Shiff (PAS) stain 60x was negative for fungi content. (**h)** and (**i)** Chest CT scan revaluation after 6 months of treatment shows structural changes at the level of the right lung base where an area of irregular densification with disorganization of the surrounding tissue was still identified.

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