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EDITORIAL

A series of narrative reviews on air pollution and respiratory health for Pulmonology: Why it is important and who should read it

Air pollution in Europe

Environmental air pollution is a worldwide problem with significant proportions of the population exposed to air pollutant levels exceeding accepted air quality standards. The European Environment Agency (EEA) in its 2020 annual report on "Air quality in Europe"[1] also confirmed that many Europeans living in cities are exposed to elevated levels of air pollution exceeding acceptable thresholds, although the latter differ between EU and the WHO. In fact, the percentage of the urban population in the EU-28 countries exposed to air pollution above EU standards was generally much lower than the proportion estimated to be above the 2005 WHO Air Quality Guidelines (AQG), since threshold levels are different according to these two systems.[2] For $PM_{2.5}$, 4% exceeded the EU standards whereas 74% exceeded the WHO AQG. For O_3, 34% exceeded the EU standards whereas 99% exceeded the WHO AQG. The NO_2 values are identical (4%) because the EU and the 2005 WHO AQG reference values were the same. These differences are expected to increase, considering the lower threshold levels of the 2021 WHO AQG.[3]

Chronic exposure to air pollution can clearly have deleterious effects. Among the health effect indicators published by the EEA, the yearly numbers of premature deaths attributable to $PM_{2.5}$, NO_2 and O_3 in 2018 are striking: 379,000 for $PM_{2.5}$, 54,000 for NO_2 and 19,400 for O_3, in the EU-28 countries. The specific figures for our two countries were: 52,300 for $PM_{2.5}$, 10,400 for NO_2 and 3,000 for O_3, in Italy; 4,900 for $PM_{2.5}$, 750 for NO_2 and 370 for O_3, in Portugal.

Another relevant indicator is the years of life lost (YLL) attributable to $PM_{2.5}$, NO_2 and O_3: for the EU-28, YLL were 4,381,000 for $PM_{2.5}$, 610,000 for NO_2 and 232,000 for O_3. The specific figures for our two countries were: 556,700 for $PM_{2.5}$, 110,400 for NO_2 and 33,500 for O_3, in Italy; 53,000 for $PM_{2.5}$, 8,200 for NO_2 and 4,100 for O_3, in Portugal.

The joint ATS-ERS statement

A comprehensive review on what constitutes an adverse effect of air pollution was jointly published by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2017.[4] It followed up other important documents published by ATS in 1985 and 2000.[5,6] The report integrated the latest scientific evidence into a general framework for interpreting the adverse effects of air pollution on human health. It gave an overview of diseases, conditions and biomarkers influenced by outdoor air pollution showing that air pollution affects almost all systems of the human body, including the respiratory, cardiovascular, central nervous, and endocrine systems. In addition, it causes adverse effects to the fetus.

Various other notions should be borne in mind. First of all, the adverse respiratory effects of air pollution span the life cycle and affect an array of illnesses (namely asthma and chronic obstructive pulmonary disease - COPD) not only in terms of clinical worsening, but also regarding risk of disease development and even premature mortality. Symptoms such as cough, sputum, wheeze, and dyspnea have an increased frequency in association with exposure to various air pollutants. Furthermore, morbidity, as measured by hospital admissions, and prevalence of disease, based on diagnoses of asthma and COPD, are all significantly related to air pollution. In this context, although many studies exist, further research is warranted. The ATS/ERS document[4] pointed out clinical and biological biomarkers, such as lung function tests, bronchial responsiveness, and the fractional concentration of exhaled nitric oxide (FeNO), that can be used to assess the detrimental pollution effects in analytical epidemiological studies in the general population.

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Why this series is important

After almost five years since the last publications cited in the ATS-ERS statement,[4] new evidence is accumulating on the health effects of air pollution, especially at low levels. The first Global Conference on Air Pollution and Health was held at WHO Headquarters in Geneva between 30 October and 1 November 2018.[7] Thus, re-analysing evidence about air pollution and its respiratory effects produced in the past five years will be one of the objectives of the current Series.

In addition, various relevant aspects affecting the relationship between air pollution and respiratory health and disease will also be analysed in this Series. This will include risk factors other than outdoor air pollution, such as indoor air pollution, occupational air pollution, climate change, urbanization and greenness. Other important aspects will also be scrutinized, including the relationship between air pollution and novel and emergent infectious diseases, as well as how inequalities in health care and communities may affect exposure, prevention and mitigation approaches to air pollution. Finally, the quite relevant issue of how to protect individuals from air pollution will also be covered.

The Global Alliance against chronic Respiratory Diseases (GARD) was launched in Beijing on March 28, 2006, as a partnership among the WHO, governmental institutions, scientific societies and patients' associations. The GARD motto is "a world where all people breathe freely." Air pollution is one of the most important risk factors to health and reducing it is a priority for the prevention and control of chronic respiratory diseases.[8]

Thus, some GARD country representatives will give their contribution to this series.

Who should read the review articles of this series

Clinicians are increasingly busy in providing health care to the aging European population. In addition, they have been asked since the beginning of 2020 to make an extraordinary effort in order to cope with the Covid-19 pandemic.[9] Thus, they may not have enough time to keep updated with all the relevant aspects of scientific literature, especially if not immediately related to their day-to-day clinical activities.

On the other hand, if one looks at the GOLD[10] and GINA[11] documents, one sees that it is recommended to take a medical history which includes environmental and occupational risk factors for COPD and asthma, respectively. Thus, we believe that reading the articles of this series will help clinicians to better understand the role of such risk factors and the importance of their removal, which may sometimes be more effective than just using a medication-based approach.

Indeed, to advocate for clean air should be a must for all health professionals, especially after the publication by WHO of the new AQG on September 22, 2021,[3] indicating levels which are largely lower than the previous 2005 WHO AQG and the current EU standards.[1]

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EDITORIAL

A call for a national strategy for indoor air quality

Since the V century B.C. we have known from the Hippocrates, "On Airs, Waters and Places", that one of the most frequent causes of disease is the bad quality of air.[1]

When a person with COVID-19 breathes, coughs or sneezes, droplets and aerosols, that contain SARS-CoV2 virus, are released.[2,3] In addition, unlike other infectious diseases, it has been shown that an asymptomatic individual with COVID-19 in the incubation period can transmit the virus by talking or breathing.[4]

In fact, contrary to the belief that bio-aerosol formation exclusively results from aerosol-generating procedures, the production of infectious aerosols may occur from normal expiratory activities, such as breathing and speaking.[5,6] Aerosol emission rate will depend on the type of the respiratory activity and loudness of speech. Small aerosols are mainly produced in lower respiratory tract. Nevertheless, activities such as speaking, singing or coughing and sneezing will induce further aerosol formation in upper areas such as the larynx and the oral/nasal regions.[7,8] The implications of these features for transmission are of particular importance in the case of indoor settings for human gatherings, such as restaurants or choirs for example, where events of increased spreading occur.[9,10] These so called super-spreading events are characterized by a large number of infections caused by a single index case, and further support the aerosol transmission mode of SARS-CoV-2.[11] The latter are implied as major drivers of the pandemic and are responsible for multiple secondary cases.[12]

The current surge of the Omicron variant, with increased infectiousness, highlights the concerns over airborne transmission supported in novel outbreak reports.[13,14]

As the transmission via aerosols is a major pathway for spreading SARS-CoV-2, promoting measures to reduce indoor concentrations, namely though ventilation improvement, can contribute to minimizing the risks. This action was recognized in March of 2021 by the World Health organization (WHO) in its document "Roadmap to improve and ensure good indoor ventilation in the context of COVID-19".[15]

Consequently, the rapid growth of knowledge of the mechanism behind the airborne transmission of COVID-19 is leading to a paradigm shift in the way we see and manage the propagation of respiratory infections.[16]

Existing legislation for water quality rules that if harmful micro-organisms are detected in the water drinking or bathing need to be immediately prohibited and actions need to be implemented to avoid health risk. The quality of the air we breathe in the multiple microenvironments should also be protected by a similar approach! In particular, in closed spaces presenting a high density of occupancy (such as schools, transports, restaurants, shared offices etc.), the indoor air quality (IAQ) should be systematically monitored, in order to identify and implement the most effective measures(ventilation, filtration and air disinfection) to ensure healthy air for all.

Indoor Air Quality (IAQ) is defined in the Glossary of Indoor Air Sciences[17] published by the International Society of Indoor Air Quality and Climate (ISIAQ) as "An indicator of the types and amounts of pollutants in indoor air that can cause discomfort or risk of adverse effects on human and animal health or damage to vegetation". To quantify it, the average concentration of one or more IAQ parameters is assessed at a representative conditions of occupancy of use of the buildings during a given period of exposure (e.g., over an interval of 8 h, corresponding to the usual time of occupancy of a building during a working day). The contaminants in indoor air can be classified into three categories:

- Chemicals (Carbon Dioxide, Carbon Monoxide, Formaldehyde, Volatile Organic Compounds, Ozone, Nitrogen Dioxide, Sulfur Dioxide and Radon)
- Particulate Matter (PM10 and PM2.5 are the size fractions that are the most analyzed)
- Microbiological agents (Bacteria and Fungi (most commonly evaluated), and Virus)

These categories are not necessarily mutually exclusive, since the particulate matter load can be composed of a certain number of bio-particles.

Achieving a target condition for IAQ means to ensure that the concentrations of the airborne contaminants are maintained lower than the reference values laid down by legal

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authorities, taking into account the state-of-the-art knowledge about the health risks associated to exposure or the caused annoyance.

To assess the risk of an adverse effect associated to IAQ, it is fundamental to evaluate the exposure dose, which is dependent on the length of evolution of the air concentration of the hazardous agent and on the duration of the exposure interval, and also influenced by individual factors. Thus, the risk of developing an IAQ-related health outcome (e.g., infection by a virus as SARS-CoV-2) is typically proportional to the concentration of the stressor in the air and on the duration of the exposure.

The first step to accurately estimating the health risks include the definition and use of robust methodologies for accurately controlling IAQ A great number of monitoring, sampling and analysis methods, equipment, probes and other devices have been developed in the area of IAQ assessment. The available solutions present a wide diversity in terms of typology (e.g., samplers, monitors, and sensors), price, performance, target parameters and of the readiness of the measuring results. In the case of the assays that require sampling followed by laboratorial analysis, as is the case with microbiological contaminants, the time to get the quantified result of the concentration at a given moment may require some days. Regarding the online instruments (monitors and sensors), they can readily measure the concentrations at high frequency, typically at one minute logging intervals, providing high time-resolved data, offering better understanding of pollutants' concentrations, especially for those episodes that exhibit relevant temporal variations. This typology includes some affordable indoor environmental quality monitoring systems, capable of measuring the levels of multiple parameters such as temperature, humidity, particulate matter and carbon dioxide (CO_2) using low-cost sensors.[18,19] These kinds of solutions have been considered reliable tools for a simplified but highly informative investigation of IAQ.

The concentration of CO_2 in indoor spaces represents an indicator of the existence of adequate air renewal and whether there is enough fresh air inside buildings. CO_2 is co-exhaled with aerosols containing SARS-CoV-2 by people infected with COVID-19 and can be used as an indirect measure of the risk of the existence of high levels SARS-CoV-2 concentrations within enclosed spaces.[20] In fact, if an indoor setting presents conditions for the accumulation of CO2, it is also prone to promoting the accumulation of other contaminants generated indoors (including SARS-CoV-2). Particulate matter (PM2.5) has been also correlated with the spread of COVID-19.[21-23]

Moreover, temperature and relative humidity sensors are highly accurate and since SARS-CoV-2 remain active at low temperatures and high relative humidity, these parameters must be monitored to allow a proper evaluation of indoor environments.[24]

Although low-cost sensors have several limitations, they can at least provide a reliable qualitative assessment of the indoor environment and detect inadequate ventilation systems. IAQ monitoring systems have been used by several researchers in the past few years. These devices can be connected to the Internet to provide real-time monitoring data. The data can be consulted anywhere and anytime. Moreover, these systems can trigger notifications when the measured values are above the defined healthy standards. These monitoring systems are easy to use and to install, are modular and provide scalability.[25,26]

Most IAQ recommendations and standards[27–29] define both the reference concentrations for some indoor pollutants, the values about the accepted annoyance level (e.g. percentage of dissatisfied people) and the ventilation requirements that, for a given emission rate of pollutants, will allow the indoor climate to comply with the two previous criteria. The quality of the air indoors may be expressed as the extent to which human requirements are met.

Possible action strategies to ensure a good IAQ inside buildings are: a) removal/attenuation of polluting sources, b) localized extraction, c) dilution of pollutants in fresh air and d) air cleaning /air filtration. The first of these strategies implies, for example, the use of building materials, coatings and furniture with low emission rates of contaminants, while the second applies to places with localized polluting sources where it is known from the outset that there will be emission rates high (e.g. in the stove area in a kitchen). Filtering and cleaning the air is justified, on the one hand, when the fresh air outside presents, from the outset, concentrations of pollutants above what is recommended, and, on the other hand, if there are multiple localized sources of pollutants in the indoor environment not known or not foreseeable and, if for the pollutant in question, there is properly efficient removal equipment. This last circumstance, corresponding to the existence of dispersed and unpredictable emission sources in terms of their location, is also treatable through the dilution of pollutants with fresh air, corresponding to what is normally called ventilation. This is defined as a process in which air is supplied or removed from a given space to control the air quality and the thermal environment. Ventilation is necessary to supply oxygen for human metabolism and to dilute the concentrations of bioeffluent gasses and other chemical, physical or biological pollutants that may be emitted or admitted into buildings.

The ventilation requirements of a given indoor compartment can be defined on the basis of the fresh air flow required for the dilution of pollutants (m^3/h/person or $m^3/h/m^2$) or on the basis of the so-called air exchange rate, usually expressed by the number of complete air volume changes per unit of time (e.g. 3 air changes per hour). The definition based on the fresh air flow-rate per occupant or per unit of area or volume is the most appropriate, as it takes into account the greater or lesser density of polluting sources present in the space, which does not happen in the case of the air exchange rate.

In most IAQ and ventilation standards, two parts are considered in the process of defining regulatory values for the fresh air flow-rate. The first takes into account the pollutant load associated with the occupants (metabolic CO_2, body odors, methane, particles, bio-aerosols, etc.) and the second, the pollutant load related to the building itself (emissions from construction materials, coatings, furniture, combustion processes, cleaning products, etc.).

Since CO_2 is the most abundant bio-effluent, with an emission rate proportional to the level of metabolic activity and with a good correlation with the emission rates associated with the remaining bio-effluents, the concentration of this gas is the most commonly used to

define reference values for the part of IAQ associated with occupancy. As there are simple analytical expressions that relate the fresh air flows, either with the instantaneous values of the spatial average concentration of CO_2, or with the values of the so-called equilibrium concentration of this gas, for a given space, it is very practical to use it as reference for defining ventilation requirements.[30] On the other hand, the fact that, in particular, CO_2 sensors based on the NDIR (non-dispersive infrared radiation) method, have evolved to present an excellent metrological price/quality ratio, makes it possible to use them extensively to manage IAQ to minimize the risk of inhaling biocontaminants at doses that could be infectious.

The typical 1000 ppm value, recommended in most international regulations, for the concentration of CO_2 in indoor environments, resulted from studies carried out in the early 1990s[31] in which an empirical analytical expression was obtained establishing the relationship between the average level of dissatisfaction and the excess of CO_2 concentration in indoor air relative to outdoor air. It was decided to limit the percentage of dissatisfied people to a maximum value of 20%, which corresponded to an excess of concentration in relation to the outside air of 650 ppm. At that time, average concentrations of CO_2 in the atmosphere in unpolluted areas were in the order of 350—380 ppm, which resulted in a value for the absolute concentration in indoor spaces of 1000 ppm.

Once this value has been defined for the indoor air concentration of CO_2, it is possible to calculate the fresh air flow that, for a given generation rate of this pollutant inside the compartment and a given concentration of CO_2 in the outdoor fresh air admitted into the room, prevents it from being overtaken. Where the space is occupied by adults, with a body mass corresponding to the 50% percentile (1.7 m in height and 70 kg in weight), with a sedentary type activity (metabolism rate of 1.2 met), the fresh air flow-rate that guarantees that the concentration of CO_2 does not exceed the 1000 ppm, is 30 m^3/(h.person).

Of course, better or worse IAQ conditions may be achieved if, for the same conditions, the fresh air flow-rate per person is increased or decreased. In the EN16798—1 standard,[32] four categories are considered for each aspect of indoor environmental quality (thermal, acoustic and visual environments and IAQ, depending on what exigency level is considered for the building. The CO_2 concentration above outdoors may range from 550 ppm to 1350 ppm, which corresponds to fresh air flow-rates of 36 m^3/(h.person) and 14.4 m^3/(h.person) respectively.

It is easy to understand that the definition of the ventilation requirements before the COVID-19 pandemic was mostly the result of a tradeoff between the targeted IAQ and the energy consumption of ventilation processes. Since the energy consumption to move the air in ventilation circuits is proportional to the third power of the air flow-rate, there was a certain reluctance to strongly increasing the flow-rates. Of course, on account of the COVID-19 pandemic the boundary conditions for this problem became completely different because the main objective became to achieve the maximum dilution of biocontaminants in indoor environments, minimizing the risk of contagion. Thus, it has been widely recommended to operate the mechanical ventilation systems with the maximum potential fresh air flow-rate. The result of this type of recommendation, in terms of the achieved indoor CO_2 concentration value, depends very much on the actual installed ventilation system. In buildings with modern mechanical or hybrid ventilation systems, indoor CO_2 concentration values of 750 ppm may be reached with fresh air flow-rates about 50 m^3/(h.person).

In recent decades, IAQ monitoring in Portuguese buildings has created potential for important evidence in characterizing IAQ conditions in different settings. The great majority of the studies aiming to evaluate IAQ developed in Portugal were conducted in educational settings.

In fact, several studies conducted in Portuguese schools consistently demonstrated that a substantial number of classrooms present mean $_{CO2}$ concentrations higher than 1000 ppm.[33 34—40] Because most schools in Portugal rely on natural ventilation, in the cold season, schools are described to be especially at risk of exhibiting poor IAQ conditions, as compliance with adequate ventilation rates often causes complaints related to issues with thermal comfort. Nonetheless, there is some evidence to show that high CO_2 levels can occur in classrooms independently of the season.[39,41] In general, findings from the studies conducted in Portugal suggest that strategies for adjusting density of occupation to the classroom characteristics, for controlling indoor sources of pollution (e.g., the use of low-emitting materials) and for promoting natural ventilation, even during teaching periods, need to be properly explored in the school building stock in Portugal. This will help identify effective measures for promoting healthy air for children and school staff while mitigating preventable environmental harm.

Studies assessing indoor environment conditions of homes of children conducted in Portugal have also provided evidence on the existence of environmental conditions in homes for exhibiting levels of IAQ indicators that do not comply with national and/or WHO guidelines. In particular, the existence of insufficient ventilation rates (estimated based on the assessed levels of CO2) have been reported as a consistent observation in the studies conducted.[42—44]

To date, most of the Portuguese geriatric studies on indoor exposure have aimed at evaluating IAQ in nursing or elderly care centres. From these activities, situations of indoor CO2 concentrations higher than 1000 ppm have been reported in some the audited facilities.[45,46] CO2 levels seem to be particularly high in the bedrooms, which were identified as the main microenvironment accounting for the elders' daily average.[45] For restaurants, although the available information is very limited, there is evidence that the monitored CO_2 concentrations in dining rooms can greatly exceed 1000 ppm, suggesting inefficient ventilation in these indoor spaces.[47]

From a comprehensive evaluation of IAQ of 20 public indoor swimming pools located in the Northern region of Portugal, it was found that peak values of CO2 exceeding 1000 ppm were found in 5 out of the 20 swimming pools for the typical periods of the highest attendance.[48]

In some Hospital areas investigated in Portugal, the recommended limits for CO_2, particles, total VOCs, formaldehyde, bacteria and fungi are exceeded.[49] Such findings reinforce the need for further IAQ assessment plans in clinical settings and for the establishment of specific regulation to guarantee that hospitals are indeed truly health-promoting environments.

Indoor spaces like restaurants have been a focus of attention during the different COVID-19 waves.[50] A recent study shows that there are significant differences in the ventilation quality in various Spanish restaurants which might translate into different infection risks.[51]

During the year 2021 a group of researchers called attention to the risk of opening schools without robust mitigating measures. One of them was the inclusion of CO2 monitors to evaluate air quality indoors.[52]

This simple measure was shown to be doable in schools[53] and provides a visual indication for improving class room air quality.[54]

Even in some Hospital areas ventilation maybe suboptimal,[55] so the optimal strategies to achieve target CO_2 levels must be implemented.[56]

How can we be so sure that mitigation strategies to improve IAQ translate into better outcomes?

In an official CDC publication, the incidence of Covid-19 was shown to be 37% lower in schools that forced teachers and staff to wear masks and 39% lower in schools that improved ventilation.[57] Ventilation strategies associated with lower school incidence of infections included natural ventilation methods alone (35% lower incidence) or in combination with filtering methods (48% lower incidence). Another recent study, sponsored by the US CDC, demonstrated that air purifiers with portable HEPA filters reduce exposure to simulated SARS-CoV-2 aerosols indoors (in a conference room) by 65%, increasing to 90% when combined with mask use.[58]

In order to ensure the acceptance and the active participation in the measures to improve IAQ and mitigate related risks, it is crucial to properly engage the populations in the process. As example, the UK's Independent Scientific Advisory Group for Emergencies (Indie-SAGE) proposed on 8 October 2021 a system to transmit technical information, in a simple way, on mechanical and natural ventilation in indoor public spaces in buildings of all sizes and typologies.[59]

The proposed scheme includes familiar visual systems in color-coded (green to red) door/room labeling using icons to represent the behavioural mitigations needed to use spaces safely and the consequent quality/safety of spaces.

So, in educational environments, restaurants, theatres, public buildings and offices the dissemination of educational materials should be considered to inform citizens about the importance of IAQ, how ventilation conditions can be improved and on how they can assess the quality of air.

Reducing the spread of SARS-CoV2 necessarily involves a combination of behavioural measures, such as the correct use of the mask, social distancing, reducing the time spent in spaces with high occupancy density, personal hygiene, respiratory etiquette, testing and isolation. In addition to these measures, the correct design and maintenance of building ventilation systems are critical in preventing the transmission of SARS-CoV-2. Thus, it is essential not only to raise awareness among the population, but also to develop clear guidelines for building managers on ventilation and maintenance routines that protect the occupants of enclosed spaces.

In order to respond to the new requirements brought about by COVID-19, several organizations around the world have developed guidelines for the management of buildings,[60-62] namely their heating, ventilation and air conditioning (HVAC) systems, with a view to the reduction of disease transmission. These guidelines converge on eight fundamental strategies:

Adapt ventilation to the needs of different spaces in a building. Ventilation plays an essential role in the dilution of pollutants in interior spaces and in the removal of infectious agents. More than ever, the area of spaces, the number of occupants and their metabolic activity should be considered when sizing the outdoor air flows to be supplied in different locations. Adequate ventilation is one of the main strategies to reduce the risk of transmission by SARS-COV-2.

Promote ventilation by opening windows. In buildings with natural ventilation it is recommended to open windows, even if it may cause some discomfort. In buildings with mechanical ventilation, ventilation provided by opening windows can also be used to increase the ventilation rate. It is recommended that windows are opened about 15 min before the spaces are occupied, especially if they were previously occupied by other people, and then reopened regularly.

Increase HVAC system uptime. In buildings with mechanical ventilation systems, it is advisable to extend the operating time of the HVAC system in order to reduce the viral load inside the building. Ventilation systems must operate 24 h a day, seven days a week, and may operate at a reduced speed during the non-occupancy period. However, at least two hours before and after using the building, the system must operate at rated speed.

Do not recirculate air in the Air Handling Units (AHUs). Air recirculation in AHUs can reintroduce and distribute viral material in spaces that are interconnected by duct networks to the same equipment. Thus, the registration of the fresh air intake of the AHUs must be activated at 100% and the air recirculation must be deactivated, even when there are air filters in the return vents, since these are rarely HEPA (high efficiency rated particulate arrestance) and, as such, are not able to effectively filter viral particles.

Control the pressure between spaces. The pressure difference between areas must be maintained so that airflow moves from less contaminated areas to more contaminated areas.

Operate the exhaust system of sanitary facilities permanently. In order to avoid the fecal-oral route of transmission, it is recommended that the exhaust system of sanitary facilities work 24 h a day and seven days a week, that the window is kept closed to guarantee the negative pressure of the space and that the toilet lid remains closed during flushing to minimize the emission of possibly contaminated droplets.

Select suitable air purifiers. Portable air purifiers can be particularly useful in confined spaces and when ventilation with outside air is not sufficient to remove pollutants. The air inside buildings contains several classes of contaminants, from particles, with different chemical and physical characteristics, to gasses with very different properties. Air purifiers are used to reduce the concentration of these contaminants and their working principle depends on the class of contaminants to be removed. When the objective is to reduce the transmission of SARS-COV-2, we are faced with the presence of particles containing very small viruses (between 0.1 and 1 μm), so the most effective purifiers physically remove the particles through the use of HEPA filters. Alternatively, devices that use electrostatic filtering principles may also have very positive results. In addition to

the filtration capacity, air purifiers must be selected according to the number of air changes they can ensure per hour, therefore, they must be suitable for the volume of the space where they will be installed.[63]

Monitor IAQ. CO_2 is an excellent indicator of ventilation effectiveness and is easily measured using low-cost sensors.[64] CO_2 sensors can be coupled to traffic light systems that indicate to occupants when it is necessary to open windows to promote greater ventilation of spaces. CO_2 sensors may also be associated with mechanical ventilation, in the so-called demand control ventilation systems, allowing an automatic adjustment of the supplied fresh air flow. CO_2 monitoring also allows building managers to identify areas at greatest risk of infection.

Conclusions

Current evidence urges the need for the architectural design to consider suitable airflow patterns that prevent cross infections between occupants. The HVAC system design should, therefore consider multiple elements such as energy, economy, emissions and also comfort and IAQ.[65] The latter, applies not only to novel constructions, but probably more importantly, to the renovation of existing buildings, especially considering the need to ease other individual restrictive measures.

The cost of providing additional ventilation may be more than offset by savings that result from the gains in productivity and the reduction of sick leave.[66,67] Transmission prevention through better indoor air quality will be effective against any airborne virus.

Government financial support is needed to implement appropriate standards. In the building sector retrofitting measures considered in the PRR, the Recovery and Resilience Plan, besides the improvement of energy efficiency, structural quality and other factors, indoor environmental quality should also be a major action point.

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COMMENT

A Different Wave — Posttraumatic Stress Disorder among healthcare professionals during the COVID-19 pandemic

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Posttraumatic Stress Disorder (PTSD) is a disorder characterized by a constellation of symptoms occurring after the experience of a traumatic event, and is historically linked to warfare. Recent editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the International Classification of Diseases (ICD-11) have expanded the concept of "traumatic event" to also include exposure to death, serious injury, or sexual aggression.[1,2]

Data regarding recent outbreaks of infectious diseases, such as the 2002—2004 Severe Acute Respiratory Syndrome (SARS) epidemic, shows an increase in PTSD prevalence among healthcare professionals working during public health emergencies.[3] Recently, several studies evaluated the relationship between the COVID-19 pandemic and the risk for PTSD development among healthcare workers. Various characteristics of the COVID-19 pandemic explain its association with a higher risk for PTSD among healthcare workers, namely an unprecedented number of critically ill patients, an unpredictable clinical course, a high mortality rate, and the absence of specific treatments and treatment guidelines (at least for a considerable amount of time during the initial phase of the pandemic).[4] In fact, studies show that PTSD prevalence among healthcare professionals during this pandemic ranged between 2,1% and 73,4%. The wide variability in prevalence rates is due to the different time points of the pandemic curve in which the studies were conducted (some during peaks and others during calmer periods), and to the disparities between countries, where distinct measures were taken to contain the spread of the disease.[3] Some individual risk factors were identified, such as female sex, young age, lower work experience, less family support and lack of formal training related to the care of COVID-19 patients.[3]

At the beginning of the COVID-19 pandemic, Portuguese healthcare services were forced to reorganize themselves to respond to a crisis of unprecedented proportions. This restructuring included not only the transient adjustments, but also the more prolonged effects. These long-lasting changes relate mainly to the creation of services and departments dedicated to the management of suspected and confirmed COVID-19 cases, and the respective allocation of resources. In many hospitals, these measures and the increased pressure on the healthcare system placed an increased strain on healthcare workers, especially those working in Pneumology, Infectious Diseases and Internal Medicine services. As we begin to worry about the possibility of "a mental health pandemic" as a consequence of the impact caused by COVID-19, it is urgent to review the available evidence and reflect on the damage the last two years have caused to the mental wellbeing of healthcare professionals — not only because of the pandemic itself, but also as a consequence of the deterioration of work conditions in this context; in all of this, it is imperative that, having failed in the past, we must not fail again in the future.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Telomere length across different UIP fibrotic-Interstitial Lung Diseases: a prospective Greek case-control study

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Abstract
Introduction: Short telomeres are recognized as risk factor for idiopathic pulmonary fibrosis (IPF). We aimed to assess the role of telomere length (TL) in fibrotic-Interstitial Lung Diseases (f-ILDs) associated with a usual interstitial pneumonia (UIP) pattern as well as in IPF acute exacerbation (IPF-AE).
Aim and methods: TL was measured from peripheral white blood cells using a multiplex quantitative polymerase chain reaction in consecutive patients with f-ILDs, all presenting UIP pattern in the high-resolution chest-computed-tomography and compared to age-matched healthy controls.
Results: Seventy-nine individuals were included (mean age 69.77 ± 0.72 years); 24 stable IPF, 18 IPF-AE, 10 combined pulmonary fibrosis and emphysema, 7 Rheumatoid arthritis-UIP-ILDs and 20 controls. TL in all patients was significantly shorter compared to controls [mean T/S ratio (SE) 0.77 (±0.05) vs 2.26 (±0.36), $p < 0.001$] as well as separately in each one of f-ILD subgroups. IPF-AE patients presented significantly shorter TL compared to stable IPF ($p = 0.029$). Patients with IPF and shorter than the median TL (0—0.72) showed reduced overall survival ($p = 0.004$). T/S < 0.72 was associated with increased risk for IPF-AE (OR = 30.787, 95% CI: 2.153, 440.183, $p = 0.012$) independent of age, gender, smoking and lung function impairment. A protective effect of TL was observed, as it was inversely associated with risk of death both in UIP-f-ILDs (HR = 0.174, 95%CI: 0.036, 0.846, $p = 0.030$) and IPF patients (HR = 0.096, 95%CI: 0.011, 0.849, $p = 0.035$).

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Conclusions: Shorter TL characterizes different UIP f-ILDs. Although no difference was observed in TL among diverse UIP subgroups, IPF-AE presented shorter TL compared to stable IPF. Reduced overall survival and higher hazard ratio of death are associated with shorter TL in IPF.

Introduction

Fibrotic interstitial lung disease (f-ILD) is the end result of a wide spectrum of rare diseases that affect the pulmonary interstitium. In this heterogeneous group, idiopathic interstitial pneumonias (IIPs), connective tissue associated-ILD as well as combined pulmonary fibrosis and emphysema (CPFE) are included.[1–3] Telomeres are DNA–protein structures that protect chromosome ends and preserve genetic information. In each cell division telomeres shorten which leads finally to apoptosis and cell cycle arrest when reaching a critical point.[4,5] The role of telomerase is crucial, a specialized polymerase responsible for restoring the telomere loss and protecting TL by adding telomere repeats - six nucleotides (TTAGGG) - to the ends of chromosomes.[6–8] Telomerase consists of two essential components: the telomerase reverse transcriptase (hTERT), a catalytic component, and an RNA component (hTR), the template for nucleotide addition by hTERT.[6–8] In patients with familial pulmonary fibrosis, mutations in either of the essential components of telomerase can be found leading to acceleration of telomere shortening.[9] Furthermore, it has been shown that patients with IIPs who do not carry the above mutations, have shorter telomeres, compared to healthy controls.[10]

Idiopathic pulmonary fibrosis (IPF) which is histologically characterized by the usual interstitial pneumonia pattern (UIP), represents the most prevalent among IIPs, carries the worst prognosis,[11,12] and is the better characterized telomere-mediated-associated ILD.[6–8,13–20] As a matter of fact, in previous studies peripheral blood telomere length (TL) has been found to be shorter in IPF patients compared to age-matched controls and thus nowadays, short telomeres constitute a well-defined risk factor for IPF.[6–8,13–20] Recently, the association of short telomeres with other ILDs, such as Rheumatoid Arthritis-UIP-ILD (RA-UIP-ILD) has also emerged.[21–23] There is still lack of evidence concerning TL in CPFE as well as IPF acute exacerbation (IPF-AE), both originally characterized by the common denominator of UIP histology. So far, to the best of our knowledge, no study has examined the association of TL across different UIP fibrotic-ILDs.

IPF patients may experience a catastrophic event representing the development of diffuse alveolar damage (DAD) upon UIP called IPF-AEs.[24–26]At present, the pathogenesis of such events is attributed to several triggering factors including infection, aspiration, and gastroesophageal reflux with or without the additional effect of air pollution.[24–27] So far, to the best of our knowledge, the potential association of TL with the appearance of IPF-AE has not been investigated despite the evidence that short telomeres are associated with limited lung tissue renewal capacity.[4,9]

The aim of the present study is to assess TL in Greek patients with sporadic fibrotic ILDs associated with UIP pattern, including IPF, IPF-AE, RA-UIP-ILD and CPFE and compare it with healthy controls.

Material and methods

Study subjects

Consecutive patients with sporadic fibrotic ILD, such as IPF, IPF-AE, RA-UIP- ILD and CPFE who presented a UIP pattern in the HRCT and with no family history of pulmonary fibrosis, referred to our department from October 2016 until November 2017 were included in this prospective study as cases. Disease diagnosis was according to international guidelines after applying a multidisciplinary approach for each case.[11,12] Special care was attributed to the clinical history of each patient using the questionnaire developed by the American College of Chest Physicians (CHEST) to uncover any potential exposure source and exclude chronic hypersensitivity pneumonitis cases.[28,29] Furthermore, the definite UIP pattern on HRCT was confirmed by the presence of honeycombing, traction bronchiectasis and bronchiolectasis after being evaluated by two independent readers (SA, SAP).[12] Patients with IPF-AE, fulfilled the proposed criteria of the international consensus, including IPF diagnosis, worsening of dyspnea within 30 days of an unidentifiable cause and not fully explained by cardiac failure, while any new ground glass opacities or consolidations were confirmed by chest computed tomography (CT) scan at the time of admission.[11,24] All patients were followed-up regularly every three months. Finally, 20 age-matched healthy individuals visiting hospitalized patients at the same time as the ILD patients in our department were selected as controls. The study protocol was approved by the local Ethics Committee (EB△ 201/23-4-14) and all participants provided written informed consent.

Study design

Information on demographics, medical history and smoking status were collected for all participants. Moreover, all participants were submitted to physical examination. Information about patients, clinical and laboratory findings including pulmonary function tests, time since first diagnosis, comorbidities as well as data on any immunosuppressive and/or antifibrotic treatment were recorded. All patients hospitalized for acute exacerbation, had computed tomography pulmonary angiogram (CTPA) performed to exclude pulmonary embolism. Also, in an attempt to reveal any

pathogens, C - reactive protein (CRP) was measured and blood, sputum and bronchoalveolar lavage (BAL) cultures, where feasible, were performed.

Blood collection-DNA extraction

A blood sample of 5 mL was collected from participants using the standardized phlebotomy. Directly after the collection, blood samples were used for DNA extraction, using the QIAamp DNA Blood Mini Kit (Qiagen, Heidelberg Germany). DNA concentration was measured by QIAexpert (Qiagen, Heidelberg Germany) and only good-quality DNA with an A260/A280 ratio of 1.7–2.0 stored long-term in TE at −20 °C for further experimental procedures.

Telomere length measurement

Telomere length of genomic DNA from circulating leukocytes was determined using a multiplex quantitative polymerase chain reaction (qPCR) method as described by Cawthon[30] which is the predominant method used to measure average telomere length. The final concentrations of reagents and the thermal cycling conditions in the qPCR were as described by Cawton.[30] Serial dilutions of a reference DNA sample from the control group served as the ''standard DNA'' and was run in triplicates to generate the standard curves used for relative quantitation. All experimental DNAs were assayed in triplicate. This method is an extension of basic PCR whereby amplification and relative quantification of target DNA occurs simultaneously. This is achieved by coupling the target DNA with a fluorescent dye, where the amount of fluorescence generated is proportional to the amount of product. Relative quantification is calculated by dividing the telomeric DNA product (T) by the reference gene (S) that is present as a single copy in the genome, to generate a (T/S ratio). All the experiments were carried out at the Rotor-Gene Real Time PCR cycler (Qiagen, Heidelberg Germany).

Statistical analysis

Continuous variable (age, telomere length etc.) differences among disease groups and controls were evaluated using non-parametric testing (Mann-Whitney *U* test for two groups, Kruskal–Wallis for more than 2). For interval/ordinal variables chi square was performed. Kaplan Meyer was used for survival analysis and a binary logistic regression model with an outcome of exacerbation in IPF patients controlling for potential confounders. All p reported were two-sided with statistically significant results reported when $p < 0.05$. Statistical analysis was performed using SPSS 25 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Released 2017).

Results

Demographic and clinical characteristics of the study subjects are presented in Table 1. In total, 79 participants were included in the study (mean age 69.77 ± 0.72 years). More specifically, 24 stable IPF (70.2 ± 1.3 years), 18 IPF-AE

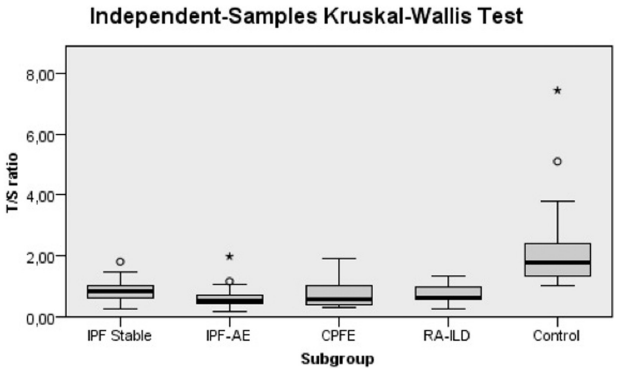


Figure 1 Telomere length in all fibrotic groups of ILDs was significantly shorter compared with those of control subjects ($p < 0.001$).

(71.2 ± 1.7 years), 10 CPFE (70.9 ± 1.4 years), 7 RA-UIP-ILD (68.9 ± 3.5 years) and 20 age-matched healthy controls (67.8 ± 1.2 years) were enrolled. In our cohort the majority of individuals were males in all studied subgroups except RA-UIP-ILD. The distribution of gender did not significantly differ between the total number of patients with a UIP pattern and controls (p'-value = 0.583) (Table 1). Among IPF patients, those with IPF-AE had significantly lower diffusing capacity of the lung for carbon monoxide percent (DLCO %) and forced vital capacity percent (FVC %) values but higher CRP ($p = 0.058$, $p = 0.003$ and $p = 0.042$, respectively). None of the patients received immunosuppressive therapy during IPF-AE whilst all received broad-spectrum antimicrobial coverage (data not shown). Also, CPFE patients had significantly lower DLCO % than IPF stable ones ($p = 0.015$).

Telomere length is shortened in patients with UIP

Telomere length detected in peripheral blood leukocytes of patients was significantly shorter compared to controls [mean T/S ratio (SE) 0.77 (±0.05) vs 2.26 (±0.36), $p < 0.001$] (Table 2). Also, shorter TL was observed in each one of the subgroups examined compared to the healthy controls [mean T/S ratio (SE) 0.87 (±0.07) in IPF stable vs. 0.66 (±0.10) in IPF-AE vs. 0.77 (±0,16) in CPFE vs. 0.74 (±0.15) in RA-UIP-ILD vs. 2.26 (±0.36) in controls, $p < 0.001$] (Table 2, Fig. 1). When we compared TL among the diverse subgroups no difference was observed except for patients with IPF-AE who had shorter TL compared to patients with stable IPF [mean T/S ratio (SE) 0.87 (±0.07) vs 0.66 (±0.10), $p = 0.029$]. Using a cut-off of 0.72, that is the median value of all IPF cases, patients with IPF-AE were significantly more frequently identified in the lower TL group (77.8% vs. 29.2% in stable IPF, $p = 0.004$).

Overall survival and telomere length

Using the same median cut-off, as mentioned above, patients were grouped in low TL and high TL. Idiopathic pulmonary fibrosis patients with lower TL (<0.72) showed reduced overall survival than those with a longer one (13.26 ± 1.62 months vs 29.7 ± 5.6, $p = 0.004$) (Fig. 2). This was not the case in CPFE ($p = 0.285$) or RA-UIP-ILD

Table 1 Patients' demographic, functional, clinical and laboratory characteristics n = 79.

	IPF stable	IPF-AE	CPFE	RA-UIP-ILD	Controls	p-value	UIP pattern overall	p'-value
n=79	24	18	10	7	20		59	
Age, years-mean (SE)	70.2 (± 1.3)	71.2 (± 1.7)	70.9 (±1.4)	68.9 (±3.5)	67.8 (±1.2)	0.477	70.4 (±0.9)	0.082
Male -n (%)	16 (66.7)	14 (77.8)	10 (100)	1 (14.3)	12 (60)	**0.002**	41 (69.5)	0.583
DLCO %pred-mean (SE)	53.5 (± 3.8)	38.7 (± 4.0)	34.0 (± 5.22)	42.0 (± 6.84)	N/A	**0.009***	(43.7 ± 2.49)	N/A
FVC %pred-mean (SE)	83.7 (± 4.3)	60.2 (± 4.3)	81.7 (± 4.4)	72.6 (± 5.5)	N/A	**0.003****	73.9 (±2.76)	N/A
LTOT-n (%)	1 (4.2)	10 (55.6)	5 (50.0)	1 (14.3)	0 (0)	**<0.001**	17 (28.8)	**0.004**
CRP, mg/dL-mean (SE)	5 (± 2)	47 (± 26)	23 (± 18)	21 (± 8)	N/A	**0.039*****	24.9 (±7.1)	N/A

Abbreviations: IPF: Idiopathic Pulmonary Fibrosis, IPF-AE: Idiopathic Pulmonary fibrosis Acute Exacerbation, CPFE: Combined Pulmonary Fibrosis and Emphysema, RA-UIP-ILD: Rheumatoid Arthritis-usual interstitial pneumonia associated Interstitial Lung Disease, UIP: Usual Interstitial Pneumonia, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of the lung for carbon monoxide, LTOT: long-term oxygen therapy, CRP: C-reactive protein. Bold represent statistically significant differences at p<0.05.

* IPF stable CPFE p = 0.015, IPF Stable – IPF-AE p = 0.058.

** IPF Stable – IPF-AE p = 0.003.

*** IPF Stable – IPF-AE p = 0.042.

Table 2 Comparison of telomere length between ILD patients presenting with a UIP pattern (subgroups and overall) and controls.

	IPF stable	IPF-AE	CPFE	RA-UIP-ILD	Controls	p-value	UIP pattern overall	p'-value*
n=79	24	18	10	7	20		59	
T/S- mean (SE)	0.87 (±0.07)	0.66 (±0.10)	0.77 (±0,16)	0.74 (±0.15)	2.26 (±0.36)	**<0.001**	0.77 (±0.05)	**<0.001**

Abbreviations: IPF: Idiopathic Pulmonary Fibrosis, IPF-AE: Idiopathic Pulmonary fibrosis Acute Exacerbation, CPFE: Combined Pulmonary Fibrosis and Emphysema, RA-UIP-ILD: Rheumatoid Arthritis-usual interstitial pneumonia associated Interstitial Lung Disease, UIP: Usual Interstitial Pneumonia. Bold represent statistically significant differences at p < 0.05.

* Patients presenting UIP pattern overall versus controls.

(p = 0.527). In Table 3 the results of cox univariate and multivariate regression analysis are presented. The association of T/S ratio (treated as a continuous variable) with the risk of death in UIP f-ILDs as well as in the IPF patients remained significant after adjusting for several confounders, lung function included (HR: 0.174, 95%CI: 0.036-0.846, p = 0.030 and HR: 0.096, 95%CI: 0.011—0.849, p = 0.035, respectively). To be precise, a 0.01 increase of TL length is associated with a 17.4% and a 9.6% decrease in the risk of death in UIP f-ILD and IPF patients respectively. Acute exacerbation of IPF had the most profound effect on overall survival (14.7 ± 3.55 months vs. 23.7 ± 1.38 months, p < 0.001). Using a binary logistic regression model we found a significant association of TL with IPF-AE (OR = 8.5, 95%CI: 2.06–35.08, p = 0.003), a finding independent of age (p = 0.636), gender (p = 0.433) and smoking (p = 0.499). This association remained significant (p = 0.020) after controlling for years from diagnosis, LTOT, DLCO, FVC, parameters that could reflect a more severe disease (Table 4).

Discussion

In this study shorter telomere length was detected in the peripheral blood of patients with sporadic IPF, IPF-AE, CPFE or RA-UIP-ILD, all associated with evidence of UIP pattern on HRCT compared to age-matched healthy controls. In addition, a significant association of TL with IPF-AE was found which was independent of age, gender, years from first diagnosis, smoking habit and lung function impairment. Moreover, in all UIP-fILD patients shorter TL was associated with increased risk of death. For IPF patients it was associated with reduced overall survival, an effect that was most consistently observed in IPF-AE.

Our results are consistent with previous studies, which have reported shorter telomeres in patients with IIPs,[6] sporadic IPF,[6–8,13–20] ILDs[10,20] and RA-ILD.[21,23] Interestingly, in line with the results of Stuart et al., no effect of TL on the survival of CPFE and RA-ILD associated with UIP pattern was observed in our study.[13,14] So far it is well known that short telomeres concern not only sporadic IPF in which approximately 25% of patients have TL below the 10th

Table 3 Risk of death in UIP f-ILDs patients.

Cox Regression	Parameters	HR	(95% CI)	p-value
Univariate Analysis				
	T/S ratio groups (Indicator: TL > median value)[a]	**3.722**	**(1.233, 11.231)**	**0.020**
	T/S ratio[b]	**0.149**	**(0.034, 0.653)**	**0.012**
	Age	0.990	(0.925, 1.058)	0.762
	Sex (Indicator: Male)	2.268	(0.755, 6.808)	0.144
	Subgroup (Indicator: IPF stable)			**0.022**
	IPF-AE	**10.092**	**(2.236, 45.550)**	**0.003**
	CPFE	**9.5494**	**(1.698, 54.202)**	**0.001**
	RA-UIP-ILD	4.733	(0.665, 33.682)	0.121
	Years from Diagnosis	**0.031**	**(1.015, 1.368)**	**0.031**
	LTOT	**3.007**	**(1.233, 7.331)**	**0.015**
	CRP	**1.006**	**(1.000, 1.011)**	**0.033**
	pCT	**48.589**	**(2.710, 871.205)**	**0.008**
	DLCO	**0.961**	**(0.924, 0.999)**	**0.044**
	FVC	0.978	(0.953, 1.004)	0.093
Multivariate Analysis (Results only for T/S ratio presented)				
	T/S ratio + Age	**0.133**	**(0.028, 0.618)**	**0.010**
	T/S ratio + Sex	**0.153**	**(0.034, 0.694)**	**0.015**
	T/S ratio + Subgroup (IPF stable, IPF-AE, CPFE, RA-UIP-ILD)	**0.224**	**(0.055, 0.910)**	**0.036**
	T/S ratio + Years from Diagnosis	**0.210**	**(0.051, 0.872)**	**0.032**
	T/S ratio + LTOT	**0.128**	**(0.029, 0.566)**	**0.007**
	T/S ratio + CRP	**0.171**	**(0.043, 0.680)**	**0.012**
	T/S ratio + pCT	**0.050**	**(0.003, 0.867)**	**0.040**
	T/S ratio + DLCO	**0.205**	**(0.046, 0.905)**	**0.037**
	T/S ratio + Years from Diagnosis + LTOT + CRP + pCT + DLCO	0.001	(0.000, 15.925)	0.115
	T/S ratio + Years from Diagnosis + LTOT + DLCO	**0.170**	**(0.036, 0.807)**	**0.026**
	T/S ratio + Years from Diagnosis + LTOT + DLCO + FVC	**0.174**	**(0.036, 0.846)**	**0.030**
	T/S ratio + Years from Diagnosis + LTOT + DLCO + FVC (IPF patients only)	**0.096**	**(0.011, 0.849)**	**0.035**

Abbreviations: IPF: Idiopathic Pulmonary Fibrosis, IPF-AE: Idiopathic Pulmonary fibrosis Acute Exacerbation, CPFE: Combined Pulmonary Fibrosis and Emphysema, RA-UIP-ILD: Rheumatoid Arthritis-usual interstitial pneumonia associated Interstitial Lung Disease, UIP: Usual Interstitial Pneumonia, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of the lung for carbon monoxide, LTOT: long-term oxygen therapy, CRP: C-reactive protein, pCT: procalcitonin. Bold represent statistically significant differences at $p < 0.05$.

[a] T/S ratio as a dichotomous variable using a cut-off of 0.72.

[b] T/S ratio as a continuous variable.

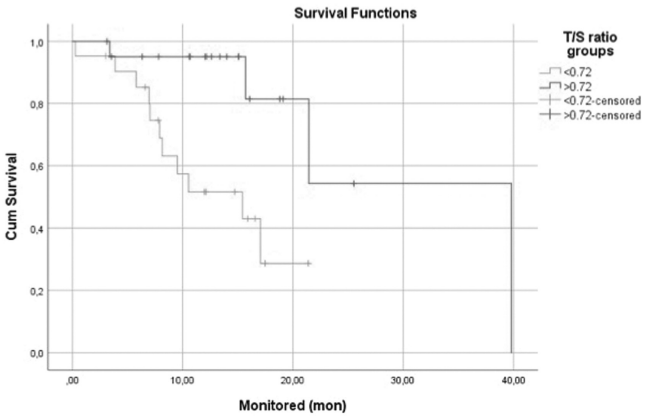
percentile,[13,16] but also may characterize other fibrotic subgroups of ILDs, such as CPFE and RA-UIP-ILD. However, to the best of our knowledge, no data exist concerning the association of TL with the UIP pattern. The association of short TL with the UIP pattern independently of the disease provenience found in the present study further reinforces the fact that the presence and extent of the UIP pattern is related to a worse prognosis.[31]

In the present study no difference was observed in TL among the diverse groups with a UIP pattern we examined, CPFE and RA-ILD included, compared to patients with stable IPF. This is apparently in contrast with the results of the study of Snetselaar et al.[10] who demonstrated that patients with sporadic IPF had significantly shorter TL compared to those with idiopathic NSIP, smoking-related-ILD and CTD-ILD. However, the authors had not focused exclusively on the UIP pattern. CTD-ILD, especially, represents a heterogeneous disease, which may include diverse patterns of lung involvement, such as organizing pneumonia, desquamative interstitial pneumonia, fibrotic non-specific interstitial pneumonia, as well as UIP, thus, making it difficult to draw safe conclusions for the whole group independently of the prevailed radiological pattern.[22,32,33] It is well known that in RA-ILD the UIP pattern predominates[32] and in our study all RA-ILD patients were included based on the presence of UIP pattern. Our results, which did not demonstrate significant difference in TL between IPF and RA-UIP-ILD, are also supported by the fact that both diseases share common phenotypic similarities and are associated with poor prognosis.[21,23,32,33] Furthermore, it was recently shown that

Table 4 Association of T/S ratio with the appearance of IPF-AE.

Binary logistic regression	Models	OR	95% C.I.	p-value
Univariate Analysis				
	T/S ratio groups[a]	**8.500**	**(2.060, 35.080)**	**0.003**
	Age	1.022	(0.933, 1.120)	0.636
	Sex (Indicator: Male)	1.750	(0.432, 7.084)	0.433
	Years from Diagnosis	**1.577**	**(1.081, 2.302)**	**0.018**
	Smoking (Indicator:No)			0.499
	Ex-Smoker	1.429	(0.388, 5.264)	0.592
	Current Smoker	0.357	(0.033, 3.916)	0.399
	CRP	**1.056**	**(0.990, 1.126)**	**0.097**
	pCT	463.385	(0.000, 3680.352)	0.465
	DLCO	**0.937**	**(0.886, 0.991)**	**0.023**
	FVC	**0.936**	**(0.895, 0.979)**	**0.004**
Multivariate Analysis				
	T/S ratio groups + Years from Diagnosis + DLCO + FVC	**30.787**	**(2.153, 440.183)**	**0.012**

Abbreviations: FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of the lung for carbon monoxide, LTOT: long-term oxygen therapy, CRP: C-reactive protein, pCT: procalcitonin. Bold represent statistically significant differences at $p < 0.05$.
[a] T/S ratio as a dichotomous variable using a cut-off of 0.72.



	Patient at risk				
Timepoint	0	10	20	30	40
Group <0.72	21	10	1	0	0
Group >0.72	21	16	3	1	0

Figure 2 Overall Survival in IPF patients using the median TL as cut-off ($p < 0.004$).

both diseases share common genetic variant associations for the development of pulmonary fibrosis, including the gain-of-function MUC5B promoter variant.[34]

It is well known that chronic hypersensitivity pneumonitis may be confused with IPF.

As Nogueira and co-authors point out in their review,[28] the identification of potential antigen sources the patient has been exposed to is essential for the diagnosis of HP. In addition, the authors state that the identification of antigen sources ''...is often hampered by the lack of recognition of some sources and/or by the absence of standardized detection methods of sensitization.''[28] In our study, to increase diagnostic accuracy and minimize misclassification we decided to use the questionnaire developed by the American College of Chest Physicians (CHEST)[29] although it does not represent a standardized method, to uncover and exclude potential chronic HP cases.

Short telomeres are known to express the limited tissue renewal capacity in the lung.[4,9,35] In IPF, a chronic lung disease characterized by irreversible fibrosis, repetitive causative stimuli force the bronchoalveolar epithelium to be constantly replaced.[6,36] Thus, it is not surprising that short TL is found in IPF patients.[6,13–20] Our results are compatible with those of previous studies, showing that IPF patients with no family history have significantly shorter TL compared to age-matched controls.[6,13,15,16,18,19] Alder and co-authors showed that although mutations in the essential components of telomerase were detected in only 1% of individuals with sporadic form of IPF, TL represented an important risk factor for the development of the disease.[6] Also, they found that IIPs patients had shorter telomeres both in peripheral blood and in the lung compared to age-matched controls.[6] It remains uncertain whether CPFE represents a distinct entity, or is a coincidental presence of two smoking-related conditions, such as emphysema and fibrosis.[37] Our results may provide some evidence that telomeropathy constitutes a potential explanation of its pathogenesis at least when it is associated with a UIP pattern on HRCT. However, further studies are needed to confirm whether telomere syndromes could be a risk factor for CPFE.

As mentioned above, several previous studies have investigated the pathogenetic and prognostic role of TL in the peripheral blood in stable IPF patients.[13–17,19–21] However so far, to the best of our knowledge, there is a lack of studies on the role of TL in the appearance of IPF-AE, which represents the development of diffuse alveolar damage (DAD) upon UIP mostly triggered by microbes.[24–26,38] The present study revealed that patients with IPF-AE had significantly shorter TL compared to the stable ones. Short telomeres have already been associated with DNA damage

response resulting in apoptosis that clinically manifests as organ failure.[9,33] In addition, it is well known that decreased TL can be the result either of the presence of increased oxidative stress or increased cell proliferation.[39] A plausible explanation of the underlying pathogenetic mechanism for our finding concerning TL and IPF-AE may be that a potential decrease of TL below a critical threshold needed for lung repair is linked to the incapacity of lung tissue to regenerate after any trigger leading to this idiopathic deterioration and organ failure. Unfortunately, one of the limitations in this study is the limited number of patients, which did not allow us to examine whether TL shortens when IPF-AE occurs or is shorter since baseline. However, our observation that the increased risk of IPF-AE was independent of lung function impairment may denote that a short TL can be predictive of the risk of IPF-AE also at baseline even when the pulmonary function is not so compromised and the disease not so severe.

Another limitation of our study is that budget constraints prevented us from performing flow cytometry (flow-FISH). It should be noted that although this method has already been validated in previous studies, it is more expensive and technically demanding.[40,41] On the other hand, real time quantitative PCR (qPCR) has been extensively adapted to measure TL; it is easier to perform, requiring only small amounts of DNA.[42] However, our study represents a prospective, single-academic center study, based on a well-selected group of fibrotic ILD patients, which for the first time in Greek patients examined the potential association of TL with IPF-AE, CPFE and RA-UIP-ILD all associated with evidence of a UIP pattern on imaging.

Conclusion

In conclusion the present study shows that patients with sporadic ILD associated with a UIP pattern on imaging have shorter telomeres compared to age-matched controls. Furthermore, the study shows that patients experiencing IPF-AE present significantly shorter TL compared to the stable IPF ones, a relationship that is independent of age, gender, years from first diagnosis, smoking and lung function impairment. Also, in all UIP-f-ILDs patients shorter TL is associated with increased risk of death. Finally, as for IPF patients, shorter TL is associated with reduced overall survival and higher risk for IPF-AE or death. Large-scale studies are needed to confirm our results.

Author contributions

I.T., A.K. drafted the paper and were involved in study conception and design, data collection, data analyses, and data interpretation. E.D.M. was involved in data collection, data management and critical revision of the manuscript. C.K., A.S. and S.A. were involved in data analyses, data interpretation and critical revision of the manuscript. S.A.P. was involved in data interpretation and critical revision of the manuscript. All authors read and approved the final version of the submitted manuscript.

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Conflicts of interest

No conflict of interest to declare for all authors.

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ORIGINAL ARTICLE

Portuguese adaptation of the S3-non-invasive ventilation (S3-NIV) questionnaire for home mechanically ventilated patients

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Abstract Short, valid and easy to use tools are needed to monitor non-invasive ventilation in clinical practice and for organization of home mechanical ventilation services. The aim of this study was to develop a professional translation and cultural adaptation of the Portuguese S^3 non-invasive ventilation questionnaire.

234 stable patients (128 male patients, 53.8%) with a mean age of 69.3 years under long-term home non-invasive ventilation were recruited from a single-center outpatient clinic. The most frequent diagnostic groups were obesity hypoventilation syndrome, chronic obstructive pulmonary disease and restrictive chest wall disorders.

The Portuguese version of the questionnaire was obtained using translation back-translation process with two professional translators. Internal consistency for the total score was good (Cronbach's α coefficient of 0.76) as well as for the ''respiratory symptoms'' and the ''sleep and side effects'' domains (Cronbach's α coefficient = 0.68 and Cronbach's α coefficient = 0.72, respectively). An exploratory factor analysis was performed leading to an explained variance of 54.6%, and resulted in 3 components.

The Portuguese version of the S3-NIV questionnaire is a simple and valid tool for the routine clinical assessment of patients receiving home NIV.

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Introduction

Home non-invasive ventilation (NIV) is indicated in patients with chronic respiratory failure (CRF) of different causes and its utilization in recent decades has been increasing both due to widening indications and improved health care setting organization.[1,2] It is well established that not only the underlying disease, but also the intervention can have a deep impact on the patients' health-related quality of life (HRQoL)[3–5]

Classical physiological variables used to monitor efficacy of NIV (such as spirometry findings and blood gas analysis) correlate poorly with reported impairment of physical function or overall health status and hence provide an incomplete picture of impaired health.[6–9]

Moreover, patients with CRF on NIV face unique challenges such as the dependence on external device for daily life, the number of hours spent on ventilation, limited possibilities to work/pursue daily activities, as well as subtle changes in disease progression. The impact of disease on patients' health, daily life and well-being must be measured directly from the patients themselves, by means of validated health status questionnaires.

The Severe Respiratory Insufficiency Questionnaire (SRI) is a multidimensional instrument with good psychometric properties designed to measure specific HRQoL in patients with CRF receiving home mechanical ventilation (HMV).[10] It was originally developed in German and has been validated in many languages including Portuguese.[11] It was developed for clinical research purposes and it is currently the most widely used HRQoL questionnaire in studies, but it is time consuming and not routinely used for clinical practice and it does not address NIV side effects which may offset some of the health benefits.

The S3-NIV questionnaire developers selected all items pertaining to ''respiratory complaints'' and ''attendant symptoms and sleep'' from the SRI questionnaire[10] and items concerning comfort and side effects were obtained by qualitative interviews with patients and other comfort scales with no previous formal psychometric validation.[12] After item analysis and reduction, the authors concluded the final instrument with 11 items, 5 related to respiratory symptoms, 2 related to sleep and 4 concerning side effects.

The authors considered that the S3-NIV questionnaire might be the most suitable tool currently available as it has been specifically developed for monitoring patients in routine clinical practice in NIV services but it is not intended to be a surrogate measure of general health status or quality of life.[12] Specific HRQoL questionnaires, such as the SRI, therefore remain a more appropriate tool for clinical investigation.

The purpose of this study was to produce a professional translation and cultural adaptation of the S3-NIV questionnaire into Portuguese.

Methods

Questionnaire

The S3-NIV Questionnaire is a self-administered questionnaire containing 11 items that patients score on a 5-point Likert-scale (0: always true; 1: mostly true; 2: sometimes true; 3: mostly untrue; 4: completely untrue) according to how true each statement has been for them in the 4 preceding weeks. The total score can be computed as the average of all answered items multiplied by 2.5. The lowest possible score (0) corresponds to the highest impact of disease and treatment, while the highest possible score (10) corresponds to the lowest impact of disease and treatment. The ''respiratory symptoms'' subscore is calculated as the average of answered items 1, 4, 5, 6 and 7 multiplied by 2.5 and the ''Sleep & Side Effects'' subscore is calculated as the average of answered items 2, 3, 8, 9, 10 and 11 multiplied by 2.5.

Portuguese translation and cultural adaptation

The Portuguese translation was obtained from the original French questionnaire, using the translation—back translation process by two independent professional translators.[13]

The equivalence of the back-translated items to the original items was evaluated and grouped into 3 categories according to previous recommendations[14]: category A - items that were fully equivalent; category B - items that were not fully equivalent or that contained different wording, but the content is similar; and category C - items that were not equivalent or that needed to be checked. Items rates A and B were left as they were and items rates C were reevaluated and rephrased accordingly with both of the independent translators being involved and the original questionnaire creator. The final version was written according to the New Portuguese Spelling Reform.

Validation

This study was conducted in the Pneumology Department at Centro Hospitalar de Vila Nova de Gaia/Espinho (Portugal), a tertiary care teaching hospital. Ethical approval was obtained from the hospital Ethics Committee and written consent was obtained from all included patients.

Adult patients with CRF, from a wide variety of causes, established on HMV for at least 30 days were eligible for the study. Exclusion criteria were refusal to participate, incapacity to understand or answer the questionnaire or an exacerbation in the preceding 3 months.

Patients were categorized into six categories: chronic obstructive pulmonary disease (COPD), combined COPD and obstructive sleep apnea (COPD + OSA), restrictive chest wall disorders (RCWD), obesity hypoventilation syndrome (OHS), neuromuscular disorders (NMD), and interstitial lung disease (ILD).

Statistical analysis

Data are presented with mean and standard deviation or median and interquartile range. T-test was used to assess differences between two groups; comparisons between the different pathologies (with respect to age, BMI, FEV1%, FVC%, S3-NIV scales) were performed using one-way Analysis of Variance (ANOVA). Normality was assessed with the Kolmogorov–Smirnov test. If normality or homogeneity of

variance assumptions were not verified, the Kruskal–Wallis (KW) test was used. Post hoc comparisons were based on Tukey's HSD or on the Mann–Whitney (MW) test with a Bonferroni correction. Spearman Rank correlation was used to investigate the associations between different variables. Internal consistency was assessed via Cronbach's alpha. An exploratory Factor Analysis was performed with Principal Component extraction and Varimax rotation. Statistical computations were performed with IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.). Two tailed significance assumed for $p < 0.05$.

Results

Considering the translation-back translation process, all items were rated as A except item 10 rated as B for questionable wording – the first translation used the term pressure and it was considered to be too technical for patients, and so after sampling different wording with colleagues and patients, all authors and translators agreed on the simplified version ''the air from the ventilator is too strong''.

Clinical characteristics of 234 included patients are reported on Table 1.

Overall, there was a slight predominance of male patients, except in NMD and most significantly in OHS patients, where almost ¾ of patients are female. The mean (Standard Deviation) age was 69.3 (11.0) with no statistical difference between different disease groups. The most common diagnostic groups were OHS and COPD (with and without associated OSA), corresponding to more than three quarters of the patients. The group of NMD patients included patients with Amyotrophic Lateral Sclerosis (6), type 1 myotonic dystrophies (3), Hereditary Myopathies with Early Respiratory Failure (3), metabolic myopathies (2) and neuroacantocitosis (1). The ILD group included idiopathic pulmonary fibrosis (2), chronic hypersensitivity pneumonitis (1) and unclassifiable ILD (1).

All patients were Portuguese native speakers.

All patients were on pressure mode ventilation, the vast majority (93.2%) on spontaneous-timed mode (median backup respiratory rate of 15) and the remainder on spontaneous mode. The most commonly used interface was oronasal mask (74.4%) and nasal mask (24.8%), with 1 patient with nasal pillows and another with tracheostomy (0.4% each). Less than on third of the patients (32.1%) were using a ventilator built-in humidifier.

Included patients were on HMV on average for 3 years, with a minimum of 3 months and a maximum of 240 months, with RCWD on longest period of time and NMD for shortest periods, although the differences are not statistically relevant.

The majority of the questionnaires were self-administered. Seventy-eight patients (33.3%) required help, because they were unable to read, had not brought their reading glasses or were physically too disabled to write (they were helped mostly by relatives). Patients took approximately 5 min to complete the questionnaire.

The rate of missing values on S3-NIV items was low for all items (1.7%). Data on total score and subscales are reported on Table 2.

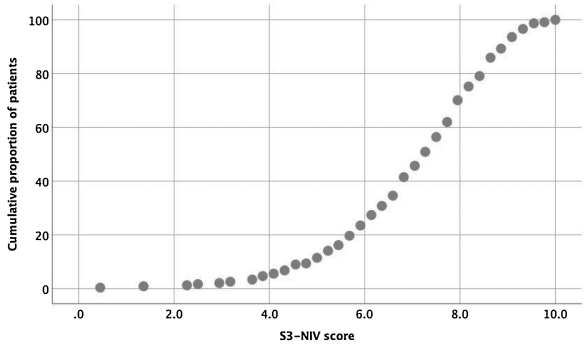

Figure 1 Cumulative distribution of the S3-NIV questionnaire total score in the study population.

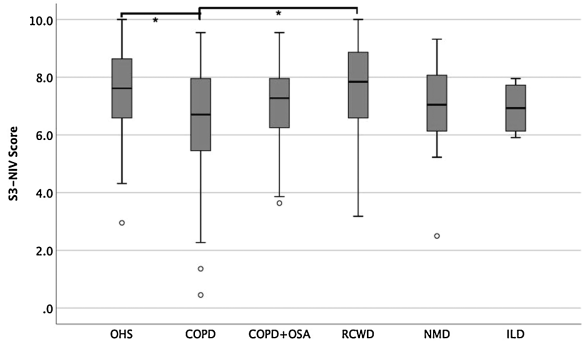

Figure 2 Distribution of the S3-NIV total score by disease category. * Statistically significant differences between disease groups ($p < 0.05$).

The entire scaling range was used in our validation study (minimum score of 0.5 and a maximum of 10). Of the 234 patients, 80% used 41% of the scaling range (5–9.1); 10% had a score <5.0 and 10% had a score >9.1 (Fig. 1).

When analyzing the reliability, the internal consistency of the total score was good, with a Cronbach's α coefficient of 0.76, a Cronbach's α coefficient of 0.72 for the ''sleep & NIV-related side effects'' dimension and slightly lower coefficient of 0.68 for ''respiratory symptoms'' dimension.

An exploratory factor analysis was carried out (data not shown) giving a Kaiser–Meyer–Olkin (KMO) of 0.80 and a significant Bartlett test to sphericity. Three factors explained 54.6% of the total variance. A varimax rotation was used and the first factor, which could be designated as daytime Dyspnea, correlated to items 1, 4, 5 and 7. The second factor, which could reflect the NIV side effects, correlated with items 8, 9, 10 and 11. The third factor that includes items 2 and 3 related breathing difficulties during sleep and headache could be perceived as sleep quality. Item 6, related to mucus production, did not correlate with any of the factors.

Fig. 2 shows S3-NIV total scores by disease category with no floor or ceiling effect in any disease category.

The median of the S3-NIV questionnaire score was 7.3 (IQR 6.1–8.2). Data on total and subscales scores are reported in Table 2 and stratified by disease. The impact of disease and treatment in COPD patients measured by S3-NIV score was statistically higher (lower scores) compared to OHS and RCWD patients. This difference is mostly related to the respiratory symptoms' component of the scale.

Table 1 Patients and ventilation characteristics.

Categories	OHS	COPD	COPD + OSA	RCWD	NMD	ILD	Total
Patients N (%)	64 (27.4)	62 (26.5)	51 (21.8)	38 (16.2)	15 (6.4)	4 (1.7)	234
Age (years)	68.6 (12.9)	71.6 (8.6)	69.6 (7.9)	68.0 (12.7)	63.7 (14.7)	73.8 (4.6)	69.3 (11.0)
Sex (% male)	18 (28.1)	39 (62.9)	37 (72.5)	23 (60.5)	7 (46.7)	2 (50)	126 (53.8)*
BMI kg/m^2	42.9 (8.1)	27.4 (5.0)	34.8 (6.1)	25.3 (6.3)	28.9 (6.7)	25.0 (8.2)	32.9 (9.5)*
HMV (hr/d)	7.5 (6.0–9.0)	8.5 (7.0–10.1)	8.0 (6.4–9.0)	8.0 (6.0–9.0)	8.5 (6.2–11.0)	4.3 (3.0–6.8)	8.0 (6.0–9.5)*
HMV (months)	27.5 (14.0–67.5)	38.0 (10.5–60.5)	36.0 (15.0–96.0)	57.0 (19.5–82.5)	18.0 (7.5–47.3)	20.0 (4.0–52.5)	36.0 (13.0–66.0)
$PaCO_2$ (mmHg)	41.9 (4.1)	47.3 (6.5)	45.4 (4.8)	45.9 (5.1)	43.4 (4.4)	52.5 (3.2)	45.0 (5.6)*
HCO_3 (mmol/L)	26.4 (2.5)	28.8 (3.0)	27.8 (2.5)	29.0 (3.4)	26.7 (1.9)	30.8 (4.6)	27.9 (3.0)*
FEV_1 (% predicted)	72.0 (59.0–85.0)	33.0 (25.5–46.0)	48.0 (34.0–56.0)	34.5 (28.8–49.3)	53.0 (40.0–62.5)	59.5 (28.5–91.3)	47.0 (32.0–65.0)*
FVC (% predicted)	73.0 (63.0–84.5)	68.0 (55.8–75.0)	66.0 (57.0–73.0)	37.5 (30.8–53.5	47.0 (38.5–58.0)	67.5 (50-0–87.3)	65.0 (50.5–75.0)*
IPAP (cmH2O)	21.5 (18.0–24.0)	22.0 (19.8–24.0)	22.0 (19.0–24.0)	20.0 (17.8–23.3)	18.0 (15.0–21.0)	18.5 (15.8–23.5)	21.0 (18.0–24.0)
EPAP (cmH2O)	8.0 (8.0–10.0)	6.0 (5.0–7.0)	8.0 (6.0–10.0)	6.0 (5.0–8.0)	6.0 (5.0–8.0)	5.3 (4.3–6.6)	7.0 (6.0–9.0)
BURR (cpm)	15 (1.6)	15.3 (1.3)	15 (1.5)	14 (1.1)	14.9 (1.4)	14.5 (1.7)	15.0 (1.4)

Abbreviations: COPD, chronic obstructive pulmonary disease; OHS, obesity-hypoventilation syndrome; RCWD, restrictive chest wall disorders; COPD + OSA, combined COPD and obstructive sleep apnea; NMD, neuromuscular disorders; ILD, interstitial lung disease; BMI, body mass index; HMV, home mechanical ventilation; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; BURR, back up respiratory rate.
Note: values are presented as mean and standard deviation, with the exception of months with HMV, FEV1 and FVC, which are presented as median and 25–75 quartiles.
* Statistically significant differences between disease groups ($p < 0.05$).

Table 2 S3NIV total and subscales' results according to pathology groups.

	S3- NIV questionnaire total score, median (IQR)	Respiratory symptoms subscore, median (IQR)	Sleep & NIV related side effects subscore, median (IQR)
OHS	7.6 (6.6–8.6)*	7.5 (6.0–9.2)	7.7 (6.7–9.2)
COPD	6.7 (5.4–8.0)*	6.0 (4.0–8.0)	7.5 (6.3–8.9)
COPD + OSA	7.3 (6.1–8.0)	6.5 (5.5–7.5)	7.9 (6.3–8.8)
RCWD	7.8 (6.6–8.9)*	7.5 (5.5–9.0)	8.3 (7.1–9.2)
NMD	7.0 (6.1–8.2)	6.5 (5.5–9.0)	7.5 (5.4–8.3)
ILD	6.9 (6.0–7.8)	6.8 (6.0–7.9)	6.7 (5.2–9.1)
Total	7.3 (6.1–8.2)*	7.0 (5.5–8.0)	7.9 (6.7–8.8)

* Statistically significant differences between disease groups ($p < 0.05$).

The S3-NIV total score did not correlate with objective measures of pulmonary function (FEV1 % of predicted: rho = 0.19, FVC % of predicted: rho = 0.02) nor with daily ventilator usage (rho = 0.06). We also found no correlation between the respiratory symptoms subscore and objective pulmonary function measurement (FEV1 % of predicted: rho = 0.21, FVC % of predicted: rho = 0.03) and between the sleep and side effects subscore and with daily ventilator usage (rho = 0.24).

There were no differences in side effects subscores in patients with or without humidifier (7.3 vs 7.6, p = 0.3), but we found that ventilation for more than 12 months had significantly higher side effects score (meaning fewer side effects) than patients being ventilated for a shorter period (7.6 vs 7.0, p = 0.04).

We also found that patients with HMV for over 12 months (78.8%) had higher ''Sleep & NIV related side effects'' subscores than patients with HMV for less than 12 months (21.2%) [7.6 vs 7.0, p = 0.04].

Except for COPD, we found that women had significant lower S3-NIV total scores across all disease groups. This was mainly driven by the ''Sleep & NIV related side-effects'' domain as illustrated in Figs. 3–5.

Patients with normocapnia (defined as pCO2 < 45 mmHg) had better scores than patients maintaining hypercapnia

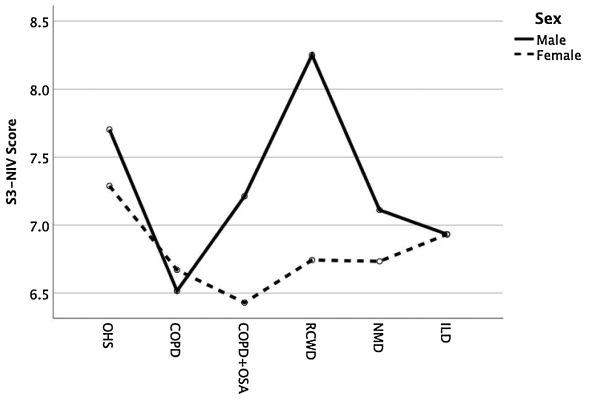

Figure 3 Differences in S3-NIV total score according to disease groups and sex.

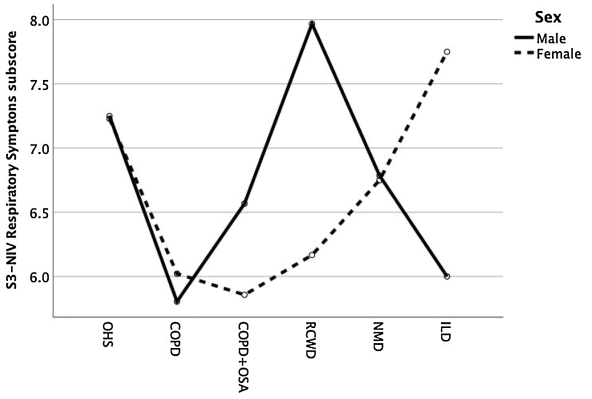

Figure 4 Differences in S3-NIV respiratory symptoms subscore according to disease groups and sex.

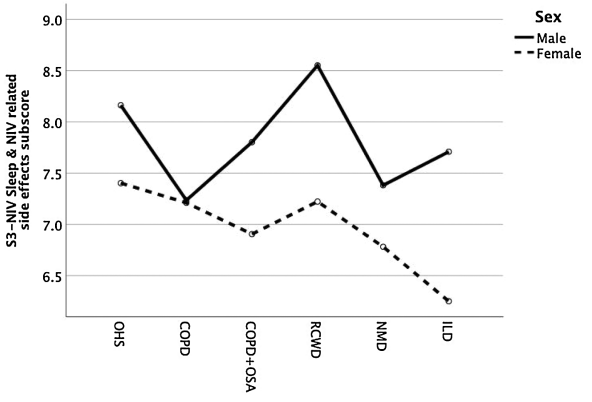

Figure 5 Differences in S3-NIV sleep & NIV related side effects subscore according to disease groups and sex.

(total score 7.4 vs 6.7, p = 0.002; respiratory symptoms 7.0 vs 6.2, p = 0.004; side effects 7.8 vs 7.2, p = 0.002)

Discussion

The S3-NIV questionnaire is a short, simple, patient-completed, specific tool that was developed to evaluate patients on home NIV in clinical practice as a complement to the monitoring of physiological variables. Although it is not formally a HRQoL questionnaire, it covers important patient centered outcomes related to NIV, i.e. respiratory symptoms, sleep quality and NIV-related side effects. This tool uses 11 items, which have been validated in a large international sample of French-speaking patients and we provide, to the best of our knowledge, the first validation, translation and cultural adaptation to a second language. Our study shows that the Portuguese version of the S3NIV, which resulted from professional translation and back-translation of the original French version, has good psychometric properties and can be used in clinical practice to monitor patients with severe CRF receiving HMV. The demand for a short, patient-oriented, self-administered tool is expected to increase greatly with the exponential development of home NIV tele-monitoring[15] and possibly the widening of indications such as evaluation of noninvasive ventilation after weaning from prolonged mechanical ventilation.[16]

It is worth noting that, even though the New Portuguese Spelling Reform has been implemented in order to unify the writing of Portuguese between different countries, not all the countries with Portuguese as the official language have accepted it. Also, some expressions are culture-dependent and may vary significantly between countries. Therefore, this translation is essentially valid for Portugal.

Our study sample included patients with the most common diagnosis with CRF requiring HMV. Compared to the original validation study, we included a much higher percentage of COPD ventilated patients (48.3% vs 21%) which is probably related to different practices in different countries as is reported in the Eurovent study, where Portugal has one of the highest percentages of lung/airway disease patients receiving HMV in Europe.[2] In our study, there was a considerably higher percentage of women (46.2% vs 25%), with similar median age (69 years) and a lower median of months on NIV (36 vs 45 months).

Our patients have a median S3-NIV score of 7.3, roughly ¾ of the scaling range and slightly higher than the original validation French-speaking cohort. With the exception of ILD patients, all the other groups have higher scores for the ''sleep and side effects'' dimension than the ''respiratory symptoms'' subscale. Although the patients have advanced diseases, this may demonstrate that patients recognize the benefits of home ventilation and have its side effects reasonably controlled, even though the majority has high inspiratory pressures.

Testing for internal consistency demonstrated acceptable to good reliability, only slightly lower than the original validation study.[2]

Measurements normally used as an index of functional damage or improvement (such as spirometry findings and blood gas analysis) correlate poorly with reported impairment of physical function or overall health status and hence provide an incomplete picture of impaired health.[6–9] In our study, we also found a weak association between the S3-NIV total score and respiratory symptoms score and FEV1 and FVC values. This reinforces the notion that symptoms questionnaires and patient reported outcome measures must always be obtained directly from the patient and should be included in regular treatment monitoring.

There might be some potential limitations to this study. Firstly, although it is a considerable sample it represents only

one center, but it represents one of only 3 highly complex multidisciplinary units in Portugal.[17] Secondly, it presents cross-sectional data, as it is most common in validation questionnaires. A prospective longitudinal study will be required to assess cut off values and the minimal clinically important difference, as well as the sensitivity of this tool to changes over time or changes induced by disease progression, NIV settings or interface modifications. Thirdly, we did not incorporate an external validation with other questionnaires. From the 11 items on the scale, eight items (concerning symptoms and sleep) were selected *ipsis verbis* from the SRI questionnaire whose Portuguese translation has been externally validated with the SF-36 questionnaire.[11] The remaining items were considered by the authors to be too different from existing questionnaires and the Quebec Sleep Questionnaire selected in the original article does not have a validated Portuguese translation and was developed to be used in obstructive sleep apnea patients.[18] Therefore, the authors decided to disregard an external validation procedure.

Conclusion

This professional Portuguese translation and cultural adaptation of the S3-NIV questionnaire has good psychometric properties and it is a simple and valid tool for the routine clinical assessment of stable patients with CRF undergoing home NIV.

The Portuguese version of the S3-NIV questionnaire is available as Supplementary Fig. S1.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pulmoe.2020.11.006.

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ORIGINAL ARTICLE

A qualitative study of patient and carer experiences with home respiratory therapies: Long-term oxygen therapy and home mechanical ventilation

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KEYWORDS
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Abstract Studies exploring the experience of patients receiving home respiratory therapies (HRT), such as long-term oxygen therapy (LTOT) and home mechanical ventilation (HMV), are still limited. This study focused on patients' and carers' experience with LTOT and HMV. An exploratory, cross-sectional qualitative study, using semi-structured focus groups, was carried out with 18 patients receiving HRT (median 71y, 78% male, 56% on both LTOT and HMV) and 6 carers

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Focus groups;
Patient experience;
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(median age 67y, 67% female). Three focus groups were conducted in three regions of Portugal. Thematic analysis was performed by two independent researchers. Patients' and carers' experience was reflected in seven major topics, linked to specific time points and settings of the treatment: Initial symptoms/circumstances (*n* = 41), Prescription (*n* = 232), Implementation (*n* = 184), Carer involvement (*n* = 34), Quality of life impact (*n* = 301), Health care support/navigability (*n* = 173) and Suggestions (*n* = 14). Our findings demonstrate a general good perception of the HRT by patients and carers recognizing a significative quality of life impact improvement, while identifying specific points where improvements in healthcare are needed, particularly about navigability issues, articulation between the hospital, primary care and homecare teams, especially regardingprescriptionrenewal. This knowledge is crucial to promote a long-term HRT adherence and to optimize HRT delivery in line with patients' experience, needs, and values. Moreover, these key points can inform the development of a specific patient-reported experience measure (PREM) for patients on HRT, which is not currently available, and foster a more integrated respiratory care model.

Background

The number of people with chronic respiratory failure using home respiratory therapies (HRT), such as long-term oxygen therapy (LTOT) and/or home mechanical ventilation (HMV), is increasing globally. The prevalence of patients requiring LTOT ranges from 31.6 to 102 and from 2.5 to 23 per 100 000 for those requiring HMV.[1] HRT presents thus a significant challenge to the capacity of health services to provide quality care.

HRT is considered one of the most important home healthcare services,[2] being effective in reducing patients' symptoms and hospitalizations and improving quality of life and survival.[3,4] The complexity of HRT, characterized by the involvement of a variety of health professionals, the need topromote patient education and increase health literacy, and the chronicity of the patient condition, are some of the key issues that may explain the value in providing HRT in real world.[5,6] Moreover, patients' non-adherence to HRT or its inadequate use are still major barriers to achieve the known benefits.[7-9] Therefore, it is of major relevance to integrate patient experience with healthcare delivery, in order to better understand difficulties regarding HRT implementation and thus contribute to improve these services.[1]

Patient experience includes relational and functional aspects of healthcare delivery valued by patients when seeking and receiving care, such as getting timely appointments, easy access to information and easy communication with health professionals.[10] In the context of HRT, evidence on patient experience is still limited. Previous qualitative studies exploring the experience of patients living with chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and obstructive sleep apnea (OSA) showed that health literacy, training, support, and carer involvement were important key-points in facilitating treatment adherence.[1] A recent study about the experience of patients with COPD and their carers with LTOT showed that this therapy has a major psychological impact on their daily lives and identified the need for a better coordination between different levels of care and the healthcare providers that supply the oxygen therapy.[7] However, the perspective of patients with distinct respiratory diseases, receiving LTOT and/or HMV is yet to be explored.

Therefore, the aim of this study was to explore patients' and carers' experience with HRT, namely with LTOT and HMV.

Methods

Study design

A phenomenological qualitative study, using focus groups, was carried out with a convenience sample of patients receiving HRT and their family carers. The focus group was the selected method due to its ability to enhance interaction amongst participants and generate a rich understanding of people's experiences and beliefs.[11] Study methods and results were reported according to the COREQ criteria for qualitative research.[12] Three focus groups were conducted at three regions of Portugal (Porto, Coimbra and Lisbon) between December 2019 and February 2020. This study was conducted in line with the Declaration of Helsinki and received approval from an Ethic Committee (P630-11/2019). All participants gave their written informed consent before any data collection.

Participants

The research team planned to recruit 6—8 persons for each focus group, balancing gender, age and types of HRT. To allow this heterogeneity, patients were conveniently selected from the database of an HRT homecare provider. Patients were eligible if they were a) receiving LTOT and/or HMV to treat chronic respiratory failure; b) 17 years old or older, and (c) able to understand the purpose and procedures of the study. The family carer was identified by the patient as being the spouse or a parent/child providing the largest amount of physical and/or supportive care. Patients and/or family carers were excluded if they showed inability to understand and co-operate. Eligible patients were contacted by telephone by a researcher, informed about the study and asked their willingness to participate. If patients consented to participate, they were asked to identify eligible family carers and the ability of both patients and carers

to cooperate with the study was screened through simple questions (e.g., capacity to communicate, express opinions, answer written questionnaires). Both patients and carers were invited to attend the focus group meeting (including patients who did not have a family carer). In anticipation of possible issues related to transportation and the autonomy of HRT equipment, all participants were offered transport to and from the focus group meeting site and resources to recharge HRT equipment were made available during the meeting.

Data collection

All data collection took place at the focus group meetings, which were held in three hotel conference rooms from different regions. Before starting the focus groups, a clear explanation of the aim of the study was provided to all participants, and consent forms were obtained. Participants completed a brief questionnaire about sociodemographic (gender, age, education, and current occupation) and clinical (diagnosis, type of HRT and duration of the treatment) data. The questionnaire also included the EQ-5D[13] to assess general health-related quality of life.

One moderator (LM) conducted all focus groups. LM is a female trained psychologist with a Master in Evidence and Decision in Health. Two group assistants (CJ and CCD) were present in each focus group to take observational notes of the group interaction and topics of discussion. One additional person was present, being responsible for the audio and image recordings. Both moderator and group assistants were experienced in conducting focus groups. Before starting the focus groups, the moderator, the group assistants, and participants introduced themselves to the group to help creating a comfortable environment and breaking the ice. Then, focus groups were conducted in a nondirective manner following a semi-structured discussion guide (Appendix A) designed to explore the experience of patients and family carers on HRT. On average, the focus group sessions lasted 60 min (range 55—63 min). The focus group sessions were digitally recorded and transcribed (verbatim transcription). During transcription, participants' identification was coded to preserve anonymity.

Data analysis

A thematic qualitative analysis was carried out independently by two researchers (EM and DO), using NVivo 12 plus (QSR International, Melbourne, Australia). First, the full transcriptions were read to obtain an overview of the collected data. To ensure the reflexivity, the researchers held regular group meetings to reflect on and discuss issues related to the study.[14] About one month after the last focus group meeting, the preliminary focus group results were presented to two patients for further validation.

Descriptive statistics were used to characterize the sample. Categorical variables were described as absolute and relative frequencies. Median and percentiles were used for continuous variables. To determine the consistency of the qualitative analysis carried out by the two researchers, an inter-rater agreement analysis using percentages of agreement (number of units of agreement divided by the total units of measure within the data item, displayed as a percentage) and Cohen's kappa (statistical measure which takes into account the amount of agreement that could be expected to occur through chance) was carried out. One focus group was randomly selected to perform this analysis.[15] The value of Cohen's k ranges from 0 to 1 and can be categorized as slight (0.0—0.20), fair (0.21—0.40), moderate (0.41—0.60), considerable (0.61—0.80) or almost perfect ($\geq$0.81) agreement.[16] All statistical analyses were carried out using SPSS Statistics (version 26.0; SPSS Inc., Armonk, NY, USA).

Results

Participants

Eighteen patients and six carers participated in the three focus groups. Participants' characteristics are summarized in Table 1. Patients were mostly male (78%), with a median age of 71 years. The majority were both on LTOT and noninvasive mechanical ventilation (56%) for a median of 3 years. Caregivers were younger (median age 67 years), mostly female (67%) and were caring for patients with chronic obstructive pulmonary disease (n = 2), neuromuscular disease (n = 1) and other conditions/unknown (n = 3) (Table 1).

Main findings

As can be seen in Table 2, 7 major categories emerged during the analysis of the focus groups. A schematic representation of the major findings is shown in Fig. 1. Inter-rater agreement between the two researchers in these major categories was found to be high (percentage of agreement 93—100%, kappa 0.497—1) (Table 2).

A brief description of each major category is provided below:

Initial symptoms/circumstances

Patients reported the first symptoms they experienced (e.g., shortness of breath, fatigue, apnea, sputum) and the exacerbation episodes (e.g., respiratory infections leading to emergency department visits/hospital stays) that were responsible for the referral to secondary health care (pulmonology departments) and consequent diagnosis/prescription of HRT. A small proportion of patients (e.g., neuromuscular diseases, cystic fibrosis) were born with the disease.

> "*I had that shortness of breath crisis and I had to go to the hospital*" (Male patient, 70y)
> *"I felt really tired"* (Female patient, 73y)

Prescription

The most common history was the prescription and introduction to HRT by a pulmonologist during a scheduled consultation or hospitalization, sometimes with the support of nurses/allied health professionals. In this first approach, patients state that the decision to initiate HRT is made by the physician, who present HRT as crucial for symptoms relief and to avoid negative outcomes in future (e.g., respiratory infections, death). Information received was mainly related with treatment regimen (type of HRT and daily hours), provided mostly orally and in written through prescription forms. Patients reported they were informed by their physician that they were free to choose the homecare

Table 1 Characteristics of the participants (n = 24).

	Patients (n = 18)		Carers (n = 6)	
Male	14	(78)	2	(33)
Age, median (p25-p75)	71	(66—74)	67	(56—76)
Region				
Porto	8	(44)	2	(33)
Coimbra	5	(28)	4	(67)
Lisbon	5	(28)	0	
Education				
Primary education - 1st cycle	6	(33)	2	(33)
Primary education — 2nd cycle	2	(11)	1	(17)
Primary education — 3rd cycle	1	(6)	1	(17)
Secondary education	6	(33)	2	(33)
Medium course/ University	3	(17)	0	
Occupation				
Retired	16	(88)	4	(67)
Employed	1	(6)	0	
Student	1	(6)	0	
Unemployed	0		2	(33)
Live alone	2	(11)	0	
Disease				
Chronic obstructive pulmonary disease	9	(50)	—	
Cystic Fibrosis	1	(6)	—	
Bronchiectasis	1	(6)	—	
Neuromuscular disease	1	(6)	—	
Others/Do not know	6	(33)	—	
Duration of the disease (years), median (p25-p75)	6	(3—16)	—	
Home respiratory therapy				
Long-term oxygen therapy	4	(22)	—	
Non-invasive mechanical ventilation	4	(22)	—	
Both	10	(56)	—	
Duration of the HRT (years), median (p25-p75)	3	(1—7)		
EQ-5D questionnaire				
Mobility problems	9	(50)	2	(33)
Self-care problems	6	(34)	0	
Usual activities problems	8	(44)	1	(17)
Pain/discomfort	13	(72)	1	(17)
Anxiety/depression symptoms	9	(50)	3	(50)
Current health condition, median (p25-p75)	68	(50—89)	85	(60—100)

Values are shown as n(%) unless otherwise indicated. HRT, home respiratory therapies; p25-p75, percentile 25-percentile 75.

Table 2 Frequency of each identified category and subcategory during focus groups.

Categories	Total
Initial symptoms/circumstances	41
Prescription	232
Implementation	184
Initial contact	73
Adjustment	12
Adherence	35
Technical difficulties	73
Problem solving	29
Carer involvement	34
Quality of life impact	301
Physical impact	29
Daily and social life impact	42
Emotional impact	64
Health care support and navigability	173
Support from the health professionals from health institutions	57
Support from the homecare provider health professionals	43
Shared decisions and personalization	16
Access and time management	66
Interactivity between health professionals	22
Administrative difficulties	22
Suggestions	14

provider, but they felt lost making this choice and commonly ask for medical advice. Discussion of the therapy benefits, adverse events and doubts was almost non-existent in this first contact.

> *"told me 'you have to sleep with this equipment'"* (Male patient, 69y)
> *"he said I should use the equipment to normalize my condition, and told it would bring advantages in future"* (Male patient, 76y)
> *"said I had to use oxygen 12 h per day"* (Female patient, 75y)

Implementation

For most patients, the first contact with the prescribed HRT was at home with the health professional of the homecare provider. This health professional provided mostly information related with daily practical aspects (device instructions, security, cleaning). Written information was commonly restricted to the device instruction manual and not included the clinical aspects of the disease. For some patients, the first experience with HRT was during an emergency department visit/hospital stay. In general, patients were firstly presented only to one device and one type of interface. However, when adverse events or technical problems occurred, there was room for personalization or decision-sharing. During the adjustment and maintenance period, patients reported device-related problems, namely asynchrony between spontaneous and device-imposed breathing, mobility restrictions and fall risk due to heavy device and wires, heat and noise nuisance caused by the device, high energy consumption and low autonomy of portable devices. Interface related problems, such as leaks, dry mouth/nose, ear discomfort, wounds, bruises were also described. These problems contributed to different adherence behaviors: while some patients report to adhere to HRT exactly as prescribed, others admit using the device less hours than those prescribed, or not using the device during social encounters/holidays.

> *"the technician went to my home and explained: how the equipment works, how to clean it..."* (Female patient, 75y)
> *"we tried one equipment, and if any problem occurred, if we were having difficulties, we talked to the doctor and the doctor talked to the homecare provider"* (Male patient, 21y)

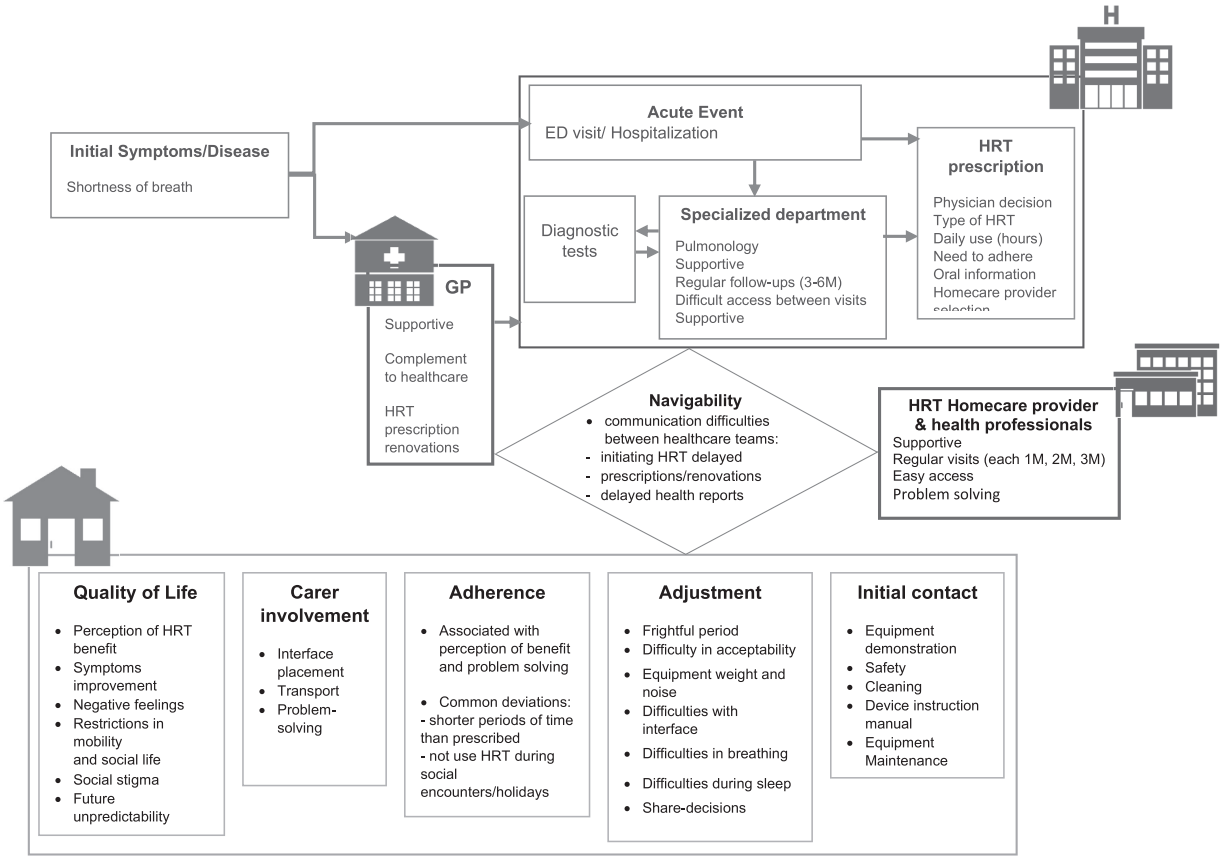

Figure 1 Schematic representation of the patients and carers experience with home respiratory therapies.

"during the night it [interface] moves a lot and I don't know how many hours I'm getting the oxygen" (Male patient, 72y)
"during the afternoon I meet my friends to entertain myself and I don't take the device" (Male patient, 68y)

Carer involvement

Most carers were spouses, and they were described as the ones responsible to look for medical help at the beginning of symptoms. Yet, most of the times they were not involved at the time of HRT prescription and decision-making. When the initial contact with HRT was at patient's home, the presence of carers was common and they were described as essential to device maintenance, transport, interface placement and problem solving.

"it is important that the person taking care of us knows how it [therapy service] works" (Female patient, 75y)
"I had a crisis at home, my bag was empty [oxygen] and my wife helped me, she opened the oxygen cylinder" (Male patient, 68y)
"At the beginning, I was as scared as he was [patient]" (Female carer, 51y)

Quality of life impact

After the adjustment period, most participants recognized the benefits achieved with HRT: reduced dyspnea and fatigue, improved sleep, easier sputum removal, and better oxygen levels. Some patients, however, reported that they had not felt an immediate improvement in their symptoms when starting to use HTR. Participants described the initial period of HRT prescription/implementation as negative, frightful, and difficult due to adverse events experienced (leaks, wounds, bruises) and the dramatic changes imposed in their life. Time and recognition of HRT benefits helped improve patients' adjustment and acceptance of the treatment. Despite recognizing the need for HRT in their daily life and experiencing its associated benefits, patients still have negative feelings (fear, sadness, exasperation, discomfort, embarrassment regarding the restrictions brought to their life ((walking, dancing, being with friends, going on holidays, traveling/flying, performing job activities), reporting the need to carefully plan their activities. They also expressed concerns about uncertainty regarding the future, namely the possible worsening of their health condition.

"without this therapy I would be dead already" (Male patient, 72y)
"it is part of life and I have to accept that; I see it as a normal thing. Nobody chooses to be sick, right?" (Male patient, 80y)
"Now, with this[therapy], I cannot dance" (Male patient, 68y)
"it requires planning and sometimes I deprive myself of long trips" (Male patient, 68y)

Health care support and navigability

Health professionals from different sectors (homecare and hospital care) were described as supportive (attentive, responsive) and available to clarify doubts and solve

problems/adverse events. Patients reported regular follow-up (each 3 or 6 months) with their pulmonologist. Access to the hospital team between scheduled visits (in-person or by phone) was not perceived as easy, although this perception differed according to the geographical areas. Contact with the primary care team was a complement, being mainly related with administrative issues: HRT prescription, namely renewal. Patients report regular visits from health professionals of the homecare provider (monthly, every other month, each 3 months). Between scheduled visits, as reported by patients, it was easy to contact health professionals of the homecare provider mainly to clarify doubts, solve technical problems/adverse events. When problems could not be solved by phone, unscheduled visits were performed in a timely manner. Patients identified some pitfalls regarding articulation between hospital, primary care, and homecare teams, especially communication difficulties when initiating HRT, delayed health reports and delayed prescription/renewal (Fig. 1).

> *"I called the hospital, I waited for hours to speak with my doctor, and nobody answered the phone"* (Male patient, 72y)
> *"I called [to homecare provider] and in a couple of hours the [health] technician was at my door"* (Female carer, 51y)
> *"and when I asked my GP to renew the prescriptions, he couldn't do it, because he needed a code that he didn't know, he had to call the homecare provider"* (Male patient, 68y)

Suggestions

Participants suggested the development of improved devices: smaller and quieter; featuring an intelligent sound alert when interface is not correctly placed. Another suggestion relates to simplifying the initial prescription/renewal process, for example, through direct communication between prescribers and homecare providers.

> *"[prescriptions] there should be a relation between the hospital and the homecare provider"* (Male patient, 72y)
> *"The oxygen equipment should be smaller, it is too big!"*(Male carer, 75y)

Discussion

This work demonstrates a general good perception of the healthcare received by respiratory patients under LTOT and HMV and their carers, with their experience being reflected in seven major topics related to specific time points and settings: Initial symptoms/circumstances, Prescription, Implementation, Carer involvement, Quality of life impact, Health care support/navigability and Suggestions. The analysis of these different topics allowed us to identify specific points where improvements in healthcare are needed. These key topics, together with the existing PREM for patients with COPD,[17] can be used to develop a specific patient-reported experience measure (PREM) for patients on HRT, which is not currently available.[1] This tool may be used as a quality indicator of HRT delivery services and thus contribute to a continuous improvement model.[18]

Initial symptoms and circumstances found in this study are in line with previous research. Dyspnea and fatigue are described as the cardinal symptoms by patients experiencing great discomfort and limitation in quality of life.[19] At the time of the initial prescription of HRT, patients reported mostly a paternalistic approach by health professionals.[20] Physicians often focus on the patient need of HRT, without a detailed discussion of the therapy benefits, adverse events, and doubts. In most cases, only hospital physicians were involved. From these experience reports, we may discern a clear need to enhance partnership and interdisciplinary and evolve to a patient-centered model, in which physicians together with other health professionals try to reach a shared understanding with patients to respond more thoroughly to their specific needs. This new approach has the potential to increase adherence to HRT, reduce morbidity, and improve quality of life.[21]

Patient health literacy should prepare patients for greater involvement and shared decision making. From the data gathered, however, health literacy took place during medical and home care visits, and was mainly related with benefits, treatment regimen and equipment. During these visits, as expected, health literacy is challenging due to multiple goals and time/workload pressures.[22,23] Yet, health literacy provided should enable patients and their carers to manage the treatment regimens and prevent avoidable complications, while maintaining or improving quality of life.[23] The specific health literacy roles can be better established, and interventions can be standardized and approachable (such as the ones integrated in pulmonary rehabilitation programs, an established standard care for patients with chronic respiratory diseases).[24] Across different time points and settings, oral information was the most common method of educating patients and carers, which is in line with the findings from a ERS/ELF survey on patients with home mechanical ventilation.[5] Written information was usually limited to the prescription forms and device instruction manuals. It is crucial that direct communication is complemented by written information,[25] yet this should be simplified to the therapy critical points. This will make information understandable to all patients, regardless of their education level.[26]

The implementation phase, which includes the challenging initial contact with the HRT and the adjustment period, was described as difficult and frightful both by patients and carers, with a number of adverse events and device-related problems commonly described in the literature.[1] However, they felt supported by the homecare provider to solve these issues.[5,7] In this period, patients considered the timing of regular visits from both hospital and homecare teams suitable. While contact (both in-person and by phone) with the homecare provider outside scheduled visits was easy, that was not the case for the hospital team. Communication with the hospital team should be enhanced for example through scheduled follow-up phone calls in-between visits. Using a more integrated respiratory care model would reduce navigability issues. Also, the administrative issues related with renewal of prescriptions should be reviewed. Despite the increased efficiency observed with the innovative electronic prescription system for HRT (PEM-CRD) implemented in Portugal since 2016, there is still has room for improvement.[27] In a previous study on LTOT,[7] this issue was not raised as renewal of prescriptions is not

required in other countries. This is an example of a possible strategy to adopt in Portugal.

Negative feelings and limitation in life reported in the initial/adjustment period persist during the maintenance period. This is of concern, as it seems patients and carers are being left alone coping with this emotional impact. Healthcare professionals need to be aware of this impact and create a non-judgmental environment during contacts in which patients are given the opportunity to ask questions, share concerns and feelings.[1] Yet, this does not replace the relevance of identifying patient/carer needs for psychosocial support, which is crucial for a healthy adjustment to HRT and to the new life circumstances.

This study has some limitations that need to be acknowledged. Most patients were on HRT for more than one year, and even though they were able to describe their experience with the initial prescription of HRT, their reports were probably modulated by the benefits perceived and expertise gathered over time. It would be interesting for future qualitative studies also explored the experience of families in an early phase of HRT. The number of excluded patients and eligible patients that refused to participate on the first telephone contact was not recorded in the study, but this information would be valuable to understand the feasibility of this real-world qualitative study. Moreover, only 6 carers participated in the focus groups, so we were not able to cover the full experience of carers. The difficulties recruiting carers were mainly related with the fact that some patients lived alone or were institutionalized, and thus did not identify a person to accompany them; there were also difficulties regarding the availability to attend the focus group meetings (all 6 carers were retired or unemployed). Similar difficulties were observed in previous studies in the context of HRT.[5,28] Although participants were recruited from different country regions, they were all being supported by the same HRT homecare provider in a universe of 8 homecare providers delivering HRT in Portugal. Also, data saturation was not assessed. Thus, we need to be careful before generalizing these findings to the national level. The agreement between the content analysis performed by each researcher has been performed only for one random focus group. But it was found to be high, which together with the validation of the preliminary results from two patients, increased our confidence in the results presented. We recognize that the patients' perspective, although central, is not enough to understand the whole picture; particularly regarding the navigability issues it would be interesting to assess the health professionals' views and experiences (quadruple aim)[29] in future studies. Only by integrating the perspective of the different stakeholders involved the current HRT model, will it be possible to identify the major drawbacks and aspire for a reform in the healthcare system to improve individual experience of care; improve the health of populations and enhance the experience of providing care.[29]

Conclusions

This study describes the experience of patients and carers with HRT in Portugal. This knowledge may be useful to health professionals and policy makers to design and delivery HRT in line with patients' preferences, needs and values.

Conflicts of Interest

None.

Acknowledgments

We would like to thank all patients and caregivers for participating in this study. We would like to acknowledge Sónia Moreira and Paula Moutinho for their contributions to English language revision.

Appendix 1. Focus groups semi-structured discussion guide

How were you given the information about the treatment? What information were you given?

Who made the decisions about your treatment? Was the caregiver involved?

What were you hoping to achieve with this treatment?

Where did you first try the treatment?

Did you test different equipment/interfaces?

What information were you given at this point?

Were you given the opportunity to talk about your doubts or fears?

Was the caregiver involved?

Do you feel that the equipment is suitable to your needs?

Does the equipment limit your life in any way?

Do you feel supported by the health professionals to clarify doubts/solve problems?

How is your condition followed up by the health professionals? How accessible are these health professionals/services?

Did the treatment meet your expectations? How could the results be improved?

Do you feel that the different health professionals are interested in knowing your point of view about the treatment and that they truly listen you? And do you feel understood? What could be different?

Did we cover the important issues of your treatment? Would you like to add anything?

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ORIGINAL ARTICLE

Recurrence of primary spontaneous pneumothorax: Associated factors

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KEYWORDS
Primary spontaneous pneumothorax;
Recurrence;
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Abstract
Introduction: Determining the risk of recurrence of primary spontaneous pneumothorax is challenging. The objective of this study was to develop a risk assessment model to predict the probability of recurrence in patients with spontaneous pneumothorax.
Methods: A retrospective study was performed of all episodes of pneumothorax diagnosed in the last 12 years in a hospital, in patients not initially submitted to surgery. Logistic regression was used to estimate the probability of recurrence. Based on a set of variables, a predictive model was built with its corresponding ROC curve to determine its discrimination power and diagnostic precision.
Results: Of the 253 patients included, 128 (50.6%) experienced recurrence (37% within the first year). Recurrence was detected within 110 days in 25% of patients. The median of time to recurrence for the whole population was 1120 days. The presence of blebs/bullae was found to be a risk factor of recurrence (OR: 5.34; 95% CI: 2.81–10.23; $p = 0.000$), whereas chest drainage exerted protective effect (OR: 0.19; 95% CI: 0.08–0.40; $p = 0.000$). The variables included in the regression model constructed were hemoglobin and leukocyte count in blood, treatment received, and presence of blebs/bullae, with a fair discriminative power to predict recurrence [AUC = 0.778 (95% CI: 0.721–0.835)].

Abbreviations: AUC, area under the curve; BMI, body mass index; PSP, primary spontaneous pneumothorax.

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Conclusion: The overall recurrence rate was high and was associated with the presence of blebs/bullae, failure to perform an active intervention (chest drainage) and low levels of hemoglobin and leukocytes in blood. Recurrence rarely occurs later than three years after the first episode. Once validated, this precision model could be useful to guide therapeutic decisions.

Introduction

Spontaneous pneumothorax is one of the most common pleural disorders, and around 86% correspond to idiopathic pneumothorax.[1] The annual incidence of primary spontaneous pneumothorax (PSP) is 18–28 cases/100,000 in men, and 1.2–6/100,000 in women[2] and this disease generally affects young patients. Recommended treatment for large PSP is active intervention (needle aspiration or chest drainage with small drain tubes). Surgery is generally reserved for episodes of pneumothorax that do not resolve, recurrences, pneumothorax associated with hemothorax, bilateral pneumothorax or risk occupations.[2–4]

There is considerable variation in the rates of recurrence of PSP reported in the literature. In a systematic review of 29 articles (4 randomized clinical trials and 25 observational studies) involving more than 13,500 patients, the overall rate of recurrence was 32%,[5] ranging between 8%[6,7] and 74%.[8] This wide range makes it difficult for physicians to determine the actual risk of recurrence and select the most effective therapy. Assuming a rate of recurrence close to the lowest estimates, it would seem reasonable to wait for a second episode prior to considering surgery. In contrast, if the highest estimates are accepted, surgery should be considered after a first episode of pneumothorax.

No factors have been identified to date as predictors of recurrence in PSP. As a result, the risk of recurrence cannot be estimated for a particular patient. Female gender, low body weight, smoking, and height in men have been postulated as recurrence risk factors.[9–12] A set of radiological findings such as bullae/blebs on CT and pleural thickening on chest X-ray have also been associated with a higher risk of recurrence.[8,13,14] To date, no treatment has been associated with a lower risk of recurrence.[15–18]

The objectives of this study were to estimate the rate of recurrence of PSP diagnosed in our hospital in the last 12 years and managed with a medical treatment (both, during the first year and by the end of the inclusion period). Another objective was to identify factors associated with recurrence, develop an individual-risk assessment model, and determine whether a specific approach is associated with a lower rate of recurrence.

Material and methods

Design

A retrospective study was conducted in patients diagnosed with PSP managed with medical treatment between January 2007 and December 2018 in a tertiary 1000-bed hospital serving a population of 450,000.

Data collection

Discharge reports were searched for the International Classification of Disease, 9th and 10th revision codes consistent with PSP (ICD-9-CM and ICD-10-CM).

Definitions

PSP: first episode of the presence of air in the pleural space not associated with a known pulmonary disease, previous trauma or medical treatments. *Recurrence of PSP*: second ipsilateral episode or first contralateral episode of PSP. *Medical treatment*: a therapeutic approach based on observation, aspiration or chest drainage. *Blebs and bullae*: the presence of subpleural air spaces with thin walls measuring <1 and ≥1 cm, respectively. *Non-smoker*: subjects who have smoked less than 100 cigarettes in their lifetime or have never smoked. *Ex-smoker*: subjects who quitted smoking at least 6 months earlier.

Selection criteria

Eligible cases were adults (≥16 years) admitted for a first episode of PSP between 2007 and 2018, inclusive. Patients were excluded if they had secondary spontaneous pneumothorax (infections, neoplasms, chronic obstructive pulmonary disease, diffuse interstitial pulmonary disease like hystiocitosis X or lymphangioleiomyomatosis, among other); traumatic; iatrogenic pneumothorax; if pneumothorax had been initially treated surgically (thoracoscopy or pleurodesis); if they were <16 years, and if all required data were not available.

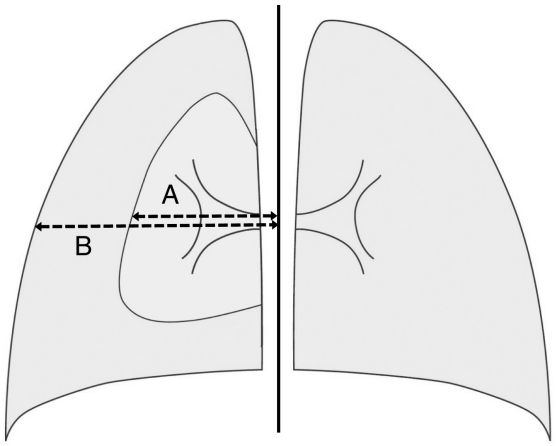

Figure 1 Light's index for estimating the size of pneumothorax. (A) Lung diameter and (B) hemithorax diameter (both measured at the level of pulmonary hilum).

Database

A database was built including the following factors: demographic [age, gender, weight, height, body mass index (BMI) (weight (in kg)/height^2 (in meters)]; clinical [smoking habit (pack-year index) and approach adopted [observation, Heimlich valve, aspiration, chest drainage (tube gauge, drain duration), etc.]; analytical (complete hemogram, coagulation tests, liver and renal function tests); and radiological data [presence of bullae/blebs, laterality, lung height (at maximum inspiration), size of the pneumothorax according to Light's index [*size of the pneumothorax* (*in %*) = $[(1-(L^3/HT^3)] \times 100$, where *L* and *HT* are the diameters of the lung and the hemithorax, respectively, both measured at the level of the pulmonary hilum] (Fig. 1),[19] and the relationship between the maximum transverse and anteroposterior internal sizes of the thorax on chest X-ray (distance between the internal surface of the ribs in the two sides and between the internal surface of the sternum and the anterior face of the vertebral body, respectively), measured at the level of the xiphoid apophysis]. Images were obtained using the digital AXIUM ARISTOS TX (Siemens) system and processed using the IDS7 work station (Sectra). Radiological measurements were performed separately by two experienced operators blind to other data. Discrepancies (presence or not of bullae/blebs and distance differences >5%) were discussed and solved by consensus.

The study was approved by the Ethics Committee of the hospital (CEIC 2019/008).

Statistical analysis

Logistic regression and survival models (time to recurrence) were built to estimate the probability of recurrence. The variables listed above found to be associated with recurrent pneumothorax were included in the models. All variables were included in the initial model. Then, the variables with the lowest weight according to the likelihood ratio were removed. Only significant variables were included in the final model ($p < 0.05$). Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated from logistic regression coefficients. A classification rule was built to estimate the probability of recurrence. ROC curves were constructed to evaluate the discrimination power of the model. Areas under the curve (AUC) were calculated with their 95% CI. Based on the predicted probabilities obtained from the models, the optimal cut-off for recurrent pneumothorax was calculated using Youden's index.[20] Also, to calculate the optimal cut-off, sensitivity, specificity, predictive values and likelihood ratio were calculated with their 95% CIs. All statistical analyses were carried out in R using ''survival'', ''rms'', ''pROC'' and ''OptimalCutpoints'' packages. These packages are freely available at cran.r-project.org.

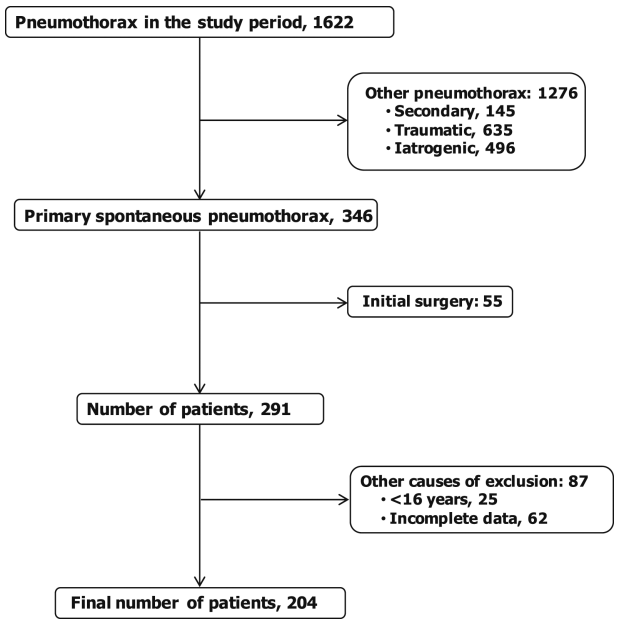

Figure 2 Flowchart of the patients studied.

Results

A total of 1622 patients were diagnosed with pneumothorax in our hospital during the study period. Fig. 2 shows the patient flow chart. The final number of patients with PSP included in the study was 253, of whom 128 (50.6%) experienced relapse during the follow-up period (overall recurrence rate). The recurrence rate during the first follow-up year was 37%. Recurrence occurred in the ipsilateral side in 98 patients (76.6%) and in the contralateral side in 30 (23.4%). The duration of follow-up ranged from 7 days (shortest time to recurrence) to 12 years (median, 26 months).

Table 1 displays the clinical characteristics of the totality of patients and study groups and provides data on the occurrence of recurrence. Raw OR are also shown. Significant differences were observed in age, smoking habits, presence or blebs/bullae, Light's index, transversal and anteroposterior chest size, hemoglobin, hematocrit and leukocyte count in blood, treatment received (observation vs chest drainage) and drainage duration. Factors found to have protective effects against recurrence included age, history of smoking habits, pack-year index, Light's index, chest drainage, transverse and anteroposterior size of the

Table 1 Clinical and demographic characteristics of the patients included in the study and odds ratio of the factors that influence the recurrence of primary spontaneous pneumothorax.

Variable	Total	No recurrence	Recurrence	OR (95% CI)	*p*
N	253	125	128 (50.6)		
Men (%)	199 (79)	97 (48.7)	102 (51.3)	0.71 (0.38, 1.29)	0.259
Age (mean)	25.9 ± 8.5	27.3 ± 8.1	24.6 ± 8.7	0.96 (0.93, 0.99)	0.011
Body mass index [weight (kg)/height^2 (in meters)]	21.3 ± 2.9	21.6 ± 2.8	20.9 ± 3	0.92 (0.83, 1.01)	0.079
Smokers					
Never-smokers (%) (Ref)	102 (43.8)	39 (38.2)	63 (61.8)		
Smokers (%)	120 (51.5)	66 (55)	54 (45)	0.51 (0.30, 0.87)	0.012
Ex-smokers (%)	11 (4.7)	8 (72.7)	3 (27.3)	0.23 (0.06, 0.93)	0.039
Packs-year	9.4 ± 6.9	9.8 ± 6.6	9 ± 7.2	0.95 (0.91, 0.99)	0.566
Right-side pneumothorax	139 (54.9)	73 (52.5)	66 (47.5)	1.32 (0.80, 2.17)	0.274
Blebs/bullae	186 (73.5)	73 (39.2)	113 (60.8)	5.34 (2.81, 10.23)	0.000
Light's index	44.1 ± 27.6	48 ± 26	40 ± 28	0.99 (0.98, 0.99)	0.004
Transverse size of the thorax (cm)	29 ± 2.5	29.3 ± 2.4	28.6 ± 2.6	0.90 (0.81, 0.99)	0.042
Antero-posterior size of the thorax (cm)	12.5 ± 2	12.9 ± 2	12.1 ± 1.9	0.82 (0.72, 0.93)	0.002
Transverse/anteroposterior size coefficient	2.4 ± 0.3	2.3 ± 0.3	2.4 ± 0.4	2.23 (1.06, 4.67)	0.032
Height of the lung (cm)	25.2 ± 2.2	25.3 ± 2.1	25.1 ± 2.2	0.95 (0.85, 1.07)	0.429
Hemoglobin (g/dL)	14.9 ± 1.2	15.1 ± 1.1	14.7 ± 1.2	0.75 (0.60, 0.93)	0.009
Hematocrit (%)	43.4 ± 3.4	44 ± 3.2	42.9 ± 3.4	0.90 (0.84, 0.97)	0.008
Leukocytes (cells × 10^3/μL)	9.8 ± 3.2	10.5 ± 3.3	9.2 ± 3	0.87 (0.81, 0.95)	0.001
Platelets (cells × 10^3/μL)	250.1 ± 59	258.4 ± 61.3	244 ± 56.2	0.99 (0.99, 1.00)	0.096
Treatment					
Observation (%) (Ref)	37 (14.6)	7 (18.9)	30 (81.1)		
Thoracic drainage (%)	216 (85.4)	118 (54.6)	98 (45.4)	0.19 (0.08, 0.46)	0.000
Diameter of chest tube [<20 F (%)]	75 (36.2)	37 (49.3)	38 (50.7)	0.72 (0.41, 1.27)	0.252
Drainage duration (days)	3.1 ± 2.1	2.7 ± 1.8	3.5 ± 2.4	1.20 (1.04, 1.37)	0.008

F, French; OR, odds ratio; 95% CI, confidence intervals; Ref, reference category.
Data are expressed as means ± standard deviation or in absolute frequencies (percentages).

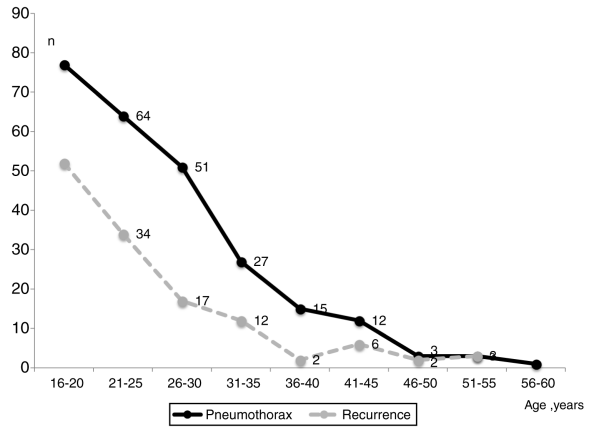

Figure 3 Cases of primary spontaneous pneumothorax (continuous line) and relapse (dotted line) by age.

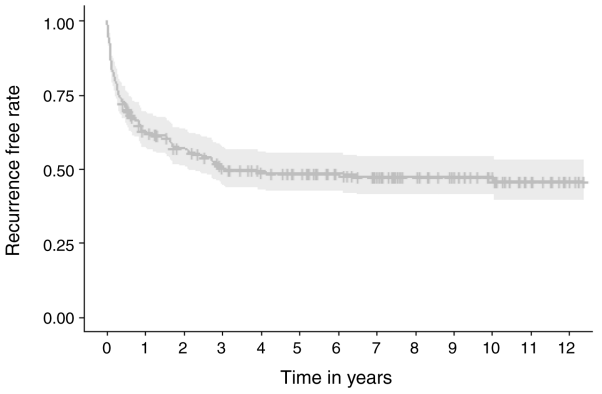

Figure 4 Rate of patients free of recurrence by follow-up time (Kaplan–Meier).

thorax; and hemoglobin, hematocrit and leukocyte count in blood. The protective value of Light's index disappeared with adjustment for treatment, as a high proportion of pneumothorax with a low Light's index were managed only with observation, whereas all pneumothorax with a high Light's index were drained. In contrast, the presence of blebs/bullae and a long chest drainage duration were identified as risk factors of recurrence.

Fig. 3 shows the number of PSP cases and recurrences and the age at which they occurred. Fig. 4 displays the rate of patients who remained free of recurrence during follow-up (Kaplan–Meier curve). In total, recurrence was detected within 110 days in 25% of patients. The median of time to recurrence for the whole population was 1120 days (∼3 years). Thereafter, only 4.7% of patients experienced a relapse.

Table 2 shows the regression model constructed to predict the risk of recurrence of PSP. The variables included in the final model were hemoglobin and leukocyte count in

Table 2 Logistic regression model for the prediction of relapse after a primary spontaneous pneumothorax.

	Coefficients	SE	OR (95% CI)	*p*
Intercept	6.6147	2.0120		
Hemoglobin	−0.3511	0.1296	0.70 (0.55, 0.91)	0.007
Leukocytes (*1000)	−0.1414	0.0482	0.87 (0.79, 0.95)	0.003
Treatment	−1.5756	0.4809	0.21 (0.08, 0.53)	0.001
Blebs/bullae	1.8639	0.3639	6.45 (3.16, 13.16)	<0.001

OR, odds ratio; 95% CI, confidence intervals.

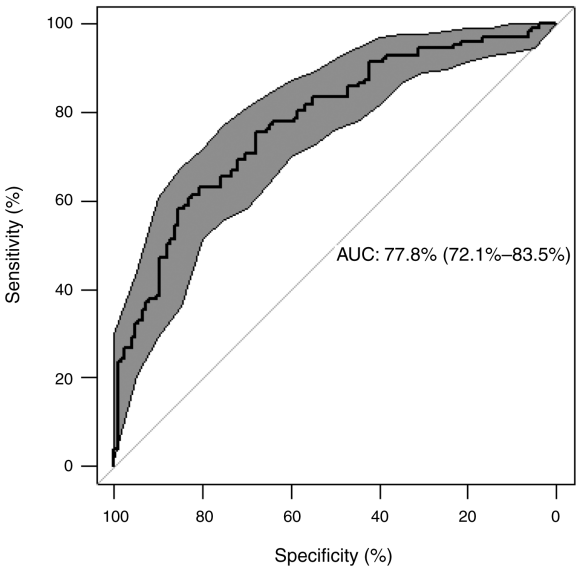

Figure 5 Discriminative power (area under the ROC curve) of the model to predict recurrence of pneumothorax.

blood, the approach (thoracic drainage or not) and presence of blebs/bullae on chest X-ray. The model demonstrated a good discriminative power for the prediction of recurrence [AUC = 0.778 (95% CI = 0.721, 0.835)] (Fig. 5).

A calculator of the probability of recurrence of PSP, and the formula used to estimate it, is available in the supplementary documentation. This tool may help clinicians use the predictive model.

Table 3 summarizes the diagnostic performance of the logistic regression model after the optimal cut-off was calculated using Youden's index (60% probability). The model has a sensitivity of 58%, a specificity of 86%, and a rate of correct classification of 71%. Table 4 shows sensitivity and specificity with different cut-off points of the predicted probability of PSP recurrence.

Discussion

The results obtained indicate a high rate of PSP recurrence (50.6%) and demonstrate that this prediction model has a fair discriminative power to predict recurrence based on the AUC obtained. Also, our results confirm that the presence of blebs/bullae on chest X-ray and the lack of an active intervention (chest drainage) in a first episode of pneumothorax increase the risk of recurrence, which rarely occurs later than three years after the first episode.

The overall rate of recurrence (50.6%) is consistent with that reported by other authors.[9–11,13] To the best of our knowledge, this is the first study to propose a model to predict PSP recurrence, although some factors had already been associated with a higher risk of recurrence. This is of relevance, as the ability to determine the risk of recurrence of a PSP may determine the therapeutic approach to be adopted.

The rate of recurrence of PSP has been reported to be higher in women,[5,9,11] while in our study no gender-based differences were observed. The reason may be that we exclude catamenial pneumothorax or underlying gender-related diseases such as lymphangioleiomyomatosis by not considering them PSP. Although age is not considered a risk factor for recurrence,[9,10] in our study, recurrence was more frequent in younger patients ($p = 0.011$). There is no consensus on the relationship between BMI and recurrence,[9] yet some studies have found some evidence.[10,11] Our results show that patients who relapsed had a lower BMI, although differences were not significant ($p = 0.079$).

PSP destroys the lung parenchyma, and the increase in low attenuation areas in PSP patients is related to smoking.[21] This suggests that patients with pneumothorax are more predisposed to the deleterious effects of tobacco. Nevertheless, there is limited evidence on the relationship between smoking and PSP recurrence.[22] Some studies have revealed a higher tendency to relapse among non-smokers.[9–11,13] In our study, recurrence was significantly higher among non-smokers (61.8%), as compared to smokers (45%) ($p = 0.012$). Thus, the risk of recurrence in smokers was half that of non-smokers (OR 0.51; 95% CI: 0.30–0.87). This inconsistency of results may be due to the detrimental effect of smoking being obscured by the high baseline rates of cigarette smoking in the included studies and the heterogeneous classifications used to define smoking status.[5]

The probability of recurrence of PSP was five-fold higher when blebs/bullae were observed on X-ray after a first episode of pneumothorax (OR 5.34; 95% CI: 2.81–10.23; $p = 0.000$). This association has been consistently reported in the literature, regardless of the imaging technique used (X-ray,[13] or CT as in our study[14]). Although CT has higher sensitivity to detect pneumothorax, in most cases it is not required for a diagnosis to be established. Remarkably, routine CT use is not recommended in clinical guidelines[2–4] to avoid the exposure of young patients to radiation.[23] An initial CT is not performed in routine clinical practice in our hospital either. The presence of blebs/bullae is known to be very frequent in PSP, although some authors have not found any evidence of their association with a higher risk of recurrence.[17,24]

The morphology of the thorax has also been linked to a higher probability of PSP. Park et al. documented that the chest of patients with PSP is flatter in the anteroposterior view, narrower in the lateral view, and higher in the craniocaudal view. This indicates that the morphology of the chest is associated with the development of pneumothorax.[25] Nevertheless, no studies have been published to establish a relationship between chest morphology and pneumothorax recurrence. In our study, recurrence was less frequent in patients with a larger size of the lung in the transverse and anteroposterior view (OR 0.90; 95% CI: 0.81–0.99; $p = 0.042$ and OR 0.82; 95% CI: 0.72–0.93; $p = 0.002$, respectively), which suggests that chest morphology may influence the recurrence of pneumothorax.

This study also reveals that lower levels of hemoglobin, hematocrit and leukocytes in blood and a low Light's index are risk factors for recurrent pneumothorax (Table 1). Nevertheless, the protective value of Light's index disappears with adjustment for treatment, as a high proportion of pneumothoraces with a low Light's index were only treated with observation, whereas all patients with a high Light's index underwent drainage. Thus, patients who underwent drainage were five-fold more likely to experience relapse that those whose pneumothorax was managed by obser-

Table 3 Classification table obtained using a logistic regression model for the prediction of relapse after pneumothorax.

Test:	Recurrence		Total
	Yes	No	
Positive	96	43	252
Negative	31	82	
Sensitivity (95% CI) (%)	58 (49, 67)		
Specificity (95% CI) (%)	86 (78, 91)		
Positive predictive value (95% CI) (%)	80 (71, 86)		
Negative predictive value (95% CI) (%)	67 (58, 80)		
Positive likelihood ratio (95% CI)	4.04 (2.57, 6.36)		
Negative likelihood ratio (95% CI)	0.49 (0.39, 0.61)		
Rate of correct classification (95% CI) (%)	71 (65, 76)		

Optimal cut-off (Youden's index), 60%.
95% CI, confidence intervals.

Table 4 Sensitivity and specificity at different cut-off point to predict relapse after a primary spontaneous pneumothorax with the model built.

Cut-off	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
10	99 (96, 100)	6 (0, 11)
20	94 (89, 98)	29 (21, 38)
30	92 (86, 96)	39 (31, 48)
40	86 (79, 91)	46 (37,55)
50	76 (67, 83)	66 (57, 74)
60	57 (48, 66)	86 (78, 91)
70	35 (27, 44)	94 (88, 97)
80	24 (17, 33)	98 (94, 100)
90	7 (3, 13)	99 (96, 100)

95% CI, confidence intervals.

vation (0.08–0.46; $p = 0.000$). All in all, a long duration of chest drainage is associated with a higher risk of recurrence of pneumothorax (OR 1.20; 95% CI: 1.04–1.37; $p = 0.008$). Although a recent study provides modest evidence that conservative management of PSP was noninferior to interventional management at 8 weeks follow-up, it does not address how many patients subsequently recurred in each group.[26]

Our predictive model is based on hemoglobin and leukocyte count in blood, the treatment administered (observation or thoracic drainage), and the presence of blebs/bullae on chest X-ray. The predictive power of the model is fair (AUC 0.778; 95% CI: 0.721–0.835), and its performance is optimized with a cut-off for the probability of recurrence of 60% (Table 4). We do not know any plausible biological hypothesis to justify the effect of the levels of these parameters on the recurrence of pneumothorax.

Given the overall rate of recurrence observed in our area (50.6%), it is recommended that patients are informed that 1 out of 2 PSP will relapse within a year (37%). This information, together with the probability of recurrence obtained using our predictive model for a particular patient can guide the therapeutic decision. Thus, a young patient with a long life expectancy and a high probability of recurrence will prefer to undergo an initial, more-aggressive treatment that spares them from the uncertainty of a potential relapse.[27] A multicentric, one-year follow-up study assessing the clinical benefits of surgery in a first episode of PSP revealed that the rate of recurrence was significantly higher in patients treated with chest drainage as compared to those who underwent VATS (34% vs 13%, respectively). The study showed that five patients would have to undergo surgery to prevent a relapse.[28] Therefore, treatments will be individualized in the future according to the clinical context.

This study has some limitations. First, it is a retrospective study, and the results obtained should be confirmed with new prospective studies. Secondly, the number of PSP was relatively low (253). Third, patients were recruited in a single center, and external validation with patients from other hospitals is required. Fourth, these results should not be applied to patients initially treated surgically (thoracoscopy or pleurodesis). Finally, estimating the probability of developing PSP requires complex calculations. However, the Excel calculator available in the supplementary material will make calculations easier for clinicians.

In summary, the overall rate of recurrence of PSP in our area is high and is associated with the presence of blebs/bullae on chest X-ray, the absence of an active intervention, and a low hemoglobin and leukocyte count in blood. Recurrence rarely occurs later than three years after the first episode. A predictive model of recurrence may help clinicians choose the most appropriate treatment. Larger, prospective, randomized, controlled trials and

cost-effectiveness studies are required to determine the most appropriate management approach in each case of PSP.

Ethical responsibilities

None declared.

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This study was performed without funding.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.pulmoe.2020.06.003.

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REVIEW

Issue 1 - "Update on adverse respiratory effects of outdoor air pollution". Part 1): Outdoor air pollution and respiratory diseases: A general update and an Italian perspective

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Abstract
Objective: to summarize the main updated evidence about the health effects of air pollution and to focus on Italian epidemiological experiences on the respiratory effects.
Results: the recent literature indicates that there is strong evidence for causal relationships between $PM_{2.5}$ air pollution exposure and all-cause mortality as well as mortality from acute lower respiratory infections, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, and lung cancer. A growing body of evidence also suggests causal relationships with type II diabetes and impacts on neonatal mortality from low birth weight and short gestation as well as neurologic effects in both children and adults. Italy, a Southern European country, faces a more threatening air pollution challenge because of the effects of both anthropogenic pollutants and natural dust (particulate matter, PM). The 2020 Report of the European Environment Agency highlighted the number of premature deaths in Italy attributable to main pollutants: 52,300 for $PM_{2.5}$, 10,400 for NO_2 and 3,000 for O_3 in 2018. In Italy, original time series and analytical epidemiological studies showed increased cardio-respiratory hospital admissions and mortality and increased risk of respiratory diseases in people living in urban areas.

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Conclusions: adverse health effects of air pollutants, even at low levels, have been confirmed by recent epidemiological studies. Further studies should focus on the potential link between air pollution exposure and respiratory infections. This topic has become particularly important in the current SARS-COV-2 pandemic.

Based on strong scientific evidence, the Italian government, which hosts the Global Alliance against Chronic Respiratory Diseases (GARD)-Italy at the Ministry of Health, the scientific respiratory societies and the patients' associations, as well as others in the health sector and civil society, must increase their engagement in advocacy for clean air policies, especially in light of the new Air Quality Guidelines of the World Health Organization.

Introduction

Air pollution is the leading environmental risk factor worldwide. Ambient and household air pollution together currently rank 4th for attributable disease and mortality among 20 major risk factors evaluated in the Global Burden of Disease (GBD) study, only after hypertension, smoking and dietary factors.[1] The World Health Organization (WHO) estimates indicate that around 7 million deaths, mainly from non-communicable diseases, are attributable to the joint effects of ambient and household air pollution, with the greatest attributable disease burden seen in low and middle-income countries.[2,3] A recent investigation indicates that regions with large anthropogenic contributions had the highest attributable deaths, suggesting substantial health benefits from replacing traditional energy sources.[4]

The recent literature indicates that there is strong evidence for causal relationships between $PM_{2.5}$ air pollution exposure and all cause-mortality as well as acute lower respiratory infections (ALRI), ischaemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), and lung cancer.[1] A growing and suggestive body of evidence also suggests a relationship with asthma, type II diabetes and impacts on neonatal mortality from low birth weight and short gestation as well as neurologic effects in both children and adults.[5,6]

The need to be informed on health effects of air pollution is reinforced by the Air quality in Europe - 2020 Report of the European Environment Agency (EEA) (https://www.eea.europa.eu/publications/air-quality-in-europe-2020-report), which highlighted the number of premature deaths in Italy attributable to main pollutants: 52,300 for particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), 10,400 for nitrogen dioxide (NO_2) and 3,000 for ozone (O_3) in 2018.

The peculiarity of Southern Europe, according to the EEA report, is to be affected by higher concentrations of outdoor air pollutants, as well as by higher percentage increases in mortality associated with 10 $\mu g/m^3$ increase in PM compared to other European areas.[7]

In addition, an adverse situation for the Mediterranean countries is the presence of desert sand dust, which can be high for many days in the year. For example, in Italy, the number of days with high African dust (up to 100 $\mu g/m^3$) ranges from 17% in the Po River Valley to 37% in Palermo, Sicily.[8]

Indeed, each 10 $\mu g/m^3$ increase in desert sand PM_{10} (particulate matter with an aerodynamic diameter less than 10 μm) is associated with increased all-cause and cardiovascular mortality, as well as respiratory hospital admissions for children and adolescents (2.38%, 95% CI: 0.09 — 4.71).[9]

The aims of this paper are: 1) to summarize the recent international evidence on the link between air pollution exposure and respiratory effects published after the ERS/ATS statement in 2017.[5] This updated information will be crucial to setting the context and future avenues for action; 2) to disseminate the results obtained in Italy when dealing with the issue of health effects of air pollution, especially useful for clinical readers.

Methods

This paper is divided into two main topics, a *general update* and the *Italian perspective*: the first one provides recent (from 2018 to 2021) quantitative estimates of the health impact due to air pollution at a global level; the second one is a confirmation at national level of the findings obtained at international level, summarizing results of different Italian epidemiological studies carried out during the last 40 years.

General update

In order to update the available evidence on respiratory health effects of outdoor air pollution after the 2017 ERS/ATS statement,[5] it was decided to focus on systematic reviews that also performed a meta-analysis to provide quantitative estimates of the associated public health impact. From an online literature search of PubMed and Embase databases from 2018 to June 2021 using the following search terms 'outdoor air pollution' and 'respiratory health' and 'meta-analysis', 16 articles were retrieved.[10-25] The English language was also an inclusion criterion.

After the articles' full-text screening, one study was discarded because it evaluated a non-respiratory outcome,[10] one for considering indoor air exposure only,[16] one for not being a systematic review,[15] and three for not reporting meta-analytic estimates for respiratory health effects.[13,20,22] Among the remaining ten articles included, six evaluated overall respiratory mortality.[11,12,17,18,19,23]

Italian perspective

The Italian perspective can be seen as the confirmation at the national level of the findings obtained at the

international level and used for elaborating the relevant documents of the major scientific societies, utilized by WHO for issuing air quality guidelines (AQG).

The first part of this section, which is built upon a recent publication of the Authors,[26] reports the main results from the studies conducted by or in collaboration with the National Research Council in Italy: the Po Delta and Pisa analytical epidemiological studies on health effects of air pollution,[27,28,29] the Palermo studies on children-adolescents,[30] and the SIDRIA study.[31]

The second part of this section reports the main results from the use of health and environment routine statistics carried out by a large collaborative multicenter study (the EPIAIR study).[32]

The last part, which is the most innovative, describes the outcome of the BEEP project, based on the use of big data and artificial intelligence.[33]

Results

General update

WHO has updated its Global Air Quality Guidelines, the final document has been published on September 22, 2021.[34] In anticipation, a series of systematic reviews investigating associations between a range of air pollutants and human health outcomes had been conducted. Table 1 summarizes the results for the systematic reviews that have evaluated exposure to various pollutants and mortality (all causes mortality as well as mortality from respiratory diseases, COPD, ALRI, and lung cancer).[12,18,23]

One meta-analysis provided quantitative global estimates for overall respiratory mortality for long-term exposure to particulate matter ($PM_{2.5}$ and PM_{10}).[12] There was clear evidence that $PM_{2.5}$ was associated with significantly increased mortality from respiratory diseases (mainly, asthma and COPD) and lung cancer. Only a few studies included in the meta-analysis were conducted in the so-called low-income countries (LIC).

This positive association between PM and respiratory mortality was also confirmed in a meta-analysis that evaluated short term exposure for all main pollutants, including NO_2 and O_3; increased risks emerged for both PM_{10} (relative risk-RR: 1.0091; 95% CI: 1.0063-1.0119), and $PM_{2.5}$ (RR: 1.0073; 95% CI: 1.0029-1.0116).[23]

Of note, another meta-analysis, focused on short-term exposure to $PM_{2.5}$ and PM_{10} originating from biomass burning (BB), did not find a significant positive association with respiratory mortality, but only with respiratory morbidity. The pooled effect estimates were 4.10% (95% CI: 2.86-5.34) and 4.83% (95% CI: 0.06-9.60) increased risk of total respiratory admissions/emergency visits per 10 $\mu g/m^3$ increases in $PM_{2.5}$ and PM_{10}, respectively. In particular, COPD rates increased by 3.92% (95% CI: 1.13-6.70) and 3.95% (95% CI: 1.65-6.24) per 10 $\mu g/m^3$ increases in BB-related $PM_{2.5}$ and PM_{10}, respectively. Similarly, for adult asthma admissions/visits, the pooled estimate for both $PM_{2.5}$ and PM_{10} was 9.59% (95% CI: 6.53-12.24). Interestingly, the evidence was less consistent for pediatric asthma: 3.52% (95% CI: -2.13-9.18) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ or PM_{10}.[19]

All three meta-analyses, focused on long-term NO_2 exposure and respiratory mortality,[11,17,18] found a significant positive association with respiratory mortality, but with evidence of substantial heterogeneity among the included studies. In detail, one meta-analysis pooling cohort studies only estimated a hazard ratio (HR) of 1.03 (95% CI: 1.01-1.05) for respiratory mortality, and of 1.05 (95% CI: 1.02-1.08) for lung cancer mortality per 10 $\mu g/m^3$ increment in NO_2 concentration.[11] A subsequent similar meta-analysis found that a 10 $\mu g/m^3$ increase in NO_2 was associated with a RR of 1.03 (95% CI: 1.01-1.05) for respiratory mortality. In addition, this study found a significant positive association for COPD (RR: 1.03; 95% CI: 1.01-1.04) and ALRI (RR: 1.06; 95% CI: 1.02-1.10) mortality.[18] The most recent meta-analysis estimated a pooled HR for respiratory mortality per 10 ppb increase in annual NO_2 concentrations of 1.05 (95% CI: 1.02-1.08), confirmed also in multi-pollutant models suggesting an independent effect of NO_2 on mortality.[17]

Among the four meta-analyses that focused on specific respiratory outcomes only,[14,21,24,25] one study evaluated the association of O_3 short-term exposure with asthma exacerbations.[21] Ozone exposures measured as 1-hour (RR: 1.012; 95% CI: 1.005-1.019) or 8-hour (RR: 1.011; 95% CI: 1.007-1.014) daily max were more consistently associated with asthma exacerbations, both in adults and children, than the 24-hour average (RR: 1.005; 95% CI: 0.996-1.014) exposure during the warm season. Another meta-analysis focused on COPD risk for NO_2 exposure;[25] the pooled effects, per 10 $\mu g/m^3$ increase in NO_2 concentration, were 17% on prevalence, 1.3% on hospital admissions, and 2.6% on mortality. The RR of COPD related to NO_2 long-term exposure was 2.5%, whilst for short-term exposure was 1.4%. The COPD effects associated with a 10 $\mu g/m^3$ increase were 1.7% for exposure to a general outdoor-sourced NO_2 and 17.8% for exposure to an exclusively traffic-sourced NO_2; importantly, the effect of NO_2 on COPD mortality emerged mainly in lag 0 models. Another recent meta-analysis, evaluating long term exposure to main air pollutants and COPD incidence, found a positive association per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (pooled HR: 1.18; 95% CI: 1.13-1.23), and in NO_2 (pooled HR: 1.07; 95% CI: 1.00-1.16), but not in PM_{10}.[24]

Finally, a meta-analysis evaluated the relationship between PM exposure and lung function decline.[14] The study estimated that a 10 $\mu g/m^3$ increase in short-term $PM_{2.5}$ exposure (days) was associated with a -7.02 mL (95% CI: -11.75 to -2.29) change in the forced expiratory volume in 1 second (FEV_1). A 10 $\mu g/m^3$ difference in long-term PM_{10} exposure was associated with a -8.72 mL (95% CI: -15.39 to -2.07) annual change in FEV_1 and an absolute difference in FEV_1 of -71.36 mL (95% CI: -134.47 to -8.24).

O_3 remained the least evaluated air pollutant: acute exposure was found associated only with asthma exacerbations in both adults and children.[21] In terms of specific respiratory outcomes, asthma and COPD were the most evaluated diseases, both for incidence, exacerbations, and mortality. For asthma incidence, the available evidence of a positive association with air pollution is stronger among children than adults, even if a just published large international study adds new supporting evidence.[35] The authors estimated HRs for adult-onset asthma of 1.22 (95% CI: 1.04$-$1.43) per 5 $\mu g/m^3$ for $PM_{2.5}$, 1.17 (95% CI: 1.10-1.25) per 10 $\mu g/m^3$ for NO_2 and 1.15 (95% CI: 1.08-1.23) per

Table 1 Association between long-term and short-term exposure to specific pollutants and mortality. Systematic reviews for the update WHO AQG. Relative risks (RR) are per 10 $\mu g/m^3$ exposure.

Mortality/pollutant	Long-term			Short-term		
	No.of studies	RR	95% CI	No.of studies	RR	95% CI
All-cause mortality (natural mortality)						
PM_{10}	17	1.04	1.03-1.06	66	1.0041	1.0034-1.0049
$PM_{2.5}$	25	1.08	1.06-1.09	29	1.0065	1.0044-1.0086
NO_2	24	1.02	1.01-1.04	54	1.0072	1.0059-1.0085
O_3 (annual exposure)	9	0.97	0.93-1.02			
O_3 (peak exposure)	7	1.01	1.00-1.02			
SO_2		NA		36	1.0059	1.0046-1.0071
Respiratory mortality						
PM_{10}	13	1.12	1.06-1.19	41	1.0091	1.0063-1.0119
$PM_{2.5}$	17	1.1	1.03-1.18	20	1.0073	1.0029-1.0116
NO_2	15	1.03	1.01-1.05		NA	
O_3 (annual exposure)	4	0.99	0.89-1.11		NA	
O_3 (peak exposure)	4	1.02	0.99-1.05			
SO_2				23	1.0067	1.0025-1.0109
COPD mortality						
PM_{10}	5	1.19	0.95-1.49		NA	
$PM_{2.5}$	11	1.11	1.05-1.17		NA	
NO_2	9	1.03	1.01-1.04		NA	
ALRI mortality						
PM_{10}	2	NA			NA	
$PM_{2.5}$	4	1.16	1.01-1.34		NA	
NO_2	5	1.06	1.02-1.10		NA	
Lung Cancer mortality						
PM_{10}	13	1.08	1.04-1.13		NA	
$PM_{2.5}$	15	1.12	1.07-1.16		NA	

ALRI: Acute Lower Respiratory Infection
NA: not available

$0.5\times10^{-5}/m^{-1}$ for black carbon exposure. For COPD, increasing evidence supports a positive association, and emerging evidence links it to long term NO_2 exposure.[24,25] The positive association with lung cancer mortality was confirmed and linked not only to PM,[11] but also to NO_2 long-term exposure.[11]

Italian perspective

I) Analytical epidemiological surveys

In Italy, two major analytical longitudinal surveys on general population samples were conducted from 1980 to 2011. The first was in Po River Delta, a rural area near Venice, before and after the construction of a large oil-burning central power plant. The second was in Pisa and its surrounding area, before and after the construction of a new highway far from the residential zones.[27,28,29,36] This epidemiological investigation used subjective (e.g. standardized questionnaire on respiratory symptoms, diseases and risk factors) and objective tools (e.g. lung function tests, bronchial responsiveness, skin prick tests, serum immunoglobuline E (IgE), inflammation and mutagenetic biomarkers).

The results of the epidemiological surveys on general population samples living in Po Delta and Pisa are summarized in Table 2.

In the early nineties, it became clear that living in the city was associated with more respiratory symptoms and diseases than living in the rural area.[28,29,37,38] Those living in the city had higher bronchial responsiveness as measured by a methacholine dose-response challenge.[39] In particular, city residents had a 41% increased risk of developing airway hyper-responsiveness compared to rural residents. The 41% increase in city-dwellers was similar to the 39% increased risk shown by smokers compared to never smokers.[39]

A cross-sectional spatial analysis of the effects of traffic-related air pollution was carried out in the urban and suburban areas of Pisa, Italy.[40] The house of each participating subject was geo-referenced and people were stratified into three groups according to the distance from the main road: less than 100 meters, 100-250 meters, more than 250 meters. People who lived closest to the traffic had significantly increased risks of respiratory symptoms and diseases and airflow obstruction, as measured by FEV_1/forced vital capacity (FVC). More recently, it was shown that a 10% increase in grey space residential exposure (assessed using CORINE Land cover classes) was significantly related to a higher probability of having allergic biomarkers/conditions and presence of serum antibodies to benzo(*a*)pyrene diol epoxide-DNA (BPDE-DNA) adducts.[41]

The chromosome aberrations (CA) frequency, determined in three samples of healthy individuals (60 living in a rural

Table 2 Air pollution effects in Italy: I) analytical epidemiological surveys (Po Delta and Pisa studies carried out by CNR).

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area
Viegi et al, 1991 (ref. 28)	1) Rural area 2) Suburban-traffic area 3) Urban-traffic area 4) Urban-traffic-industry area	Traffic, industry	Chronic cough prevalence (%)	1) 9 2) 10 3) 11 4) 17
			Chronic phlegm prevalence (%)	1) 9 2) 9 3) 7 4) 14
			Attacks of wheezing with dyspnea prevalence (%)	1) 5 2) 8 3) 9 4) 9
			Dyspnea prevalence (%)	1) 14 2) 22 3) 26 4) 28
			Rhinitis prevalence (%)	1) 5 2) 17 3) 13 4) 25
			Chronic bronchitis or emphysema prevalence (%)	1) 2 2) 5 3) 7 4) 8
			Asthma prevalence (%)	1) 5 2) 7 3) 12 4) 5
Viegi et al, 1999 (ref. 37)	Rural area vs urban-suburban area	Traffic, industry	Cough prevalence (%)	Males 25-64 yrs: 15 vs 21 Males > 64 yrs: 18 vs 37 Females 25-64 yrs: 11 vs 15
			Phlegm prevalence (%)	Males <25 yrs: 13 vs 6
			Wheeze prevalence (%)	Males > 64 yrs: 27 vs 39 Females 25-64 yrs: 14 vs 19
			Attacks of wheeze prevalence (%)	Males <25 yrs: 6 vs 12 Males 25-64 yrs: 5 vs 8 Females 25-64 yrs: 4 vs 6
			Dyspnea grade 1 prevalence (%)	Males <25 yrs: 6 vs 2 Males 25-64 yrs: 17 vs 10 Females <25 yrs: 11 vs 3 Females 25-64 yrs: 29 vs 19 Females >64 yrs: 48 vs 33
			Dyspnea grade 2 prevalence (%)	Females <25 yrs: 6 vs 3
			Chronic bronchitis prevalence (%)	Males 25-64 yrs: 3 vs 5
			Emphysema prevalence (%)	Males 25-64 yrs: 2 vs 8 Males > 64 yrs: 7 vs 22
Viegi et al, 2004 (ref. 38)	1) Rural area 2) Urban-suburban area	Traffic, industry	Obstructive lung diseases prevalence (%)	1) 6.9 2) 10.9
Maio et al, 2009 (ref. 39)	Urban-suburban area vs rural area	Traffic, industry	Bronchial hyper-responsiveness (OR, 95% CI)	1.41 (1.13-1.76)

Table 2 (*Continued*)

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area
Nuvolone et al, 2011 (ref. 40)	Urban-suburban area	Distance from main roads: <100m (a) 100-250m (b)	Persistent wheeze (OR, 95% CI)	Males: (a) 1.76 (1.08-2.87)
			COPD (OR, 95% CI)	Males: (a) 1.80 (1.03-3.08)
			GOLD airway obstruction (OR, 95% CI)	Males: (a) 2.07 (1.11-3.87) (b) 2.53 (1.42-4.53)
			Dyspnea (OR, 95% CI)	Females: (a) 1.61 (1.13-2.27)
			Skin prick test positivity (OR, 95% CI)	Females: (a) 1.83 (1.11-3.0)
Maio et al, 2021 (ref. 41)	Urban - suburban area	10% increase in grey spaces residential exposure Traffic	SPT positivity (OR, 95% CI)	1.07 (1.02-1.13)
			seasonal SPT positivity (OR, 95% CI)	1.12 (1.05-1.19)
			polysensitization (OR, 95% CI)	1.11 (1.04-1.19)
			allergic rhinitis (OR, 95% CI)	1.10 (1.04-1.17)
			co-presence of SPT positivity and asthma/allergic rhinitis (OR, 95% CI)	1.16 (1.08-1.25)
			asthma/allergic rhinitis (OR, 95% CI)	1.06 (1.00-1.12)
			presence of serum antibodies to BPDE-DNA adducts positivity (OR, 95% CI)	1.07 (1.01-1.14)
Milillo et al, 1996 (ref. 42)	Urban - suburban area vs rural area		Chromosome aberrations (mean number %)	In non smokers: Chromosome gaps: 0.35-0.38 vs 0.21 Chromosome breaks: 1.00 — 0.88 vs 0.64 Chromosome rearrangements: 0.18 — 0.18 vs 0.11
Barale et al, 1998 (ref. 43)	Urban area vs suburban area	Traffic	Sister chromatid exchanges (mean ± SD)	Females: 8.87±1.62 vs 6.81±1.35 Males: 8.77±1.65 vs 6.89±1.36
Petruzzelli et al, 1998 (ref. 44)	Urban area vs suburban area	Traffic	Serum antibodies to Benzo(a)pyrene Diol Epoxide-DNA adducts (OR, 95% CI)	1.49 (1.16-1.92)
Maio et al, 2016 (ref. 45)	Urban area vs suburban area	Traffic	Allergic rhinitis (OR, 95% CI)	1.19 (1.05-1.35)
			Usual phlegm (OR, 95% CI)	1.30 (1.12-1.49)
			COPD (OR, 95% CI)	1.54 (1.25-1.90)
Maio et al, 2019 (ref. 46)	Urban-suburban area	Incident vehicular traffic exposure	Asthma attacks incidence (OR, 95% CI)	2.20 (1.00-4.50)
			Allergic rhinitis incidence (OR, 95% CI)	1.80 (1.20-2.80)
			COPD incidence (OR, 95% CI)	2.40 (1.10-5.20)

OR: odds ratio; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

area (Po Delta), 134 in Pisa downtown and 116 in Cascina, a small town near Pisa), was statistically significantly higher in the Pisa sample than in the Po Delta sample.[42] Sister chromatid exchanges (SCE), determined in lymphocytes cultures from 2000 participants, were significantly higher in the urban than in the suburban area.[43] Urban residents were also 49% more likely to have increased serum antibodies to BPDE-DNA adducts, compared to suburban residents.[44]

Three cross-sectional surveys conducted in Pisa and suburbs from 1985 to 2011 have shown increased prevalence rates of respiratory symptoms and diseases, especially allergic rhinitis. Living in the urban area was associated with increased risks for allergic rhinitis (+19%), cough (+14%), phlegm (+30%), and COPD (+54%), compared to those living in the suburban area.[45]

The 18-year cumulative incidence of respiratory and allergic symptoms, diseases and risk factors from the Pisa epidemiological study was published in 2019. The cumulative incidence values ranged from 3.2% for asthma to 31.7% for allergic rhinitis. The incidence of vehicular traffic exposure yielded significantly increased risks for the incidence of asthma attacks (+120%), allergic rhinitis (+80%), and COPD (+140%).[46]

The results of the epidemiological surveys on pediatric population samples living in Palermo and other Italian cities are summarized in Table 3.

A total of 2150 Italian schoolchildren were cross-sectionally investigated through respiratory questionnaire, SPT, and spirometry in Palermo, Sicily.[30] A proportional Venn diagram quantified the distribution of current asthma, rhinoconjunctivitis, and eczema. Avoiding exposures to measured environmental risk factors would prevent 41% of current asthma (15.1% considering only traffic) and 34% of rhinoconjunctivitis (7.8% considering only traffic); avoidance of traffic would also prevent 14.1% of impaired lung function.

More recently, the effects of "green", "grey" and air pollution exposure were simultaneously assessed on respiratory/allergic conditions and general symptoms in Palermo schoolchildren.[47] Exposures to greenness and greyness at the home addresses were measured using the normalized

Table 3 Air pollution effects in Italy: I) analytical epidemiological surveys (other studies with CNR collaboration).

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area
Cibella et al, 2011 (ref. 30)	Urban area	Traffic	Current asthma (OR, 95% CI)	1.84 (1.14 – 2.95)
			Rhinoconjunctivitis (OR, 95% CI)	1.39 (1.08 – 1.79)
			Impaired lung function (OR, 95% CI)	1.78 (1.12 – 2.83)
Cilluffo et al, 2018 (ref. 47)	Urban area	Exposure to NDVI $\leq$0.15 (1st quartile)	Nasal symptoms (OR, 95% CI)	1.47 (1.07-2.03)
		Living in CUF areas	Ocular symptoms (OR, 95% CI)	1.49 (1.10-2.03)
			General symptoms (OR, 95% CI)	1.18 (1.00-1.48)
		Exposure to $NO_2 \geq$ 60 $\mu g/m^3$ (4th quartile)	General symptoms (OR, 95% CI)	1.28 (1.10-1.48)
Ciccone et al, 1998 (ref. 31)	Metropolitan areas of SIDRIA1	Exposure to lorry traffic	Early Respiratory Diseases:	
			Recurrent bronchitis (OR, 95% CI)	1.69 (1.24-2.30)
			Bronchiolitis (OR, 95% CI)	1.74 (1.09-2.77)
			Pneumonia (OR, 95% CI)	1.84 (1.27-2.65)
			Current Respiratory Disorders:	
			Persistent phlegm for > 2 months (OR, 95% CI)	1.68 (1.14-2.48)
			Severe wheeze limiting speech (OR, 95% CI)	1.86 (1.26-2.73)
Migliore et al, 2009 (ref. 48)	Cities in SIDRIA2	High traffic density	Cough or phlegm (OR, 95% CI)	1.24 (1.04-1.49)
			Asthma symptoms (OR, 95% CI)	1.17 (1.03–1.33)
		Continuous car traffic	Cough or phlegm (OR, 95% CI)	1.32 (1.08–1.63)
			Asthma symptoms (OR, 95% CI)	1.16 (1.00–1.33)
		Continuous truck traffic	Cough or phlegm (OR, 95% CI)	1.67 (1.36–2.06)
			Asthma symptoms (OR, 95% CI)	1.27 (1.08–1.50)

NDVI: normalized difference vegetation index; CUF: continuous urban fabric; OR: odds ratio.

difference vegetation index (NDVI), residential surrounding greyness (RSG) and the CORINE land-cover classes (CLC, divided in "discontinuous urban fabric - DUF" - and "continuous urban fabric - CUF"). A very low exposure to NDVI $\leq$ 0.15 (1st quartile), living in CUF areas, living in proximity ($\leq$200 m) to High Traffic Roads (HTRs), and high exposure to NO_2 ($\geq$ 60 $\mu g/m^3$) were associated with nasal, ocular or general symptoms.

The group at CNR also collaborated in the realization of the Italian branch of the International Study on Asthma and Allergies in Childhood (ISAAC), which was named SIDRIA from the acronym of the name in Italian standing for Italian

Table 4 Air pollution effects in Italy: II) use of routine statistics.

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area
Alessandrini et al, 2013 (ref. 50)	25 Italian cities	PM_{10} (10 $\mu g/m^3$ increase)	Natural mortality (% increase, 95% CI)	0.51 (0.16-0.86) (lag 0-1)
			Cardiac mortality (% increase, 95% CI)	0.93 (0.16-1.70) (lag 0-5)
			Respiratory mortality (% increase, 95% CI)	1.41 (-0.23-3.08) (lag 2-5)
		$PM_{2.5}$ (10 $\mu g/m^3$ increase)	Natural mortality (% increase, 95% CI)	0.78 (0.12-1.46) (lag 0-5)
			Cardiac mortality (% increase, 95% CI)	1.25 (0.17-2.34) (lag 0-5)
		NO_2 (10 $\mu g/m^3$ increase)	Natural mortality (% increase, 95% CI)	1.10 (0.63-1.58) (lag 0-5)
			Respiratory mortality (% increase, 95% CI)	1.67 (0.23-3.13) (lag 2-5)
Scarinzi et al, 2013 (ref. 51)	25 Italian cities	PM_{10} (10 $\mu g/m^3$ increase)	Cardiac hospitalization (% increase, 95% CI)	0.34 (0.04-0.63) (lag 0)
			Respiratory hospitalization (% increase, 95% CI)	0.75 (0.25-1.25) (lag 0-5)
		$PM_{2.5}$ (10 $\mu g/m^3$ increase)	Respiratory hospitalization (% increase, 95% CI)	1.23 (0.58-1.88) (lag 0-5)
		NO_2 (10 $\mu g/m^3$ increase)	Cardiac hospitalization (% increase, 95% CI)	0.57 (0.13-1.02) (lag 0)
			Respiratory hospitalization (% increase, 95% CI)	1.29 (0.52-2.06) (lag 0-5)

Studies on Pediatric Respiratory Disturbances and the Environment.

The first population-based survey (SIDRIA1) was conducted in 10 areas of Northern and Central Italy (1994-1995) in two age groups (6-7 and 13-14 years) (n= 39,275).[31] In the metropolitan areas, a high frequency of truck traffic in the street of residence was associated with significantly increased risks for many adverse respiratory outcomes. Among early respiratory diseases, significantly increased risks were found for recurrent bronchitis (+69%), bronchiolitis (+74%) and pneumonia (+84%), as well as for current respiratory symptoms such as persistent phlegm for $>$ 2 months (+68%), and severe wheeze limiting speech (+86%).

The 2nd survey (SIDRIA2) was conducted in 2002 in 12 centers in Northern, Central and Southern Italy, on 33,632 children and adolescents (6-7 and 13-14 years old). Overall traffic density was associated with asthma symptoms but there was a stronger association with cough or phlegm (high traffic density: excess risk of 24%). Car and truck traffic were independently associated with asthma symptoms and cough or phlegm.[48]

II) Use of routine statistics

The results of epidemiological studies using routine statistics in some Italian cities are summarized in Table 4.

A large multicenter study using routinely collected statistics has been carried out in several cities throughout Italy, with the collaboration of CNR. The first survey, EPIAIR (from the acronym of the Italian name standing for Air pollution and health: epidemiological surveillance and prevention interventions), was conducted in ten cities in the period 2001-2005.[32,49]

More recently, the study has been enlarged to include data on 25 cities (EPIAIR2) during the period 2006-2010. An immediate effect of PM_{10} on natural mortality was found. More relevant and prolonged effects (lag 0-5) were found for $PM_{2.5}$ and NO_2. Increases in cardiac mortality were associated with PM_{10} and $PM_{2.5}$, while exposure to NO_2 as well as PM_{10} had an important role in respiratory mortality.[50]

Furthermore, the study has analyzed 2,246,448 urgent hospital admissions for non-accidental diseases in 25 Italian cities during the period 2006-2010. A relationship to an increment of 10 $\mu g/m^3$ of air pollutants was estimated. Increases in cardiac and respiratory hospitalizations were associated with PM_{10} and NO_2.[51]

Notably, pollution reduction actions as prescribed by the European Union legislation, i.e. a 20% reduction up to 20 $\mu g/m^3$ for PM_{10} and up to 18 $\mu g/m^3$ for $PM_{2.5}$, would have saved, overall the cities covered by this study, 42% and 51% of all attributable deaths, respectively.[52]

III) Use of big data

One of the biggest challenges of modern environmental epidemiology is being able to collect and link, in a complex

way, large amounts of geographical, environmental and health data, to obtain comprehensive information otherwise not available. Within this context, the Italian National Insurance Institute against Work-related Accidents (INAIL) has funded a project named "Big data in environmental and occupational epidemiology" (BEEP) (acronym from the Italian "Big data in Epidemiologia ambiEntale ed occuPazionale") (2017-2019).

The main goal of the BEEP project has been to estimate, through BIGDATA methodology, the health effects of air pollution, noise and meteorological parameters on the Italian general population. The project consists of specific objectives focused on different special domains, from the whole nation to the urban micro-scale.

Some publications have been so far realized: their results are summarized in Table 5.

One has dealt with the improvement of the estimation of NO_2, O_3, $PM_{2.5}$ and PM_{10} concentrations in 6 Italian metropolitan areas, using chemical-transport and machine learning models, and assessment of the exposure

Table 5 Air pollution effects in Italy: III) the use of big data.

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area
Gariazzo et al, 2021 (ref. 54)	Metropolitan area	PM_{10} (IQR increase) (200m resolution)	Natural mortality (HR, 95% CI)	1.020 (1.008-1.031)
			Cardiovascular mortality (HR, 95% CI)	1.042 (1.024-1.061)
		NO_2 (IQR increase) (200m resolution)	Natural mortality (HR, 95% CI)	1.018 (1.007-1.028)
			Cardiovascular mortality (HR, 95% CI)	1.037 (1.020-1.055)
Marinaccio et al, 2019 (ref. 55)	Italy	Heat	Occupational injuries (RR, 95% CI)	1.17 (1.14-1.21)
		Cold	Occupational injuries (RR, 95% CI)	1.23 (1.17-1.30)
Renzi et al, 2021 (ref. 56)	Italy	PM_{10} (10 $\mu g/m^3$ increase) at lag 0-5 days	Total respiratory diseases (% difference of risk, 95% CI)	1.20 (0.92-1.49)
		$PM_{2.5}$ (10 $\mu g/m^3$ increase) at lag 0-5 days	Total respiratory diseases (% difference of risk, 95% CI)	1.22 (0.76-1.68)
Fasola et al, 2020 (ref. 57)	Urban area	PM_{10} (unit increase) (1Km resolution)	Incidence of COPD (OR, 95% CI)	2.96 (1.50-7.15)
		$PM_{2.5}$ (unit increase) (1Km resolution)	Incidence of rhinitis (OR, 95% CI)	2.25 (1.07-4.98)
			Incidence of chronic phlegm (OR, 95% CI)	4.17 (1.12-18.71)
Fasola et al, 2021 (ref. 58)	Urban area	PM_{10} (10 $\mu g/m^3$ increase) (1Km resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.268 (1.085-1.483) (lag 0)
		PM_{10} (10$\mu g/m^3$ increase) (200m resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.365 (1.103-1.690) (lag 0)
		$PM_{2.5}$ (10 $\mu g/m^3$ increase) (1Km resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.273 (1.053-1.540) (lag 0)
		$PM_{2.5}$ (10 $\mu g/m^3$ increase) (200m resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.264 (1.006-1.589) (lag 0)
		NO_2 (10 $\mu g/m_3$ increase) (200m resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.477 (1.058-2.061) (lag 0)

IQR: interquartile range; HR: hazard ratio; RR: relative risk; OR: odds ratio; COPD: chronic obstructive pulmonary disease

effect on population by using information on urban population mobility.[53]

Another paper has aimed to compare the effect estimates of the long-term exposure of air pollutants on cause-specific mortality in the Rome Longitudinal Study, using exposure estimates obtained with different modelling techniques and spatial resolutions (from 4 m to 1 Km). All the exposures were assigned to the residential addresses of 482,259 citizens of Rome 30+ years of age who were enrolled in 2001 and followed up until 2015. Natural cause and cardiovascular diseases (CVD) mortality outcomes were all positively associated with the interquartile range (IQR) of NO_2 and PM_{10} with a tendency of larger effect for lower resolution exposures.[54]

A nationwide epidemiological study has also been carried out to estimate the risk of injuries for workers exposed to extreme temperatures and identify economic sectors and jobs most at risk. The study considered 2,277,432 occupational injuries occurred in Italy in the period 2006-2010 and showed a significant increase of occupational injury for heat and cold exposure.[55]

Nationwide data of air pollution from PM and daily hospitalizations for respiratory diseases in Italy have been recently published.[56] A total of 4,154,887 respiratory admissions were registered during 2006-2015, of which 29% for lower respiratory tract infections, 12% for COPD, 6% for upper respiratory tract infections, and 3% for asthma. Daily mean PM_{10} and $PM_{2.5}$ concentrations over the study period were 23.3 and 17 $\mu g/m^3$, respectively. Excess risks of total respiratory diseases, stronger for asthma and COPD, in association with a $\mu g/m^3$ PM_{10} increase were found. Higher effects were reported in the elderly and in less urbanized areas. In addition, the compliance with a theoretical daily PM_{10} standard of 25 $\mu g/m^3$, a value suggested by 2005 WHO annual guideline, would have avoided about 4,900 respiratory admissions. Similarly, a total of 8,917 admissions were attributable to $PM_{2.5}$ daily concentrations exceeding 10 $\mu g/m^3$ in 2013-2015.

Using data from the longitudinal analytical epidemiological study in Pisa, individual risk factors recorded during the 1991 survey were considered, and new cases of respiratory diseases were ascertained until 2011. Average PM_{10} and $PM_{2.5}$ exposures ($\mu g/m^3$, year 2011) were estimated at the residential address (1-km^2 resolution) on the subsample of subjects living at the same address from 1991 to 2011. Significantly increased risks of incidences of rhinitis and chronic phlegm were associated with increasing $PM_{2.5}$ and an increased risk of incidence of COPD was associated with increasing PM_{10}.[57]

In another recently published study in Pisa, exposure effects were estimated using the case-crossover design and conditional logistic regression (OR 95% CI for 10 $\mu g/m^3$ increase; lag 0-6). During the period 2013-2015 (69 cardiovascular hospitalizations), significant effects at lag 0 were observed for PM_{10} and $PM_{2.5}$ at 1 km resolution, as well as for $PM_{2.5}$ and NO_2 at 200 m resolution; significant effects were observed up to lag 2. Larger ORs were observed in males and in subjects reporting pre-existent cardiovascular/respiratory diseases.[58]

The results of the BEEP project, beyond opening new scientific research perspectives which are being pursued within the ongoing INAIL - BIGEPI project (https://bigepi.it/index.php/en/), have provided useful indications for public decision-makers in the field of air quality, planning of urban environments and public health protection.

Discussion

General update

We acknowledge that the approach to the literature search was not systematic and there was no formal qualitative appraisal of the retrieved evidence; however, we have summarized below some considerations, and suggestions for future research in the field.

Among the included meta-analyses, when bi/multi-pollutants models were used pooled risk estimates generally decreased or lost statistical significance, due to known high correlation between air pollutants. No evaluation of specific PM compositions, especially as adsorbed toxicants, was performed. Toxicity assessment of PM is currently typically based on mass concentration rather than the physicochemical properties of the constituents, and this may hamper evaluation of underlying etiopathogenetic pathways of respiratory diseases.

A few studies evaluated dose-response relationships; usually, they appeared linear and with no threshold identified of no effect as previously reported,[59] highlighting the concept that even in countries where governmental exposure limits are enforced, no safe levels of air pollution exist.

There was a limited adjustment for potential confounders. For example, in relation to COPD risk, an important effect of adjustment for occupational exposures was reported in air pollution studies[60] as a key determinant of socioeconomic status. Among the included meta-analyses, less than half of them were adjusted or restricted for occupational confounders.[12,18,19,23,24] High heterogeneity between studies emerged, especially among those evaluating long term NO_2 exposure,[11,17,18] making pooled estimates less reliable. Identification of variability sources via meta-regression was hampered by the limited number of included studies.

Studies conducted in LICs are still limited both in quality and quantity of available data.[12] Instead, further studies in these countries should be encouraged given the likely higher level of pollution from industrial sources and lack of stringent air pollution regulations.[61] Also, further studies should focus on the potential link between air pollution exposure and respiratory infection diseases. Only one meta-analysis reported estimates for infectious outcomes.[12] This topic has become particularly important in the current SARS-COV-2 pandemic which has generated the debated hypothesis that air pollution may act as a booster and even a carrier of the virus, so increasing infection susceptibility and severity and subsequent mortality from the COVID-19 disease.[62] Further research on how these two silent killers interact in increasing global morbidity and mortality is warranted.

Italian perspective

The Global Alliance against chronic Respiratory Diseases (GARD) was launched in Beijing on March 28, 2006, as a partnership among the WHO, governmental institutions,

scientific societies and patients' associations. The GARD motto is "a world where all people breathe freely." Air pollution is one of the most important risk factors to health and reducing it is a priority for the prevention and control of chronic respiratory diseases.[63]

The GARD initiative in Italy was launched on June 11, 2009, at the Ministry of Health, which assumed the role of national coordinator. Its main objective is to promote the development of a coordinated Chronic Respiratory Diseases program in Italy. Effective prevention implies setting up health policies against tobacco smoking, indoor/outdoor pollution, obesity, and communicable diseases, with the support of healthcare professionals and citizen associations at national, regional, and district levels. Respiratory diseases prevention cannot and should not be the responsibility of doctors alone, but must involve politicians/policymakers, as well as the media, local institutions, and schools.[64] The Italian government, GARD, scientific societies, and other members of the health community must increase their engagement in advocacy for clean air.

Awareness of environmental exposures is increasing in the general population and assisted by the use of the risk charts, such as those for COPD elaborated in collaboration with the National Institute of Health.[65] The charts let people calculate their risk of getting COPD in the next ten years, based on gender, age, smoking habits and environmental exposures.

Conclusions

Air pollution is an avoidable health risk that places a great burden on society in terms of death and health disorders, at a huge social and economic cost. Within Europe, the southern countries face a difficult situation because they experience the effects of anthropogenic and natural air pollution.

The air quality standards of the EU are laxer than the WHO AQG published in 2005 and studies have shown significant health effects even below the most stringent current standard. The differences between the EU and the WHO recommended values are now much larger after the publication of the new WHO AQG[33] on September 22, 2021, indicating levels that are largely lower than the previous ones.

Based on abundant evidence, the Italian government, which hosts the Global Alliance against Chronic Respiratory Diseases (GARD)-Italy at the Ministry of Health, the scientific respiratory societies and the patients' associations, as well as others in the health sector and in civil society, must increase their engagement in advocacy for clean air policies, especially in light of the new WHO AQG.

Conflicts of interest

None.

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REVIEW

Pulmonary tuberculosis in intensive care setting, with a focus on the use of severity scores, a multinational collaborative systematic review

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Abstract
Background and aim: Tuberculosis (TB) is associated with a high mortality in the intensive care unit (ICU), especially in subjects with Acute Respiratory Distress Syndrome (ARDS) requiring mechanical ventilation. Despite its global burden on morbidity and mortality, TB is an uncommon cause of ICU admission, however mortality is disproportionate to the advances in diagnosis and treatment made. Herein we report a systematic review of published studies.
Methods: Our Literature search was conducted to identify studies on outcomes of individuals with TB admitted to ICU. We report and review in-hospital mortality, predictors of poorer outcomes, usefulness of severity scoring systems and potential benefits of intravenous antibiotics. Searches from Pubmed, Embase, Cochrane and Medline were conducted from inception to March 2020. Only literature in English was included.
Results: Out of 529 potentially relevant articles, 17 were included. Mortality across all studies ranged from 29-95% with an average of 52.9%. All severity scores underestimated average mortality. The most common indication for ICU admission was acute respiratory failure (36.3%). Negative predictors of outcome included hospital acquired infections, need of mechanical ventilation and vasopressors, delay in initiation of anti-TB treatment, more than one organ

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failure and a higher severity score. Low income, high incidence countries showed a 23.4% higher mortality rate compared to high income, low TB incidence countries.
Conclusion: Mortality in individuals with TB admitted to ICU is high. Earlier detection and treatment initiation is needed.

Introduction

Tuberculosis (TB) was within the top ten causes of death and second cause of death from a single infectious agent worldwide in 2020.[1–4] The aim of treatment is to reduce the incidence of resistance and achieve full bacterial clearance, thereby limiting the risk of transmission.[5,6] Success of drug susceptible TB under trial conditions is up to 95% in non-critical subjects; this success is underpinned by adequate concentrations of these drugs in the blood.[7]

Although TB most commonly manifests sub-acutely or chronically, some individuals especially those with extensive disease may progress rapidly, requiring admission to intensive care unit (ICU). Up to 3% of all patients with TB require ICU admission, a high proportion considering the availability of curative treatment.[8] The most common indication for ICU admission is respiratory failure and acute respiratory distress syndrome (ARDS).[9–11] The mortality for TB patients admitted to ICU is extremely high, more than any other cause of respiratory failure including pneumonia.[12] Reported mortality rates are variable across studies, and can range from 24% to 81% in individuals requiring mechanical ventilation.[13] The mortality for ARDS secondary due to TB has not changed significantly over time, despite advances in new treatment regimens and ventlilatory strategies in ICU. The heterogeneity of disease presentation and the difficulty in diagnosis remain a challenge. Co-morbidities including HIV, immunosuppressive disorders and diabetes increase the risk of complications in patients with TB.[9] Poor prognostic indicators include high Acute Physiology And Chronic Health Evaluation II (APACHE II) or Simplified Acute Physiology Score (SAPS) II scores, nosocomial infections, sepsis and delayed start of anti TB treatment.[14] The full extent of the association of TB with Covid-19 and the risk of admission to ICU and the need for mechanical ventilation is currently not known.[15–18]

Delays in diagnosis and treatment of pulmonary TB are principal causes of death, especially in patients with acute respiratory failure.[11,19,20] Early diagnosis and start of effective treatment is needed to prevent ICU admission and complications.[9] It is imperative that the absorption of anti-TB treatment is maximised; a challenge in the critically ill individual. Deranged physiological functioning and poor gastric absorption can lead to sub-therapeutic drug levels.[21] Intravenous antibiotics may overcome these obstacles. Despite the bioavailability of parenteral routes, the use of intravenous antimicrobials is seldom used in TB. If intravenous rifampicin, was more widely available, it may negate the need for more toxic regimens.

Severity scoring systems such as APACHE II have been proven to predict mortality in individuals admitted to ICU.[22] This may not be the case for individuals with TB related ARDS and septic shock, as some studies have suggested they consistently underestimate mortality in these groups.[23,24] The low prevalence of TB in ICU is a further challenge. In published studies, small sample sizes limit the potential generalisation of results.[25] Further research and studies with larger patient groups are needed.

This review aims to identify factors affecting poor outcomes and mortality of individuals with pulmonary TB admitted to ICU. Further objectives include identifying factors leading to TB-related complications, the relevance of ICU severity scores and the role of using first line intravenous anti-TB drugs in critically ill subjects. We hypothesise that identifying predictors of poor outcomes in TB patients admitted to ICU can contribute to risk stratification and personalised treatment.

Methods

Search strategy

To avoid any influence of the effects of pandemic on recent publications,[26] Pubmed, EMBASE, Cochrane and Medline databases were searched from inception until March 2020. Keywords included: ("Outcome*" or "mortality" or "impact" or "recovery" or "effect*") and ("Mycobacterium tuberculosis" or "tuberculosis" or "TB" or 'MTB") and ("intensive care unit*" or "intensive treatment unit*" or "critical care" or "CCU" or "ARDS" or "Acute respiratory distress syndrome" or "mechanical ventilation" or "respiratory failure") and ("scor*" or "severity" or "APACHE" or "APACHEII" or "GCS" or "SOFA" or "SAPS" or "Charlson"), "Intravenous" or "antibiotic*" or "Rifampin" or "Isoniazid" or "ethambutol" or "Pyrazinamide".

Study selection

Published studies were included if they reported on outcomes of cohorts of patients with pulmonary TB admitted to ICU Studies involving, individuals $<$ 18 years and those involving $<$10 patients were excluded. Conference abstracts, posters, patient case studies and articles with no reported outcomes were excluded.

In the first stage, we screened the titles and abstracts of all citations for potentially relevant papers. In the second stage, we examined in detail the full texts of the retrieved papers.

Data extraction

Information on study design, setting, population characteristics including comorbidities, reason for ICU admission as well

as ICU outcomes were obtained (see Table 1). Factors affecting outcomes were also recorded in a separate Table 2, and including information on mechanical ventilation, length of hospital and ICU stay, ICU related complications were obtained. Tuberculosis related outcomes such as time to initiation of anti-TB treatment, drug susceptibility pattern, concomitant treatments, were recorded (Table 2). All ICU related severity scores were recorded. (Table 3).

Quality assessment of included studies

The Newcastle-Ottawa assessment scale (NOS) for cohort studies was used to assess study quality and risk of bias.[35] The Newcastle-Ottawa assessment scale evaluates three parameters; selection, comparability and outcome, awarding a certain number of points. The maximum number a study can receive is 9 points, indicating low risk of bias. Less than 5 points indicate a high risk of bias. The outcome used for the checklist was mortality.

Fig. 1. PRISMA flow diagram of selected studies.

Results

Characteristics of the studies

Seventeen out of 529 studies fulfilled the inclusion criteria and were included in the review. The studies ranged from 1995 to 2018. The studies included were from high (South Africa, South Korea, India) and low/intermediate TB incidence countries (Canada, Germany, Taiwan, France, Turkey, Portugal). All studies were retrospective except Balkema et al.[29] which was prospective. A total of 947 cases with active pulmonary TB who required ICU admission were included across all studies, of which 652 were male.

Quality of studies

Quality of studies was generally high when assessed using NOS checklist. Selection bias across studies was greatest risk due to clinician selected cohort groups, with small sample sizes. All had follow up resulting in outcomes with all subjects accounted for, and outcomes were clearly defined in all studies. No study had an overall outcome <7 points indicating low risk of bias (Table 4).

To aid an inclusive qualitative analysis, the averages of medians and means were calculated, with each study weighted equally, regardless, of the number of cases. The mean or median age of cases ranged between 31.6−76.9 years with 12/17 studies having a mean/median age $>$ 41 years. Common comorbidities included HIV co-infection (27.1%), alcohol abuse (12.5%), diabetes (7.7%) and malnourishment (5.0%). 21% of cases were smokers. Thirty-eight% of cases had a diagnosis of TB prior to ICU admission. The most common indication for ICU admission was respiratory failure and ARDS (36.3%) followed by pneumonia (9.3%), sepsis (4.3%) and massive haemoptysis (3.8%).

Acute Physiology and Chronic Health Evaluation II was the most commonly used scoring system, reported in 13 studies, however SAPS II, quick Sequential Organ Failure Assessment (qSOFA) which identifies high-risk patients for in-hospital mortality with suspected infection outside the ICU and the Glasgow Coma Scale (GCS) were also used across the studies. The average of the mean APACHE II score was 20.2 and median 19.1, across 8 and 6 studies, respectively. The average of the median SAPS II score was 42.8 across 4 studies and median SOFA was 5.8 across 6 studies. The mean and median values for severity scores were consistently higher in fatalities than survivors in all studies except for Pecego et al. with survivors having a higher SAPS II score (Table 3).[36] The average of the mean APACHE II score was 22 and 16.4 for fatalities and survivors, respectively across 5 studies. The average of the median of these scores were 23.3 and 16.5 for fatalities and survivors, respectively, across 5 studies.

Individuals requiring mechanical ventilation ranged from 37.5% to 100%. Across all studies 67.2% of cases required mechanical ventilation and the duration in days was 14.5 and 13.25 days for the median and mean values, respectively. There was a large variation for example Erbes et al. provide a mean of 26 and a range of 1-106,[14] similarly Lanoix et al.[30] provide a median of 8 with an interquartile range (IQR) of 1-129.

Duration of hospital stay was reported in 9 studies. The average of the median was 20.2 days across 6 studies and for the mean 51.2 days across 3 studies. The duration of ICU stay was reported in 14 studies, the average of the median was 7.8 days across 9 studies and mean was 15.6 across 4 studies. Similarly, for the duration of stay for both hospital and ICU, there was a large spread of data throughout some studies, reflected by the large interquartile ranges in Table 2.

Delay in initiation of anti TB treatment (ATT) within hospital was only reported in 8 studies, the lowest being 0 days and the largest mean value was 45 days in Penner et al.[27] The prevalence of drug resistance pattern was reported in 11 studies and ranged between 0% to 28.6%, 4.9% of cases having drug resistant strains when combining all studies. Steroids were given to 11.5% of cases and vasopressor support was given to 15.0% of cases. Other treatment management was given to a smaller number of individuals including extracorporeal membrane oxygenation, tracheostomy and renal replacement therapy.

The most common reported complication was ARDS affecting 19.5% of all cases, followed by ventilator associated pneumonia (10.8%), multiple organ failure (10.5%), sepsis (9.5%) and hospital acquired infections (8.2%). Other reported complications included shock, disseminated intravascular coagulation, acute kidney infection, single organ failure and pneumothorax. In-hospital mortality ranged from 29% to 95.1% giving a mortality rate of 52.9% across all studies. In two studies a lower ratio of arterial oxygen tension to fractional inspired oxygen (PaO_2/FiO_2) indicated a poorer prognosis.[38,33] Causes of death were reported in 6 studies with septic shock and organ failure (including respiratory failure) with, respective values of 4.7% and 3.8% of total cases as the most common causes. Other causes of death included hospital acquired infection, raised intracranial pressure, pulmonary embolism and hypoxaemia.

No studies using first line intravenous anti TB medications in ICU were found.

Table 1 Studies of patients with tuberculosis in the intensive care setting.

Study	Country *(incidence per 100.000)*	Study Duration	Study Design	Patients *n*	Mean* age of patients (years)	M:F	Co-morbidities *n* (%)	TB diagnosis before ICU admission *n* (%)	Indication for ICU admission
Penner et al [27] (1995)	Canada *(6)*	1984–1994	Retrospective	13	47 ± 14.0	6:7	Alcohol abuse 6 (46.2) Malnourished 7 (53.8)	7 (53.8)	NR
Erbes et al [14] (2006)	Germany *(7)*	1990–2001	Retrospective	58	44.7 ± 17.7	36:12	Malnourished 30 (51.7) Liver damage 38 (65.5) Alcohol abuse 35 (60.3) Smoking 40 (69.0)	46 (79.3)	ARDS 47 (81.1%)
Sharma et al[20] (2006)	India *(199)*	1980–2003	Retrospective	29	31.6 ± 10.9	16:13	Liver damage 11 (39.3) Alcohol abuse 3 (10.3) Diabetes 2 (6.9) Pregnancy/post partum 4 (13.8)	6(19)	NR
Ryu et al [7] (2006)	Korea *(66)*	1995–2005	Retrospective	32	**69 (25–88)**	20:12	Diabetes 4 (12.5) Tuberculosis destroyed lung 4 (12.5) Immunosuppressive therapy 5 (15.6)	6 (19)	NR
Lin et al [28] (2009)	Taiwan *(61)*	2004–2005	Retrospective	59	76.9 ± 9.8 (F) 70.8 ± 18.9 (S)	46:13	COPD 12 (20.3) CHF 11 (18.6) DM 13 (22.0) Chronic steroid use 13 (22.0) Malignancy 12 (20.3)	NR	NR
Valade et al [13] (2012)	France *(9)*	2000–2009	Retrospective	53	41 [32–52]	40:13	HIV 12 (23.6) Smoking 32 (60.4) Alcohol use 22 (41.5) IVDU 6 (11.3)	40 (75)	NR
Balkema et al [29] (2014)	South Africa *(520)*	2012–2013	Prospective	83	36.5 ± 12.9	38:45	HIV 44 (53) DM 9 (10.8) COPD 6 (7.2)	32 (38.6)	ARDS 56 (67.5)
Lanoix et al [30] (2014)	France *(9)*	2000–2009	Retrospective	97	47.4 ± 14.7	77:20	HIV 40 (41.2)	NR	Sepsis 7 (7.2) ARF 42 (43.3) Neurological disorder 25 (25.8) Haemoptysis 7 (7.2)
Rollas et al [8] (2015)	Turkey *(16)*	2009–2014	Retrospective	16	45 [24–74]	9:7	Immunosuppression 8 (50) Heart failure 2 (12.5)	NR	Neurological 5 (31.3) Sepsis 5 (31.3) Haemoptysis 1 (6.3) ARF 5 (31.3)
Filiz et al [31] (2016)	Turkey *(16)*	2010–2013	Retrospective	35	47 [16–83]	27:8	DM 8 (22.9) Silicosis 2 (5.7)	NR	ARF 20 (57.1) Sepsis 7 (20) Massive haemoptysis 3 (8.6) Extrapulmonary TB 3 (8.6)

Table 1 (*Continued*)

Study	Country *(incidence per 100.000)*	Study Duration	Study Design	Patients *n*	Mean* age of patients (years)	M:F	Co-morbidities *n* (%)	TB diagnosis before ICU admission *n* (%)	Indication for ICU admission
Kim et al [21] (2016)	Korea *(66)*	2011–2014	Retrospective	41	**56.3 [47–73]**	35:6	Hypertension 6 (14.6) DM 5 (12.2) Liver damage 4 (9.8) Malignancies 3 (7.3)	10 (24.4)	NR
Duro et al [32] (2017)	Portugal *(24)*	2007–2014	Retrospective	39	**52 (37.5-62.8)**	29:10	Immunodeficiency 18 (46.2) Smoking 13 (33.3) Alcohol abuse 8 (20.5) Drug addiction 9 (23.1) COPD 8 (20.5) Malnourished 10 (25.6)	39 (100)	ARF 20 (51.3) Septic shock 8 (20.5) Post surgical 5 (12.8) Post CPR 4 (10.3) LOC 2 (5.1)
Kim et al [33] (2018)	Korea *(66)*	2005–2016	Retrospective	125	66 (57-74)	104:21	Smoking 59 (47.2) Diabetes 25 (20.0) Hypertension 31 (24.8) CHD/CVD 40 (32.0) Chronic lung disease 53 (42.4) Liver disease 8 (6.4) Chronic kidney disease 5 (4.0) Malignancy 13 (10.4)	NR	Pneumonia 73 (58) Acute exacer-bation 20 (16) Haemoptysis 19 (15)
Muthu et al [34] (2018)	India *(199)*	2001–2016	Retrospective	63	37.3 ± 19	27:36	NR	55 (87.3)	NR
Tatar et al [19] (2018)	Turkey *(16)*	2004–2010	Retrospective	40	55 (43-63)	33: 7	Smoking 22 (55) COPD 12 (30) Diabetes 7 (17.5) Cardiovascular disease 3 (7.5) Psychiatric disorder 3 (7.5)	7 (17.5)	ARF 40 (100)

Table 2 Summary of studies showing patient variables and outcomes in ICU.

Study	ICU Severity score	Invasive MV *n* (%)	Duration of MV (d)	Duration of hospital stay (d)	Duration of ICU stay (d)	Delay in ATT (d)	DR*n* (%)	Additional treatment *n* (%)	ICU complications *n* (%)	In-hospital/ ICU Mortality *n* (%)	Predictors of fatality	Cause of death *n* (%)
Penner et al [27] (1995)	APACHE II, 26 ± 4	13 (100)	15 ± 10	50 ± 35	19 ± 12	45 ± 33	0 (0)	Steroids, 8 (61.5%)	Sepsis, 6 (46.2) MOF, 6 (46.2) Pneumothorax 2, (15.4) DIC, 1 (7.7) ARDS, 8 (6.2)	9 (69.0)	NR	MOF 6 (46.2) RF 3 (23.1)
Erbes et al [14] (2006)	APACHE II, 13.1 ± 5.6	22 (37.9)	26 (1-106)	87.1 (3-340)	21.6 (3-229)	0	7 (12.1)	Steroids, 40 (68.9)	ARDS 7 (12.1) Pneumothorax 8 (13.8) ARF 7 (12.1) Sepsis 15 (25.8) MOF 2 (3/4) HAI 39 (67.2)	15 (25.9)	ARF, MV, Chronic pancreatitis, Sepsis, ARDS, Nosocomial pneumonia	NR
Sharma et al [20] (2006)	APACHE II, 18.5 ± 5.7	23 (79.3)	**5 (3-26)**	**14 (3-90)**	**7 (3-90)**	NR	NR	Steroids, 6 (20.7)	UTI 5 (17.2) DIC 5 (17.2) MOF 4 (13.8) Pneumothorax 1 (3.4)	12 (41.4)	APACHE II>18, hyponatremia PaO2/FiO2 ratio <108.2	NR
Ryu et al [7] (2006)	APACHE II, **16 [8-36]**	32 (100)	9 (2-86)	**20 (4-144)**	**11 (2-18)**	**2 (1-43)**	2 (6.3)	NR	ARDS 9 (28.1) MOF 7 (21.9) HAI 9 (28.1) Sepsis 16 (50)	19 (59)	APACHE II >20, TDL, Sepsis	NR
Lin et al [28] (2009)	APACHE II, 21±6.5	59 (100)	NR	NR	NR	NR	3 (5.1)	NR	VAP 29 (49.1) ARF 6 (10.2) GI bleed 14 (25)	40 (67.8)	MOF, Nosocomial pneumonia, treatment delay >30d	NR
Valade et al [13] (2012)	GCS, **14 [12-15]** SAPS II, **31 [22-50]**	24 (45)	6 (3-17)	NR	**6 [3-16]**	3 (0-21)	2 (3.8)	Vasopressor 15 (28)	HAI 11 (21) VAP 11 (20.8)	20 (38)	Miliary TB, MV and vasopressor requirement	Organ failure 5 (9.4) HAI/co-infection 14 (26.4) PE 1 (1.9)
Balkema et al [29] (2014)	APACHE II, 20.7 ± 8.3	NR	NR	NR	11.9 (1-56)	1.6 (0-17)	3 (3.6)	NR	ARDS 26 (31.3) Renal failure 31 (37.3) VAP 19 (22.9) Septic shock 23 (27.7) DIC 15 (18.1) MODS 25 (30.1) Haemoptysis 14 (16.9) CAP 38 (45.8)	49 (59)	CD4 <200 Absent lobar consolidation Higher APACHE score, ARF	NR
Lanoix et al [30] (2014)	SAPS II, **38 [6-121]** SOFA, **4 [0-17]**	45 (46.4)	**8 [1-129]**	NR	**7 [3-15.5]**	NR	8 (8.25)	Steroids 32 (33) Vasopressor 36 (37.1)	VAP 18 (40)	32 (33.3)	Higher SAPS II/ SOFA score, 2+ infections, MV, ARDS, RRT Vasopressor support, Low GCS Lymphocytopenia	
Rollas et al [8] (2015)	APACHE II, **21.5 (6-36)** SOFA, **6 (1-**	10 (62.5)	**7 (3-45)**	**41 (6-122)**	**10.5 (5-122)**	1 (0-20)	1 (6.3)	NR	Hypoproteinaemia HAI 8 (50)	VAP 7 (7.2) 7 (43.8)	Sepsis, MV requirement, HAI, higher APACHE II	Septic shock 5 (31.3)

Table 2 (*Continued*)

Study	ICU Severity score	Invasive MV *n* (%)	Duration of MV (d)	Duration of hospital stay (d)	Duration of ICU stay (d)	Delay in ATT (d)	DR*n* (%)	Additional treatment *n* (%)	ICU complications *n* (%)	In-hospital/ ICU Mortality *n* (%)	Predictors of fatality	Cause of death *n* (%)
	12) GCS, **11 (3-15)**											ARF 2 (28.6)
Filiz et al [31] (2016)	APACHE II, **18 (7-32)** SOFA, **6 (1-14)**	24 (68.6)	NR	NR	NR	NR	10 (28.6)	NR	Shock 19 (54.3) MOF 17 (48.6) ARF 13 (37.1)	20 (57.1)	Shock, MOF, MV, DR	NR
Kim et al [21] (2016)	Charlson, 0.76 ± 1.28 APACHE II, 20 ± 6.7 SOFA, **7 (4-9)**	41(100)	**6.3 [3-14]**	**13.2 [7-28]**	**7.8 [3-17]**	**1**	4 (9.8)	NR	ARDS 19 (46.3) VAP 15 (36.6) Sepsis 30 (73.2) Shock 38 (92.7) AKI, 12 (29.3) MOF, 27 (65.9)	39 (95.1)	NR	Hypoxemia 9 (23.1) Septic shock 16 (41.0) MOF 14 (35.9)
Duro et al [32] (2017)	APACHE II, 26 ± 15.75 SAPS II, **55 [27.5]**	29 (74.4)	**17 [39]**	NR	NR	0 [4]	NR	Steroids 5 (12.8) Vasopressor 21 (53.8) ECMO 2 (5.1)	ARDS 7 (17.9) ARF 8 (20.5) MODS 11 (28.2) HAI 11 (28.2)	21 (53.8)	Delayed ATT >3d post ICU admission MODS/Sepsis HAI	NR
Kim et al [33] (2018)	APACHE II **19 [15-24]** SOFA, **8 [4-11]**	125 (100)	**8 [5-17]**	**20 [12-43]**	**11 [7-18]**	NR	NR	Vasopressor 58 (46) RRT 10 (8)	NR	46 (37)	Age, vasopressor use, low PaO2/FiO2 ratio, BNP	NR
Muthu et al [34] (2018)	APACHE II, 16.1 ± 7.2 SOFA, 1.8 ± 1.6	56 (88.9)	7.5 ± 9.1	16.4 ± 1.2	9.8 ± 11.4	NR	NR	Tracheostomy 9 (14.3) Steroids 18 (28.6)	ARDS 18 (28.6) VAP 10 (15.9) Pneumothorax 4 (5.8)	28 (44.4)	Baseline APACHE and SOFA score higher,	Severe sepsis 16 (25.4) Raised ICP 7 (11.1) Hypoxemia 5 (7.9)
Tatar et al [19] (2018)	APACHE II, **22 [15-26]**	30 (75)	**4 [2-18]**	**13 [5-27]**	**5 [2-18]**	NR	1 (2.5)	NR	ARDS 40 (100) ARF 6 (15) Cardiac failure 8 (20) Hepatic failure 4 (10)	29 (72. 5)	APACHE II >18 Dyspnoea Need for MV 1+ organ failure	NR

n= number of patients (d)=days
Incidence is reported as estimated rate of tuberculosis per 100,000 from gov.org last updated 2019 (high incidence is > 40/100,000)
All averages are mean ± SD unless stated otherwise; Median is signified in **bold** with (range) or [IQR]
APACHE II is worst score in 24 h of admission
Mortality is reported as 'in-hospital mortality' unless stated otherwise
F: fatalities
S: survivors
NR: data not reported
MV: mechanical ventilation
DR%: percentage of patients with drug resistant strains
ATT= anti-tuberculosis treatment
ARDS= acute respiratory distress syndrome
VAP=ventilator assisted pneumonia

Table 3 Severity scoring for survivors vs fatalities.

Study	Severity Score	All patients	Survivors	Fatalities
Erbes et al [14] (2006)	APACHE II	13 ± 5.6	12.3 ± 5.8	15.7 ± 4.1
Lin et al [28] (2009)	APACHE II	21 ± 6.5	17.0 ± 5.8	23.2 ± 5.8
Valade et al [13] (2012)	SAPS II	31 (22–50)	28 (20–34)	50 (36–69)
Balkema et al [29] (2014)	APACHE II	20.7 ± 8.3	18.1 ± 7.4	22.6 ± 8.5
Lanoix et al[30] (2014)	SAPS II	38 (6-121)	33.58 ± 16.46	64.24 ± 26.42
	SOFA	4 (0–17)	3 (0–15)	11 (0–17)
Rollas et al [8] (2015)	APACHE II	21.5 (6–36)	17 (6–29)	27 (18–36)
	SOFA	6 (1–12)	4 (1–9)	9 (4–12)
Filiz et al [31] (2016)	APACHE II	18 (7–32)	14 (7–21)	22 (16–32)
	SOFA	6 (1–14)	2.5 (1–7)	9 (2–14)
Duro et al [32] (2017)	APACHE II	26 (15.75)	20.5 (17)	30 (12.75)
	SAPS II	55 (27.5)	42.5 (38.50)	58.0 (23.5)
Kim et al [33] (2018)	APACHE II	19 (15–24)	18 (15–23)	21 (18–28)
	SOFA	8 (4–11)	7 (4–10)	9 (7–11)
Muthu et al [34] (2018)	APACHE II	16.1 ± 7.2	14.2 1 ± 5.8	18.5 1 ± 8.2
	SOFA	1.8 ± 1.6	1 (1.4)	2.8 (3.3)
Tatar et al [19] (2019)	APACHE II,	22 (15–26)	17 (15–22)	23 (20–26)

Discussion

Acute respiratory failure, although a rare complication of TB, carries a high fatality rate. There is little research focus on the outcomes and factors affecting mortality in these patient groups, thereby hindering the ability of clinicians to change clinical practice and improve prognosis.

Mortality and ARDS

In this systematic review, average in-hospital mortality across 17 studies was 52.9%. This value is especially high considering availability and efficacy of ATT worldwide and the advancements in intensive care medicine. Attributable factors include delay in diagnosis and ATT initiation, altered drug absorption in critically ill patients, comorbidities and TB related complications. The most common complication and indication for ICU admission across the studies was found to be ARDS/acute hypoxaemic respiratory failure. Tuberculosis related acute respiratory failure carries a mortality rate of up to 60%, pneumonia carries a 25% mortality.[38–40]

Multiple organ failure and sepsis were present in 10.5% and 9.5% of cases, respectively and were included as predictors of mortality in 9 studies. Three studies documented individuals with disseminated intravascular coagulation. This can be caused by miliary TB and is a negative predictor for survival, with individuals more likely to develop ARDS than those with isolated pulmonary TB; it carries a high mortality in the ICU setting, mostly attributed to septicaemia and subsequent multiple organ failure.[10] HIV/AIDS, alcohol abuse, diabetes, smoking status and chronic pancreatitis identified as independent risk factors for mortality.[14]

HIV and TB

Tuberculosis is the main cause of death in people living with HIV.[41] People living with HIV are 30 times more likely to develop active TB, with more severe and atypical pulmonary forms as the most common presentation.[37] Two studies reported an earlier age of hospitalisation and higher rate of respiratory failure.[36,37] Threshold for clinical suspicion should be lower in these individuals, given their diminished symptom presentation.[12,42]

ICU complications

Several ICU complications were reported. Critically unwell individuals are prone to drug interactions and adverse effects due to complex pharmacology, polypharmacy, disease severity and organ failure.[43] Hepatotoxicity is a particular risk with isoniazid, rifampicin and pyrazinamide.

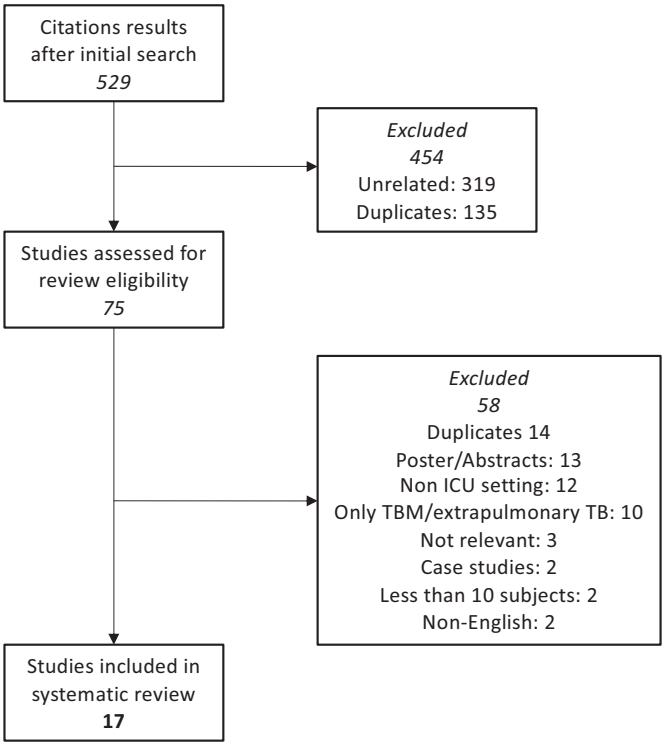

Figure 1 Flow-chart of study selection.

Table 4 Bias according to the Newcastle-Ottawa assessment scale.[35]

Study	Selection Score	Comparibility Score	Outcome Score	Total Score
Penner et al [27] (1995)	2	2	3	7
Erbes et al [14] (2006)	2	2	3	8
Sharma et al [20] (2006)	3	2	3	7
Ryu et al [7] (2006)	2	2	3	7
Lin et al [28] (2009)	2	2	3	7
Valade et al [13] (2012)	2	2	3	7
Balkema et al [29] (2014)	2	2	3	7
Lanoix et al [30] (2014)	2	2	3	7
Rollas et al [8] (2015)	2	2	3	7
Filiz et al [31] (2016)	2	2	3	7
Kim et al [21] (2016)	2	2	3	7
Pecego et al [36] (2016)	2	2	3	7
Duro et al [32] (2017)	2	2	3	7
Kim et al [33] (2018)	2	2	3	7
Muthu et al [34] (2018)	2	2	3	7
Tatar et al [19] (2019)	2	2	3	7
Ferreira et al [37] (2018)	2	2	3	7

Patients with underlying hepatic sequelae including prior hepatitis, alcoholic liver disease are more vulnerable. Acute kidney injury and glomerular hyperfiltration can affect anti-TB drug elimination with pyrazinamide and ethambutol renally excreted.[44] Decompensated or end stage renal failure in ICU negatively influences patient outcome especially in those requiring dialysis, 45 individuals across these studies had renal failure.[14] Patients in multiple organ failure are less tolerant to the toxic side effects of anti-TB drugs, creating clinical dilemmas as therapy interruption can increase risk of drug resistance and death.

Hospital acquired infections (HAIs) were found to be a negative predictor of survival and were present in 8.2% of cases. Tuberculosis suppresses monocyte activity, causing immunosuppression and increasing infection risk.[34] Lin *et al* reported nosocomial pneumonia incidence was four times higher in non-surviving individuals with pulmonary TB.[28] Ventilator associated pneumonia was found in numerous individuals who had been ventilated,[14] and was independently associated with hospital mortality.[14] Other infections include urinary tract and central venous catheter associated bloodstream infections which are associated with length hospital stay. Hospital acquired infections can prolong length of stay, contributing to an already elevated mortality rate.[45]

Diagnostic delay

Smear microscopy and culture have turnaround times of few days and several weeks, respectively. GeneXpert NAAT TB-PCR test and urinary LAM (Fujifilm) may allow for results within hours.[9] Despite the growing availability of fast and reliable point of care tests, thinking of TB remains a challenge. Misinterpretation of clinical and radiological presentation, and lack of resources contribute to unreliable diagnosis and delays in treatment initiation. It can be challenging to radiologically distinguish TB from severe bacterial pneumonia as a cause of ARDS, many individuals are treated incorrectly before TB is considered in the differential. Empirical fluroquinolone could be beneficial covering both conditions, Tseng *et al* reported oral fluoroquinolone usage as independently associated with better survival in those with TB mimicking severe pneumonia in ICU.[46]

Survival of individuals with TB can be significantly improved if therapy is started within 14 days of hospitalisation.[46] Erbes *et al* found a significant increase in mortality in individuals not receiving optimal treatment including isoniazid and rifampicin.[14] In addition, Duro *et al* found that starting ATT within 3 days of ICU admission improved survival.[32] Two studies with the longest delay in treatment initiation were from lower incidence countries.[13,27] Delays are common in areas with fewer TB cases, probably as a result of lack of experience.[47] Almost half of the studies did not report on treatment delay. The variation in delay ranged from 0-45 days globally, and may contribute to poorer prognosis. This review found only 38.3% of individuals diagnosed prior to admission.

Drug resistance

Rifampicin resistance is increasing and a major threat, with half a million people currently estimated to be infected with rifampicin resistant strains carrying a higher mortality.[2,24] The number of individuals with drug resistant TB was 46 (4.9%). Drug resistance may have been under reported in these studies and this might explain why resistance was not found to be a predictor of mortality.

Intravenous anti-TB treatment

Tuberculosis treatment in ICU is complicated by organ dysfunction, drug toxicity and sub-therapeutic levels. First line drugs such as rifampicin and isoniazid are generally well absorbed when administered orally at the correct dose. In critically unwell individuals, absorption and pharmacokinetic drug properties are altered. The pharmacokinetic profile of anti-TB drugs has shown that there is a dose dependent relationship between concentration and clinical outcomes.[48] Critical illness alters gut motility, impairs

mucosal barrier integrity, distorts commensal flora, delays gastric emptying leading to reduced absorption.[10,25,49] Hypoalbuminemia was found to be a predictor of mortality in this review with 47 individuals suffering from malnutrition pre-admission.[37] Hypoalbuminemia may lead to oedema, increasing the volume of distribution of drugs, as well as impair drug absorption all leading to lower drug concentrations in serum.[44,50] Parenteral administration or higher doses of drugs may be required to reach therapeutic effect.

Although no studies regarding intravenous antibiotics were found, a study by Hill suggested a role for their use.[25] They compared patient groups over 2 weeks, administering standard oral versus a 33% higher dose of intravenous rifampicin, finding a three times higher 'geometric mean area under the time concentration curve' up to 6 h, in the intravenous group. Mortality was substantially lower in individuals given intravenous rifampicin with no reported increase in toxicity. They also found an increased survival compared to the standard oral dose, including more rapid resolution of coma and reduced mortality at 2 months and 8 months.[25] Koegelenberg *et al* investigated the pharmacokinetics of enteral anti-TB drugs in intensive care individuals, finding that a fixed dose of rifampicin administered via nasogastric tube resulted in sub-therapeutic plasma concentrations in the majority of individuals.[48]

Although intravenous rifampicin is available, it is not widely accessible in low income countries.[51] Other first line drugs are not always accessible or available,[48] with no intravenous ATT formulation included current WHO Model List of Essential Medicines (2019).[52] This leads to use of second line drugs such as fluroquinolones and aminoglycosides in the ICU setting.[53]

Mechanical ventilation and steroids

Several studies identified mechanical ventilation as a risk factor for mortality.[8,30] The four highest mortality rates reported were from Kim et al. 2016 (95.1%),[21] Ferreira et al. (78.3%),[37] Tatar et al. (72.5%),[19] and Penner et al. (69.0%),[27] having the highest proportion of mechanically ventilated individuals (75-100%). Studies with the lowest proportion of mechanically ventilated individuals had the lowest reported mortality, such as Erbes et al.[14] with 37% ventilated and 25.9% mortality.[13,14,30] Those with more severe, disseminated forms of disease were more likely to require mechanical ventilation and develop ARDS, reflecting a referral bias, most unwell more likely to die.[12] Duration of mechanical ventilation has been associated with worse prognosis, possibly due to more HAIs, and pneumothorax.[14]

Adjuvant corticosteroid use is indicated for meningeal and pericardial disease, and pulmonary TB related ARDS.[12,32] Some studies have shown that systemic glucocorticoids are associated with improved prognosis, however this was non-specific for the critically unwell population.[54] The benefit of steroid use in TB individuals in ICU specifically remains unclear. We found that steroid use did not alter prognosis. Vasopressor support was found to be a predictor of fatality.

Severity scoring systems in ICU

Scoring systems for critically ill individuals are commonly used for estimating general ICU mortality, guiding clinical decision making and influencing distribution of hospital resources.[55] Individuals with a higher mortality risk may benefit from earlier, targeted and potentially more aggressive treatment, given the small intervention window and a higher risk of death; this may outweigh risk of iatrogenic harm.[56]

Many studies have shown APACHE II and SAPS consistently underestimate mortality among individuals with pulmonary TB, especially those with ARDS and the mechanically ventilated.[55,31] This highlights a shortfall in accurate risk stratification in these individuals, with a need for better tailored, ARDS specific scoring systems. APACHE does not include mechanical ventilation as an adverse outcome predictor a factor in its inaccuracy.[22] In the literature it has been reported than an APACHE score >18 is associated with a higher mortality giving a predicted mortality of $>29\%$.[44] The average of mean APACHE II produced about 36% predicted mortality and using median a value about 32%. The median SAPS II and SOFA scores gave an estimated about 25% and $<10\%$, respectively. Most of these results drastically underestimate the calculated mortality of 52.9%. The data set in Table 3 showed that the fatalities vs survivors had a higher score throughout (except for Pecago et al. [36]).

Villar et al. designed an outcome score calculating 24hr post ARDS diagnosis, age, PaO_2/FiO_2 and plateau pressure.[56,57] Similarly Kim et al. developed a mortality prediction model for individuals with TB-destroyed lung on mechanical ventilation.[33] This model included age, vasopressor use, PaO_2/FiO_2 ratio and Brain Natriuretic Peptide (all predictors of ICU mortality in these individuals) finding this score more accurate at mortality prediction than APACHE II and SOFA.[33] Lung injury severity 24 h after ARDS onset is a key determinant of outcome, reflecting the necessity for a reliable mortality prediction.[56] Two studies found a low PaO_2/FiO_2 ratio to be a predictor of fatality.[38,33] Although promising results have been obtained, further studies with perhaps additional variables are needed for external validation.[58]

High vs low burden areas

Nine out of the 17 studies were from high burden areas. Percentage of individuals diagnosed before admission was higher in low prevalence, resource rich areas, ranging from 53.8% to 75% over 4 studies (one not reported).[13,14,30,27] In comparison to 24.4% to 38.6% (two not reported) over 4 studies,[21,29,33,28] showing that more individuals are living with undiagnosed tuberculosis in poorer areas. This difference may be due to better diagnostic tools available in wealthier regions. The mortality in the low prevalence areas was 41.5% compared to the high prevalence at 64.9% with the highest mortality being the Kim *et al* 2016 study at 95.1%.[21] The association between TB and low-income areas is known, with poverty being a cause and consequence of infection. Many risk factors for disease reactivation and predictors of mortality in ICU are associated with a lower socioeconomic background, including HIV infection, malnutrition, alcohol use disorder and smoking.

More individuals were mechanically ventilated in high prevalence areas with higher mortality. Mechanical ventilation remains a predictor of mortality even in low burden areas. In these areas renal failure, sepsis, ARDS and APACHE II scoring are non-specific risk factors to TB.[30] There was no difference in the APACHE II score, in contrast to the differing

mortality rates between the grouped studies. This may reflect the inefficiency of severity scoring systems to accurately estimate mortality in critically unwell TB individuals.

Limitations

This review only included individuals admitted to ICU which may reflect referral bias, as some lower income countries may not have had access to ICU beds. There was study heterogeneity in data reported, making meta -analysis challenging. No publication bias was assessed due to small sample sizes. No long term outcomes were reported.

Conclusion

The results across this review and previous literature are varied, reflecting the heterogeneity of patient presentation and aetiology of illness. The studies had relatively small sample sizes sand all save one were retrospective. There was disproportionate and variable mortality across studies only one-third of individuals were accurately diagnosed initially and 5% completed treatment successfully, highlighting the overwhelmingly poor outcomes for these individuals. A large number of individuals are undiagnosed until acutely unwell, leaving a small window for prompt diagnosis and treatment. Therapeutic intervention might be improved by administration of intravenous ATT, and may reduce complications and mortality. Current severity scoring systems underestimate mortality in ARDS related tuberculosis.

Though TB is treatable, individuals admitted to ICU with TB have an uncertain and desperate fate confronted with high mortality and plethora of complications, barriers to diagnosis and treatment challenges. Practice within ICU may need to change to detect and treat TB earlier and more aggressively, in order to improve outcomes. Tuberculosis in critically ill patients continues to be associated with significant mortality.[59,60]

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Declaration of Competing Interest

None.

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LETTER TO THE EDITOR

Non-invasive ventilation in post-extubation respiratory failure due to Reinke's edema

Dear Editor

Reinke's edema (RE) is a rare benign disease characterized by edema of the vocal cords, with a prevalence of less than 1%.[1] Risk factors include cigarette smoke, voice abuse and laryngopharyngeal reflux.[1,2] Typical clinical features include dysphonia and hoarseness, but it can also cause dyspnea and inspiratory stridor in severe cases, and it may complicate airway management causing difficulties in intubation or extubation.[1,2,-3] Reinke's edema was identified as a risk factor for post-extubation laryngeal edema, together with female gender, prolonged intubation, use of large tube size and high cuff pressure, and difficulty in intubation.[4,5] Post-extubation laryngeal edema usually presents as stridor and may progress to respiratory failure. The preferred treatment for established post-extubation respiratory failure includes steroids combined with nebulized epinephrine and reintubation, which should be performed immediately,[4] since non-invasive ventilation (NIV) is not recommended in these cases.[4,6]

The authors report a case of success in the management of post-extubation respiratory failure with NIV, in a patient diagnosed with RE. A 46-year-old female, with a medical history of depression, anemia, smoking history and alcohol abuse, presented odynophagia and dyspnea, with further clinical worsening. She was admitted to the emergency department with tachypnea, dyspnea, inspiratory stridor and desaturation. Treatment with bronchodilators, intravenous antibiotics and steroids was initiated as well as NIV in bilevel mode. Nasopharyngolaryngoscopy (NPL) was performed, showing vocal cord edema. The etiology of RE in this patient was considered multifactorial, due to smoking habits, alcohol abuse and gastroesophageal reflux. Despite the treatment, she presented clinical worsening and was intubated the same day. After three days of invasive ventilation, given clinical and respiratory improvement, the cuff-leak test was performed, which was positive, so the patient was not extubated and the dose of steroids was increased. In the next day, a new cuff-leak test was performed, which was negative, and we proceeded to extubation. However, in the hours following extubation, she presented respiratory worsening with tachypnea (30 breaths per minute) and inspiratory stridor. High-flow oxygen therapy was initiated and NPL was repeated, showing swelling of the vocal cords and the left arytenoid, with mild bilateral paralysis of both vocal cords. Respiratory insufficiency developed, with increased tachypnea (35 breaths per minute) and use of accessory muscles of respiration, with an arterial oxygen tension to inspiratory oxygen fraction ratio (PaO2/FiO2) of 149. NIV was initiated with a full-face mask in bilevel mode (IPAP of 16 cmH2O and EPAP of 6 cmH2O) with helium/oxygen mixture, with good tolerance and response. Helium at a concentration of 100% was applied at the outlet of the ventilator, where it was mixed with oxygen from the ventilator. Helium was regulated by a flow meter, starting at 2 liters per minute with FiO2 of 100% in the ventilator, and then adjusted according to the oxygenation objective. Clinical evolution was favourable (Fig. 1) and it was possible to descale NIV into high-flow oxygen therapy in the first 24 hours and then into low-flow oxygen therapy, until it was suspended. High-flow oxygen therapy was started with a flow of 60 liters per minute and a FiO2 which was 10% higher than the FiO2 previously administered through NIV, with a temperature of 34°C. Then, we gradually decreased FiO2 to maintain oxygen saturation between 92 and 96%. In the last control NPL performed, there was improvement of the previous findings.

Post-extubation laryngeal edema is a frequent complication of intubation and leads to reintubation in up to 10% of all extubated patients.[4] Pre-treatment with corticosteroids following extubation seems effective in the prevention of laryngeal edema, but it is difficult to predict which at-risk patients will benefit from this prevention treatment. In our case, the patient presented some risk factors for post-extubation failure, such as female gender and previous vocal cords edema, hence extubation was cautious, with intensification of treatment with corticosteroids and performance of the cuff-leak test before extubation. Nonetheless, and despite all measures, post-extubation respiratory failure occurred. The cuff-leak test is an easy non-invasive test, which predicts the occurrence of post-extubation obstruction. Despite the excellent specificity of this test, its sensitivity, as described in several studies, is variable.[7] Thus, this test is better for confirming than excluding a potential post-extubation airway obstruction.

The management of post-extubation respiratory failure due to laryngeal edema is controversial, with most authors defending reintubation as the first line approach, and not

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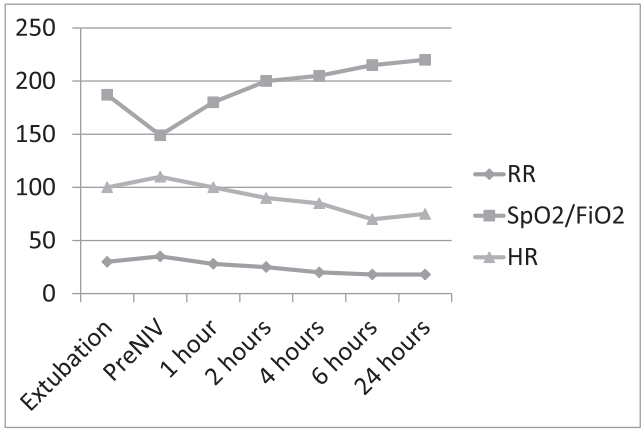

Fig. 1 evolution of respiratory and hemodynamic variables before and after the start of non-invasive ventilation
Legend: FiO2: fraction of inspired oxygen; HR: heart rate; NIV: non-invasive ventilation; RR: respiratory rate; SpO2: oxygen saturation.

recommending the use of NIV since it does not seem to improve outcomes and it might increase mortality.[4,6] However, NIV has an established role in the management of acute and chronic respiratory failure due to a variety of etiologies, such as preventing post-extubation respiratory failure in high-risk patients.[4,6] Moreover, there has been an increasing interest in its use during the post-extubation period to shorten the length of invasive ventilation, to prevent extubation failure in high-risk patients, and to rescue failed extubation.[4,6] Despite NIV not being recommended in these cases, we decided to use NIV given the continuous monitoring conditions of the unit and the high experience of the ICU with NIV, namely in partial obstruction of the upper airway and in post-extubation respiratory failure. According to some published studies,[6] the main reason for the high mortality in these patients is the delay in intubation, which can be overcome with early reassessment and closer monitoring. Furthermore, reintubation of these patients is associated with several complications and increased morbidity and mortality, which has exceeded 40% in some studies; reintubation increases the risk of aggravation of the laryngeal edema.[5] Taking this into account, it is essential to find alternatives which avoid reintubation.

Patient's consent

Written informed consent was obtained for the publication of this case report.

Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Intermittent versus equivalent constant-load cycle training in COVID-19 patients

Dear Editor,

While the need to implement evidence-based training following COVID-19 is imperative, no consensus exists as to how such programmes should be designed.[1-3] Between 20 July 2020 and 30 April 2021, we assessed tolerability and safety of high-intensity constant-load exercise (CLE) and high-intensity intermittent exercise (IE) in 14 patients presenting pneumonia and acute respiratory failure (ARF) (mean age: 63±13 years) with ongoing symptomatic COVID-19 from 4 to 12 weeks following the infection. Anthropometric data, body mass index (BMI), and the number of comorbidities were recorded. Patients undertook spirometry (FEV_1, FVC, FEV_1/FVC, transfer factor for Carbon Monoxide (DLCO), blood gases in room air (PaO_2, $PaCO_2$, pH), functional status (the Short Physical Performance Battery-SPPB test and the 6-minute walking distance [6MWD: in meters and as a percentage of predicted]), an incremental cardiopulmonary exercise test (CPET) [assessing oxygen uptake (VO_2), carbon dioxide output (VCO_2), oxygen uptake at the anaerobic threshold (AT), respiratory exchange ratio (RER), minute ventilation (V_E), tidal volume (V_T) and respiratory rate] using a portable metabolimeter; transcutaneous carbon dioxide tension ($TcCO_2$) was also recorded continuously. In this cross-over study (Ethics Committee approval on 30 June 2020, Procotol No. 2449CE), training exercise intensity was balanced to provide the same average work rate for IE and CLE modalities. CLE was set at 70% of peak work rate (WRpeak) and IE consisted of one minute of exercise at 100% WRpeak, alternated with one minute at 40% WRpeak, to the limit of tolerance (Tlim). Dyspnea and leg muscle discomfort (1-10 Borg scale), heart rate and safety were assessed. Of the 220 consecutively admitted patients at the Respiratory Rehabilitative Unit - ICS Maugeri of Lumezzane (BS) - as inpatient and outpatient between 20 July 2020 and 30 April 2021, 14 patients were eligible for the study. We excluded from this study 63 patients presenting symptoms for less than four weeks following infection, 35 patients with more than 12 weeks following infection, 44 clinically unstable patients, 20 patients with severe orthopedic diseases, 15 patients with cognitive impairment, 29 patients with previous severe heart disease (congestive heart disease, severe aortic stenosis, atrial fibrillation). We did not successively exclude patients for technical reasons or missing data.

Table 1 shows the study population and cardiorespiratory function at peak exercise; two patients presented mitral valve insufficiency and one chronic atrial fibrillation, while two patients suffered from mild COPD. At study entry, patients showed breathlessness (71.4%), fatigue (64.3%), cough (14.4%), palpitations (21.4%) and pain (35.7%), respectively. Patients presented the following lung function data: FEV_1 % predicted (prd): 83.2±15.7, FVC, % prd: 79.1± 15.8., FEV_1/FVC: 84.1±8.5, DLCO % prd: 56.7±26.6, PaO_2: 73.7±11.8 mmHg, $PaCO_2$: 36.9±3.01 mmHg. We reported no adverse events for either of the two modalities. We detected no ECG abnormalities during or after IE or CLE. At peak exercise, WRpeak and $\dot{V}O_2$peak were reduced below normal predicted levels. Premature metabolic acidosis was evident by the low fraction of predicted normal VO_2 when the anaerobic threshold (AT) was detected (AT at 48±9% VO_2 prd). Overall, respiratory reserve was not exhausted in patients with COVID-19. Ventilatory equivalents for VO_2 (V_E/VO_2) and VCO_2 (V_E/VCO_2), and transcutaneous carbon dioxide tension ($TcCO_2$) were compatible with exercise hyperventilation (Table 1). A recent study in survivors from COVID-19 pneumonia has suggested that exercise hyperventilation after COVID-19 is frequent and principally due to enhanced chemoreflex sensitivity rather than increased V_D/V_T.[4] We observed a mild reduction in arterial oxygen saturation (SpO_2). Arterial blood pressure was normal, whereas the mean heart rate reached approximately 80% of predicted normal value. Sensations of breathlessness and leg discomfort were indicative of severe symptoms. The predominant symptom for stopping exercise was breathlessness (6/14), leg discomfort (2/14) or both dyspnoea and leg discomfort (6/14). Exercise endurance time was not different between IE compared to CLE (p = 0.1594, Table 2). The average cycling work rate did not differ between IE and CLE. The same was also the case for VO_2 and for both ventilatory equivalents (Table 2). At the limit of cycling tolerance, none of the ventilatory or cardiovascular responses differed between IE and CLE (Table 2) and there was no difference in the intensity of breathlessness or leg discomfort between the two modalities. The ventilatory reserve, reflected by the ratio of V_E/maximal voluntary ventilation (V_E/MVV), did not differ between IE and CLE. During CLE and IE 36% and

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Table 1 Demographic, anthropometric and clinical characteristics.

Measures	
Patients, n	14
Age, years	63.1±12.9
BMI, kg/m^2	28.0±5.2
Male, n (%)	11 (78.6%)
Comorbidities	
None, n (%)	9 (64.3%)
Cardiac, n (%)	3 (20.0%)
Respiratory, n (%)	2 (14.3%)
Diabetes, n (%)	1 (7.1%)
Hypertension, n (%)	9 (65.0%)
Days since acute hospitalisation, n	54.6± 22.0
Functional status	
SPPB, score	9.9±1.9
6MWD, m	411.4±111.6
6MWD, % of predicted	77.3±17.9
Physiological responses at the limit of tolerance during the CPET	
WRpeak, Watts	87.1±31.5
WRpeak, % predicted	59.4±22.1
VO_2peak, ml/kg/min	12.7±4.6
VO_2peak, % of predicted	57.6±16.2
VCO_2peak, ml/kg/min	13.0±4.8
VO_2-AT, ml/kg/min	10.6±3.2
VO_2-AT, % VO_2peak predicted	48.2±9.4
V_E/VO_2 peak	50.4±10.4
V_E/VCO_2 peak	40.6±9.2
RER peak	1.1±0.1
$TcCO_2$ peak, mmHg	37.4±5.3
$V_E$peak, l/min	46.8±20.7
V_E/MVV, %	42.5±17.1
SBPpeak, mmHg	171.8±26.4
DBPpeak, mmHg	96.6±14.2
SpO_2peak, %	92.5±3.3
HRpeak, beats/min	124.3±2.3
HRpeak, % of predicted	79.0±10.4
Borg dyspnea at peak exercise, score	7.4±2.3
Borg Leg discomfort at peak exercise, score	5.8±3.1

Legend: Results are expressed as mean± Standard Deviation; BMI, body mass index; SPPB, Short Physical Performance Battery; 6MWD, six minute walking distance; CPET, cardiopulmonary exercise test; WRpeak, maximum load in watts at peak exercise; VO_2, oxygen uptake; V_E, ventilation; SpO_2, peripheral oxygen saturation; $TcCO_2$, transcutaneous carbon dioxide tension; VO_2-AT, oxygen uptake at the anaerobic threshold; RER, respiratory exchange ratio; V_E/VO_2; ventilatory equivalent for VO_2, V_E/VCO_2, ventilatory equivalent for VCO_2; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR, heart rate.

21% of patients, respectively, ended the test with a HR greater than 80% of maximal predicted. Forty-three percent of patients ended CLE and 50% ended IE with a decrease in SpO_2 greater than 4%, compatible with exercise-induced arterial oxygen desaturation. The fraction of patients who reasoned dyspnoea as the limiting factor was identical between IE and CLE corresponding to 57%. The fraction of patients who stopped exercise because of leg discomfort was relatively low for IE (n=2, 14%) and for CLE (n=3; 21%). Both dyspnoea and leg discomfort as the limiting factors were reported by n=4 for IE (29%) and n=3 for CLE (22%). At exercise iso-time and the limit of tolerance during IE and CLE protocols, V_E, SPO_2 and VO_2 did not differ (Table 2). Moreover, symptoms for breathlessness, leg discomfort, heart rate or blood pressure measurements were not different during IE and CLE protocols.

The lack of adverse events occurring during exercise modalities was in line with previous studies on COVID-19 survivors.[5] Moreover, several studies on other 'high risk' patients' groups (e.g., such as ischemic heart disease and heart failure) showed that high-intensity exercise is considered safe.[6,7] Recent studies in COVID-19 survivors[4,8] have attributed early metabolic acidosis to myopathic changes occurring for medications administered during the hospital stay (e.g., steroids) as well as because of the potential direct or indirect myopatic damage from COVID-19 rather than muscle disuse.[7] Hence, several opinion papers and guidelines favour low-intensity exercise with gradual increases in intensity, mostly due to safety concerns.[2,3] Early experiences of rehabilitation in post-COVID-19[5] individuals show that low-to-moderate intensity of exercise in this population is safe and effective in improving exercise tolerance and peripheral muscle strength. Accordingly, our study was designed to investigate the safety and tolerability of high-intensity (continuous or interval) exercise in this population.

Individuals with ongoing symptomatic COVID-19 could successfully and safely undertake high-intensity exercise performed continuously or intermittently. These findings are relevant both for a better understanding of consequences of COVID-19 on exercise tolerance. They also provide a clearer suggestion to survivors on how they should undertake regular exercise when expecting to resume their previous lifestyle.

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Author contributions

MP (Guarantor) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. MV, IV, MP and MVe contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. BS, LB contributed to data collection and interpretation. All Authors reviewed the manuscript.

Table 2 Responses at the limit of tolerance (Tlim) to constant-load exercise (CLE) and interval exercise (IE) protocols.

	Tlim_CLE	Tlim_IE	P
Cycling responses			
Work rate, Watts	59.6±23.4	60.0±23.2	0.4845
Endurance time, min	12.7±8.5	14.7±9.0	0.1594
Cadence, rpm	60.2±7.1	59.1±7.0	0.9150
Total work, kJ	45.9±31.2	54.3±40.2	0.1580
Metabolic and ventilatory responses			
VO_2, ml/kg/min	12.3±3.8	11.9 ±3.2	0.6494
VO_2, % VO_2peak	94.6±18.9	95.6±24.3	0.8676
RER	0.9±0.1	0.9±0.1	0.4513
V_E, L/min	46.9±22.3	44.3±16.8	0.5767
V_E/MVV, %	41.4± 2.9	41.5±19.3	0.9927
VE/VO_2	47.6±8.0	47.1±10.2	0.8157
V_E/VCO_2	52.0± 9.6	50.6± 10.6	0.2317
Ti, sec	0.7± 0.1	0.7±0.2	0.6128
Ti/Ttot	0.4±0.0	0.4±0.0	0.8041
Bf, breaths/min	35.9±6.4	36.1±7.1	0.8970
SpO_2, %	92.9±3.6	92.3±3.4	0.1788
$TcCO_2$, mmHg	33.4±4.0	32.5±4.5	0.2289
Cardiovascular and symptoms responses			
Mean BP, mmHg	119.9±18.7	113.1±8.2	0.1494
HR, beats/min	117.1±17.2	114.6 ±13.4	0.4712
HR, % of predicted	74.7±8.6	73.4±8.2	0.5681
Borg dyspnea, score	6.6±2.6	6.4±2.8	0.3456
Borg leg discomfort, score	5.0±3.0	4.3±3.3	0.2206

Legend: Results are expressed as mean± Standard Deviation; VO_2, oxygen uptake; V_E, minute ventilation; arterial oxygen saturation; $TcCO_2$, transcutaneous carbon dioxide; CPET, cardiopulmonary exercise test; RER, respiratory exchange ratio; V_E/VO_2, ventilatory equivalent for VO_2; V_E/VCO_2, ventilatory equivalent for VCO_2; BP, blood pressure; HR, heart rate.

Declaration of competing interest

The authors declare no conflict of interest related to this manuscript.

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LETTER TO THE EDITOR

KIF5B-MET fusion variant in non-small cell lung cancer

Dear Editor,

Lung cancer is the cancer type with the highest mortality rates worldwide.[1] The treatment of lung adenocarcinoma (LADC) changed dramatically since the recognition of actionable oncogenic abnormalities.[1,2] MET is a receptor tyrosine kinase activated by binding of its ligand hepatocyte growth factor,[3] and a known oncogenic driver of lung cancer.[4] Abnormal MET signaling can occur through a different number of mechanisms such as amplification, mutation and fusion.[3,5] The most frequent oncogenic alteration of MET kinase involves MET exon 14 skipping mutations.[2] MET fusions are rare in LADC.[3] Kinases activated by gene fusions represent an important class of oncogenes [6] being ALK, RET and ROS1 fusion, the most frequent in LADC.[1]

Two reports suggest that MET signaling (through MET amplification) could also trigger resistance to ALK kinase inhibition in *ALK* rearranged tumors.[2,7,8] Although the MET kinase fusions identified in two LADCs fulfill the criteria of primary oncogenic drivers, the MET Kinase domain (MET-KDD) rearrangement may be specifically associated with the ceritinib resistance phenotype in an ALK-rearranged background.[2] Recently, a KIF5B-protein tyrosine kinase fusion transcript — KIF5B-MET — has been discovered in LADC patients, consisting of a chimeric fusion of exons 1—24 of KIF5B to either exons 14—21 or exons 15—21 of the MET proto-oncogene. This was denoted as K24:M14 or K24:M15 based on the last KIF5B and first MET exons in the fusion, respectively.[4] KIF5B-MET variant was demonstrated to have an oncogenic function in cancer cells. Furthermore, a novel fusion partner for MET was observed - STARD3NL.[5]

The authors present the case of a 56-year-old Caucasian male, with stage IA lung adenocarcinoma - cT1bN0M0 (TNM classification, 8th edition), never-smoker. The patient started follow up due to image findings requested during a chest pain investigation. Clinically, denied constitutional symptoms, hemoptysis, dyspnea, cough or other relevant symptoms. Patient reported family history of premature coronary disease and mentioned past medical history of hypothyroidism, arterial hypertension, diabetes mellitus, dyslipidemia, and anxiety. There were no known respiratory disorders. Thorax CT revealed a nodule with ground glass texture and a central solid portion, measuring 14 mm and 5 mm, respectively, in the lateral segment of the lower left lobe, adjacent to the large fissure. Also, scattered throughout the pulmonary parenchyma, micronodular lesions were found; the largest, in the medial segment of the middle lobe, with 7 mm (assessed, after discussion in multidisciplinary meeting, as intrapulmonary lymph node — no biopsy was performed). Positron Emission Tomography (PET) showed the nodule in the lower lobe of the left lung does not have significant FDG uptake. CT-guided biopsy was performed, confirming the diagnosis of adenocarcinoma (TTF1, Napsin A and CK7 positive; CK20 — negative).

Immunohistochemical PD-L1 expression, using the 22C3 antibody concentrate (DAKO), showed low/intermediate positive results (1-49%). Next Generation Sequencing (NGS) was performed using the Oncomine Focus Assay on DNA and RNA obtained from tumor biopsy, that allows detection of SNVs and indels in genes AKT1, ALK, AR, BRAF, CDK4, CTNNB1, DDR2, EGFR, HER2, 3 e 4, ESR1, FGFR2 e 3, GNA11, GNAQ, HRAS, IDH1 and 2, JAK1, 2 and 3, KIT, KRAS, MAP2K1 and 2, MET, MTOR, NRAS, PDGFRA, PIK3CA, RAF1, RET, ROS1 and SMO; CNVs in genes AKT1, ALK, AR, BRAF, CCND1, CDK4, CDK6, EGFR, HER2, FGFR1, 2, 3 and 4, KIT, KRAS, MET, MYC, MYCN, PDGFRA, PIK3CA; and gene fusions in genes BL1, AKT3, ALK, AXL, BRAF, EGFR, HER2, ERG, ETV1, 4 and 5, FGFR1, 2 and 3, MET, NTRK1, 2 and 3, PDGFRA, PPARG, RAF1, RET, ROS1. This NGS technique, validated locally, allows detection of nucleotide substitutions with allelic fraction >5% and rearrangements in 1% of the RNA, in samples with more than 20% of neoplastic cells, with a sensibility >99%. Our fixed tissue sample was representative of the tumor and had approximately 10% neoplastic nuclei.

Mutation c.2917G>T (p.Asp973Tyr), in exon 22 of the NF1 gene and rearrangement of KIF-5B (24)-Met (15) were found. Thus, a rare fusion variant involving the MET gene-KIF5B-MET (K24:M15) in a patient with LADC was identified, concomitant with a NF1 mutation of undetermined significance.

The MET protooncogene is implicated in a variety of cancers, particularly in papillary renal cell carcinoma, where a number of somatic mutations have been described.[6] In a mutation review, single MET fusions were found in four other cancers: low-grade glioma, hepatocellular carcinoma, thyroid carcinoma and lung adenocarcinoma, being KIF5B—MET fusion present in these last two cases.[6] There are only two known types of KIF5B-MET gene fusion in LADC: K24:M15 and K24:M14. In the literature we found a total of five cases — three K24:M15 and two K24:M14.[2,4] Our case is the 6th

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reported case of KIF5B-MET gene fusion, the 4th reporting a K24:M15 fusion and the only one reporting a NF1 commutation. The fusion gene between exon 24 of KIF5B and exon 14 of MET (K24:M14) was originally reported as 1 out of 513 LADC samples in a mutation review without mention to any treatment.[3,6] Later on, an additional case with the variant was described, being the first documented case of a patient with a MET fusion−positive tumor (K24;M14) exhibiting a significant and sustained response to treatment with crizotinib in LADC.[3]

The first patient identified with K24:M15 variant was a 33-year-old female with stage IV LADC treated with off-label crizotinib, having shown maintained clinical benefit, decrease in both tumor size and FDG uptake in PET/CT, and minimal side effects for at least 8 consecutive months.[2] The other two cases were reported in a patient with a mixed-type LADC-sarcomatoid tumor, and in a patient with pulmonary sarcomatoid tumor.[4] The patient with mixed type of LADC-sarcomatoid tumor had poor conventional chemotherapy (pemetrexed-cisplatin) response and the patient with pulmonary sarcomatoid tumor had supportive care; both had poor overall survival.

In our case, the patient was submitted to left uniportal video-assisted thoracoscopic surgery (VATS) with segmentectomy (S8) and exeresis of lymph node stations 5L, 8L 9L, N11 and N12. Pathologic examination of surgical piece revealed visceral pleural invasion (pT2N0), and adjuvant chemotherapy was started. Our case was radically treated, so no MET inhibitor was introduced; however, in case of future tumor progression, this might be an option.[2,3,6]

Fusions beyond ALK, RET, and ROS1 have been documented in lung adenocarcinomas without associated oncogenic mutations.[1] The authors present the 4th case in the world with a mutation of KIF5B-MET (K24:M15), but the single one describing a NF1 commutation (the first being described with any MET fusion). The significance of this association remains unknown, especially regarding the role of a MET inhibitor in its treatment efficacy. The authors also highlight the importance of performing NGS in all patients with LADC, since recognition of oncogenic activation events represents targeted intervention opportunities, even if it is off label use in rare forms of presentation.

Declarations section

Ethics approval and consent to participate: consent for use of clinical data and publication was asked and accepted by the patient.

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LETTER TO THE EDITOR

Pregnancy in Alpha 1 Antitrypsin (AAT) Deficiency and the role of intravenous AAT therapy

Alpha 1 Antitrypsin Deficiency (AATD) is a genetic disorder that results in reduced plasma levels and/or functionality of Alpha 1 Antitrypsin (AAT), a serine protease inhibitor. Deficiency in AAT predisposes patients to greater risk of early-onset chronic obstructive pulmonary disease/emphysema due to excessive proteolysis of lung parenchyma, in addition to liver disease as a result of polymerisation of certain mutant AAT proteins.[1] Weekly intravenous (i.v.) infusion of human AAT (AAT therapy) is currently the only condition-specific treatment for AATD-associated disease, and clinical data suggest that AAT therapy may slow the progression of emphysema in patients with AATD.[2]

There is evidence indicating a role for AAT in conception and pregnancy. Indeed, AAT has been suggested as important to angiogenesis and vascularisation of the endometrium, as well as trophoblast invasion and embryo implantation.[3] Associations between low AAT levels and pregnancy-related complications, such as preeclampsia, spontaneous abortion, and preterm labour, have also been described.[4] Nevertheless, evidence is still limited regarding the clinical consequences of AATD on pregnancy, and less so regarding the use of AAT therapy in pregnant women. Here, we present a case detailing the clinical course of a pregnant woman with AATD, including the initiation of AAT therapy during pregnancy. The patient signed informed consent for use of her de-identified clinical data for research, analysis, and reporting.

The patient, a 31-year-old, underweight (BMI: 24.3), non-smoking female, had been diagnosed with AATD (Pi*SZ genotype) at the age of 21. She was tested for AATD following a lack of response to treatment for severe asthma, but had no family history of AATD. She had a complex clinical profile including a history of spontaneous pneumothorax, severe asthma and common variable immune deficiency. At the time of diagnosis, she refused AAT augmentation therapy due to practical difficulties related to infusion time and frequency of infusions. On average, she experienced ten moderate exacerbations a year requiring oral antibiotics and/or corticosteroids, and four severe exacerbations a year requiring hospitalization. The patient became pregnant at 29 years of age. Pulmonary Function Tests (PFTs) performed at her last pulmonology consultation prior to pregnancy (6 months pre-pregnancy) showed a severe restrictive ventilatory impairment. (Table 1). Serum AAT level was slightly reduced.

During pregnancy, pulmonology consultation, serum AAT testing and PFTs were performed on a regular basis. The patient experienced one moderate exacerbation at Week 17 of pregnancy, and at Week 18; moreover, a significant drop in her forced expiratory volume in the 1st second (FEV_1) (-0.25 L) compared to Week 9 value was recorded at Week 18. Serum AAT level was markedly reduced. So, intravenous (i.v.) augmentation therapy was initiated and was regularly continued throughout pregnancy at a dose regimen of 60 mg/kg/week aimed at maintaining serum AAT level consistently above the protective threshold of 80 mg/dL (11 μM/L).[6] No adverse event associated with augmentation therapy was reported. The patient experienced a severe exacerbation at Week 28 of pregnancy; however, there were relevant improvements to respiratory function parameters (Table 1). Following consultation with a multidisciplinary care team on the risks (in particular severe respiratory tract infection) and benefits of continuing her pregnancy, the patient consented to undergo a caesarean section at 32 weeks, delivering a healthy baby.

At a follow-up visit conducted 4 weeks post-partum, she reported mild exertional dyspnea. A mild exacerbation with uncomplicated clinical course was reported at 3-month follow-up. Over the next 2 years, exacerbations had reduced relative to pre-pregnancy/AAT therapy to three moderate and one severe per year on average. At the patient's latest consultation (30 months post-partum), PFT showed mild obstructive impairment with recovery of FEV_1 to her pre-pregnancy values (Table 1). A lung CT scan was performed, showing a diffuse low attenuation area in the right upper lobe (Fig. 1).

Data regarding AATD and pregnancy are limited, possibly due to the underdiagnosis of women of childbearing age; indeed, patients with AATD are usually identified in their 40s or 50s.[7] Complications associated with preterm labour, preeclampsia and spontaneous abortion and the risk of rapid decline in PFTs[8] highlight a need for close monitoring of the patient throughout pregnancy.[3] Care of

Abbreviations: AAT, Alpha 1 Antitrypsin; AATD, Alpha 1 antitrypsin deficiency; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity.

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Table 1 Time course of Alpha 1 Antitrypsin level and lung function. ERS Task Force Global Lung Initiative 2012 reference values [5] were used for lung volumes. (AAT= Alpha 1 Antitrypsin; FEV_1= forced expiratory volume in the 1st second; FVC= forced vital capacity; NA= not available; TLC= total lung capacity).

	AAT level (mg/dL)	FEV_1, L (% predicted)	FVC, L (% predicted)	TLC, L (% predicted)
6 months pre-pregnancy*	74	0.79 (31)	1.13 (31)	2.77 (54%)
9 weeks pregnant	NA	1.90 (59)	2.18 (59)	NA
18 weeks pregnant**	38	1.65 (51)	2.06 (56)	NA
23 weeks pregnant	NA	1.46 (45)	1.72 (46)	NA
26 weeks pregnant	108	1.7 (53)	1.89 (51)	NA
30 months post-partum	68	1.90 (61)	2.22 (62)	4.87 (96)

* Acute asthma exacerbation.
** Initiation of Alpha 1 Antitrypsin therapy.

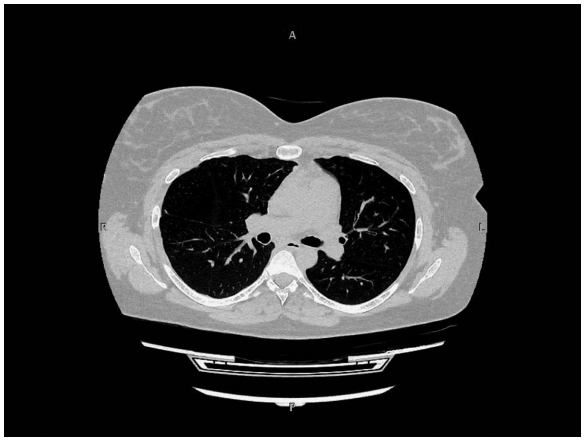

Fig. 1 The lung CT scan at the patient's latest consultation (30 months post-partum), showing a diffuse low attenuation area in the right upper lobe.

pregnant women with AATD currently follows guidelines for general lung disease, with emphasis on the management of respiratory symptoms and prevention of exacerbations. Whether to initiate AAT therapy relies on expert opinion and clinical experience; however, there is currently little evidence to guide this decision.[4] Although there are no known pregnancy-specific safety concerns with augmentation therapy, data for the use of AAT therapy in pregnancy are limited to a single recent case report by Gaeckle *et al.*, which describes a patient who continued with AAT therapy throughout pregnancy and delivered a healthy baby at term.[4]

This case adds to the very limited data regarding AAT therapy during pregnancy, supporting the argument that it can be safely initiated in response to severe impairment of respiratory function. The case also adds to the evidence that it is possible for patients with AATD to experience no pregnancy-related complications and deliver a healthy baby; however, close patient monitoring is essential to a positive outcome.

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Conflicts of interest

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LETTER TO THE EDITOR

Advantages and limitations of the ROX index

Dear editor

We have read with interest the study by Vega et al[1] published in the latest issue of the journal, where the authors propose the ROX index as a predictor of failure of high-flow nasal cannula (HFNC) therapy in patients with pneumonia due to SARS-CoV-2, and we would like to share some considerations on the advantages and disadvantages of using this index.

Non-invasive ventilatory support has gained relevance in recent years with the popularization of HFNC in patients with pneumonia. This therapy has been shown to be more effective than standard oxygen therapy and is recommended as first-line treatment for acute hypoxemic respiratory failure (AHRF).[2] These patients usually present dyspnea, hypoxemia, respiratory alkalosis, impaired gas exchange and consolidation images on chest tomography, similar to SARS-CoV-2 patients who also present fever and cough requiring a more advanced oxygen therapy.[3,4]

By demonstrating its effects on gas exchange and respiratory mechanics, a possible delay in endotracheal intubation and invasive mechanical ventilation was quickly observed due to the possibility of masking the deterioration of the clinical picture. To avoid this situation, the ROX index (ratio of oxygen saturation as measured by pulse oximetry/FiO_2 to respiratory rate) was proposed for patients with pneumonia and AHRF, and it showed accuracy in predicting HFNC failure at 12h of treatment (ROC 0.74 CI95% 0.64-0.84 p< .002), with <4.88 being the cut-off value associated with intubation (HR 0.273 CI95% 0.121-0.618 p .002).[5]

In the last 5 years, this index has been widely used due to its easy application at the bedside, which requires non-invasive variables for its measurement and can be evaluated at any time, even by non-medical health professionals. However, this same characteristic could cause small variations in its components to produce very dissimilar results. We must consider that the parameters to be evaluated can easily vary throughout the day or in different clinical situations (fever, mobilization, fatigue, pain, acidosis, hypotension). In addition, it could be considered as a static index that refers to a specific moment in time and not to the clinical evolution of the patient. Another disadvantage is that the index does not include the flow rate provided and it has been reported that changes in the flow rate can modify the result of the therapy[6] because it can generate a continuous pressure effect in the airway and favor the lavage of the dead space, increased end-expiratory volume and decreased respiratory rate and work of breathing. Due to these possible biases, other monitoring alternatives have been proposed, which we have discussed elsewhere.[7] The role of lung ultrasonography (LUS) has also been mentioned as a tool to predict intubation: in addition to the evaluation of the excursion and diaphragmatic contraction, at bedside and non-invasively, LUS has proven the worsening of the disease in the presence of B lines pattern and the lack of aeration when dyspnea and hypoxemia were present.[4]

Vega et al demonstrated the usefulness of the ROX Index to guide the intubation decision in patients with COVID-19 pneumonia outside the ICU with a cut-off level <5.9,[1] however we suggest that the other parameters are not ignored, when taking decisions in scenarios of low vigilance, such as neurological deterioration, work of breathing, mental status alterations, agitation, drowsiness or stupor.

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Conflicts of interest

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CORRESPONDENCE

COVID-19 pneumonia and ROX index: Time to set a new threshold for patients admitted outside the ICU. Author's reply

We appreciate the interest of Gallardo et al. in our paper "COVID-19 Pneumonia and ROX index: Time to set a new threshold for patients admitted outside the ICU".[1] We are grateful to the authors for their positive comments, and brilliant insights on the advantages and disadvantages of using the ROX index as a predictor of failure of high-flow nasal cannula in patients with pneumonia due to SARS-CoV-2. We believe these remarks will foster an important debate regarding the interpretation of the ROX index.

The first issue regards the specific strategy to treat acute hypoxemic respiratory failure (AHRF). In their letter,[2] they state that high flow nasal cannula (HFNC) has been shown to be more effective than standard oxygen therapy and it is recommended as first-line treatment for AHRF. This, however, is not true in patients with COVID-19—related acute hypoxemic respiratory failure in which there was no significant difference between an initial strategy of HFNC compared with conventional oxygen therapy. Instead, an initial strategy of continuous positive airway pressure (CPAP) significantly reduced the risk of tracheal intubation or mortality compared with conventional oxygen therapy.[3]

Secondly, it is very true what the authors suggested regarding that the parameters that are evaluated can easily vary throughout the day or in different clinical situations (fever, mobilization, fatigue, pain, acidosis, hypotension). Nevertheless, our study assessed the ROX index 4 times in the first 24 hours, so that in this time frame it is very possible to detect any major clinical variation. Indeed, there are already on the market instruments able to monitor continuously this index,[4] and therefore in the right context it should not be considered a static index.

Furthermore, we totally agree with the authors that a small effect may be observed in the ROX index using different flow in terms of the pressure effect in the airway and favour the lavage of the dead space or increased end-expiratory volume and decreased respiratory rate and work of breathing. Owing to the fact that the large majority of the studies have mainly used the setting at 50-60 $L.min^{-1}$ in patients with acute respiratory failure,[5—7] we used the same flow rate in all patients so as not to bias the sample. Indeed, the index has been so far proposed only in hypoxic patients and some of these physiological mechanisms you are referring to are typical of hypercapnic patients (i.e. lavage of dead space). Also, the generation of airways pressure is never constant, despite the flow used. In other words, HFNC is not equivalent to CPAP in terms of pressure, as you stated. While HFNC controls the flow with a variable pressure, CPAP controls the pressure with a variable flow rate.[8] Moreover, during HFNC, pressure is also strongly dependent on the closure of the mouth and on average quite small, not overpassing the limit of 4-5 cmH_20.

In conclusion, above all, we would like to congratulate Gallardo et al who were able to clearly summarize in a few words which parameters to take into account when using the ROX index to monitor a patient with AHRF.

Conflicts of interest

The authors have no conflicts of interest to declare.

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PHOTO

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: A rare and under-diagnosed condition

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Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) was first described in 1992.[1] DIPNECH is a rare and poorly understood disorder that is believed to be underdiagnosed.[2,3] It falls under the spectrum of neuroendocrine cell proliferations and it is characterised by marked and extensive hyperplasia of the neuroendocrine tissue of the bronchial and bronchiolar walls. It is considered a preinvasive lesion for lung carcinoid tumours by the World Health Organization.[3] This proliferation of cells causes bronchiolar obstruction with subsequent constrictive bronchiolitis.

We present the case of a 75-year-old female who was referred to the pneumology department in the context of a history of more than one year of nocturnal non-productive cough associated with progressive dyspnoea. She reported no other symptoms. Stress echocardiography showed elevated systolic pulmonary artery pressure with exercise (47 mmHg). Functional respiratory tests showed no abnormalities. In order to rule out interstitial pathology, the study was completed with a chest High Resolution Computed Tomography (HRCT) that showed multifocal bilateral pulmonary micronodules, bronchiectasis with bronchial wall thickening and extensive mosaic attenuation areas due to air trapping (Fig. 1A,B). DIPNECH diagnosis was proposed. The patient underwent video-assisted wedge lung resection thoracic surgery. The histologic description showed a clustered intramucosal proliferation of spindle-shaped cells with salt and pepper chromatin and positivity to neuroendocrine markers (Fig. 1C,D).

DIPNECH has been typically described in middle-aged, non-smoking women.[4,5] Although it is most often an incidental finding, there is the possibility of its presentation as an insidious clinical picture of dyspnoea and dry cough. On HRCT, DIPNECH manifests as multiple small bilateral pulmonary nodules that represent neuroendocrine cell aggregates that can narrow the lumen of the distal airway with subsequent thickening of the bronchial walls and, therefore, bronchiectasis, mucus plugs and air trapping develop. Histologic analysis gives the definitive DIPNECH diagnosis.[4] Aggregates of round, oval or spindle-shaped neuroendocrine cells with salt-and-pepper chromatin and immunoreactivity to chromogranin and synaptophysin are observed. The rarity of this condition poses some clinical challenge and DIPNECH treatment must be individualised. It can have a variable prognosis, but most studies show a good clinical outcome with follow-up and observation.[3,4] There is no evidence to support treatment with chemotherapy.[3] Surgical resection is possible if any area progresses to carcinoid tumours during follow-up.

The authors contributed in equal proportion to the realisation of the article.

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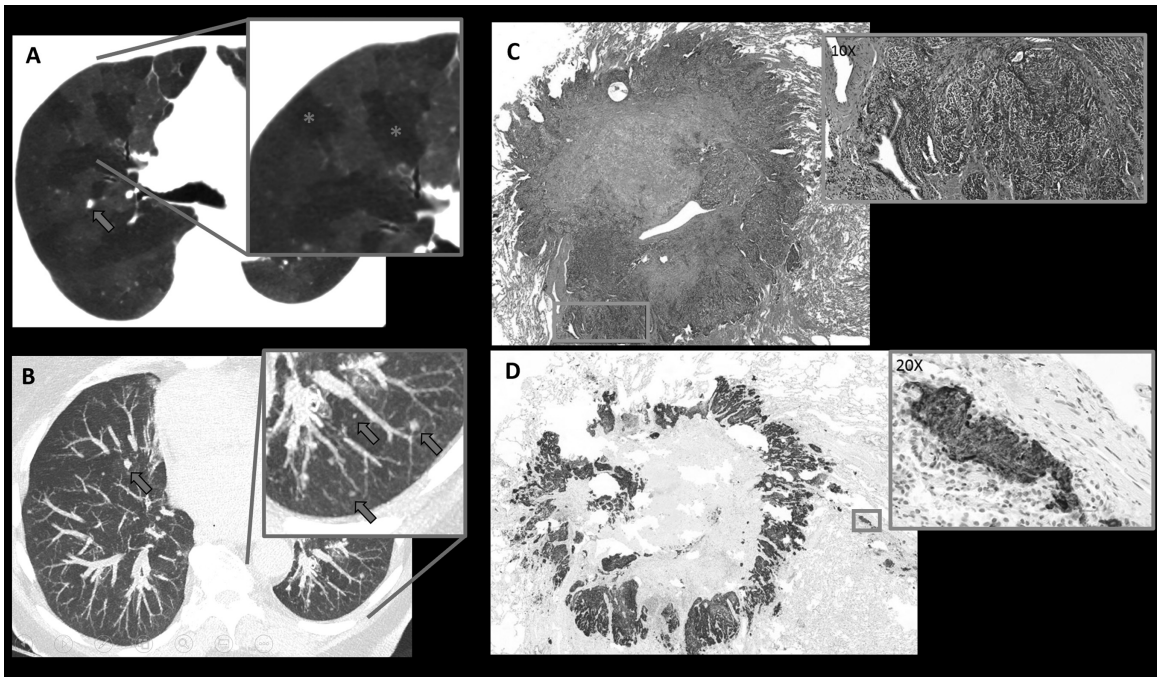

Fig. 1 Axial chest HRCT images: (A) MinIP image showing a mosaic attenuation pattern suggestive of air trapping (red asterisks in detail image). (B) MIP image showing countless bilateral millimetric pulmonary nodules (red arrows). (C) Haematoxylin-eosin stain of lung wedge resection fragment: a subpleural carcinoid tumour is seen, in the magnified image x10 high power fields (HPF) cells with neuroendocrine features can be seen: spindle-shaped, without mitotic figures or necrosis (blue box). (D) Chromogranin stain (neuroendocrine marker) shows diffuse positivity in nests of neuroendocrine cells (x20 HPF) (green box).

Declaration of Competing Interest

None of the authors have any conflicts of interest to disclose.

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