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EDITORIAL

Implementation of European Alpha-1 Research Collaboration (EARCO) in Portugal: the future starts now

Characterised over 50 years ago,[1] AATD is considered one of the most common hereditary disorders, but its epidemiology remains unknown in many countries, mainly due to its underdiagnosed state and a lack of registries of patients already identified.[2–4] In recent years, some countries are trying to fill this gap by creating diagnose and management guidelines and national and international patient registries.[5]

The European Respiratory Society (ERS) statement on AATD[6] has highlighted the differences in access to specialised care and specific treatments for patients with this rare disorder in Europe. In addition, there is a lack of prospective, standardised, follow-up data to understand the natural history of the disease in Europe and the influence of the risk factors, other genetic determinants, and augmentation therapy in the prognosis of the disease. Regarding augmentation therapy, the ERS statement summarised the inequalities of access to augmentation therapy in different European countries,[6] which were confirmed in a recent European survey,[7] but even in countries where augmentation is available and reimbursed there are differences in prescribing habits.[8] In Portugal, it is estimated that 1:5249 individuals 2000 individuals have a ZZ genotype, and that 1:281 individuals 37,400 individuals have a SZ genotype. Multiple rare alleles have been identified in Portugal but their frequencies in random populations are still unknown.[9–12] Nonetheless, the real burden of the disease is still unrecognized since there is no national registry. The Portuguese consensus document for the management of AATD was published in 2018.[13]

A study published in 2018 describes the current situation of AATD in Portugal.[14] In a 10 years' time frame, from 2006 to 2015, 417 individuals (almost 25% of tested cases) were confirmed as having severe or very severe AATD. These included 158 ZZ cases, 188 SZ and different combinations of rare and null alleles (n = 71). This study represents the most complete survey of AATD in Portugal so far and discloses a high rate of severe and very severe deficiency cases, attributed not only to ZZ and SZ genotypes but also a large number of rare combinations with other null and deficiency alleles.

Trying to answer fundamental questions about epidemiology, genetics, physiopathology, clinical management and prognosis of lung disease associated with AATD, a group of experienced and new researchers across Europe joined to form the European Alpha-1 Research Collaboration (EARCO).[15]

The EARCO is a Clinical Research Collaboration (CRC)[16] of the European Respiratory Society (ERS) Assembly 5 (airway diseases, asthma and chronic obstructive pulmonary disease) and aims to establish a collaborative effort that brings together multiple stakeholders, including researchers, healthcare providers, patients and industry, with the aim of advancing understanding through clinical and scientific research and improving the quality of life of patients with AATD.

The core project is the pan-European AATD Registry, a collaboration which will offer longitudinal real-world data for patients with AATD. The EARCO registry is modelled in part on the Alpha One International Registry (AIR) group established in 1997, which included representatives from 14 European countries.[17] The AIR group was successful in stimulating international collaborative research and organising and developing clinical trials; however, no real-life, longitudinal data were systematically collected.[5] The EARCO registry will also take advantage of the existing AATD registries that have been developed at the national level. However, these registries differ in terms of inclusion criteria, data collected and follow-up. One of the key tasks of EARCO will be harmonising the data collection and assessing the quality of the data included prospectively.[18]

In addition to the development of the registry, there are other initial objectives of EARCO for the next 3 years. Among these objectives, it is of great importance to build a network of patient representatives, researchers and clinical investigators, to identify informed research needs and establish an

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agenda for AATD research, and to attract young investigators to the area of clinical management and research of AATD for the future. In this respect, two surveys are being conducted, one for patients and the second for healthcare providers, particularly in order to understand the key research needs in the field of AATD in Europe.

Another project of EARCO is the evaluation of laboratory diagnostic methods of AATD in Europe. Developing reliable standards for laboratory diagnosis of AATD is crucial. There are different diagnostic algorithms in different reference laboratories in Europe,[19] which are usually adapted to the demands of the countries or to the needs of the target population for whom diagnosis is required. Although all these algorithms can provide an accurate diagnosis, it is important to establish an external quality control programme that can also be used for new laboratories, in order to ensure reliable test results.[20] The quality control programme of laboratory diagnosis will set the standards for the correct diagnosis of the condition across Europe.[21]

An ongoing international survey, on the initiation and indications of augmentation therapy, will provide insights into the current practice of augmentation therapy in those European countries where it is available.

Over the next 3 years, EARCO will set up the new European-based AATD registry and establish the roadmap for clinical and translational research in the field. It will also make a substantial contribution in advocacy and education in AATD and we appeal to all ERS members to be part of this. EARCO can be contacted through the group members, the national representatives, or directly through the website (www.ersnet.org/research/earco-european-alpha-1-research-collaboration). Portugal has a group of dedicated researchers in the field of AATD that are contributing to the different work-packages of EARCO; it is estimated that approximately 100 patients with severe deficiency could be included in the EARCO registry and some centers are already completing the regulatory process necessary to participate in this important international initiative. We encourage all health care providers involved in the care of patients with AATD to join EARCO by contacting the national or international representatives and start to improve the future of patients with this disease. The collaboration of all stakeholders, and in particular the inclusion of patients as active participants in the development of EARCO, makes it highly likely that EARCO will generate new knowledge with direct impact on patients' quality of life and clinical s care.[15]

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EDITORIAL

End-tidal carbon dioxide and alveolar dead space – an alternative in the diagnosis of acute pulmonary embolism?

Acute Pulmonary Embolism (PE) has been identified as one of the leading causes of deaths worldwide. Exact or nearly exact numbers only exist in the western hemisphere e.g. in North America and Western, Europe. It seems to be clear that mortality depends on early diagnosis followed by proper treatment by which mortality rates fall from over 39% to below 10%.

The high variability of clinical symptoms or the lack of symptoms whatsoever helps to establish an exact diagnosis with or without suspicion as early as possible. Mortality rates are high since 50% of patients with suspicious PE do not have any symptoms. Computed tomography (CT) pulmonary angiography is the gold standard for diagnosing PE.[1]

The ability to rule out PE was already demonstrated by Kline et al.,[2] over 20 years ago by combining alveolar dead space fraction calculations and plasma D-dimer levels. A normal alveolar dead space fraction and a negative D-dimer shows a high sensitivity (100%) to excluding PE in outpatients, however specificity was only 65%. Steady-state end-tidal alveolar dead space fraction and D-dimer were used also as bedside tests to exclude PE.[3] Measuring end-tidal CO_2 tension was also used as a screening tool to exclude PE.[4–6]

In the current issue of *Pulmonology* Yucel et al.,[1] stated that the combined use of end-tidal carbon dioxide ($ETCO_2$) and alveolar dead space fraction (AVDSf) values is an important and valuable tool in diagnosing PE, a very important diagnosis in internal medicine, cardiology, pneumonolggy and other specialities in medicine. In that study[1] one-hundred patients with suspected PE were included and evaluated using clinical prediction rules – Wells score – and the modified Geneva score.[7,8] Pulmonary embolism was ruled out with normal D-dimer analysis (<0.55 mg/dl). Patients' ET CO_2 values were measured using time versus waveform capnography before performing CT-angiography. Simultaneously arterial puncture was performed for arterial blood gas analysis. Pulmonary embolism was detected in 36% of patients and classified into high-, moderate-, and low-risk groups according to the Wells- and modified Geneva scores, respectively, when ETCO2 was 28.5 mmHg. Diagnosis of acute or subacute PE was excluded in 100% of patients with low Wells- and Geneva-scoring system with AVDSf < 0.128. On the other hand high Wells- and high modified Geneva scores were helpful in diagnosing PE based on ETCO2 and AVDSf values calculated using capnography as a simple bedside measure with clinical prediction rules and D-dimer test using an alternative?[4–6] Several similar studies have been performed using this method described in the article of this issue.

Kline et al.,[2] were the first to show the ability to rule out PE by combining alveolar dead space fraction calculations and plasma assays. In 70 outpatients the combination of a normal alveolar deadspace fraction and a negative D-dimer fraction showed a 100% sensitivity to excluding PE with a lower sensitivity of only 65%. Rodger et al.,[9] reported 246 patients (inpatients, outpatients and patient admitted to the emergency ward) with suspected PE. Pulmonary embolism was excluded with a negative D-dimer result and a sensitivity of 83% and a specificity of 58%. At low steady state end tidal alveolar dead space fraction PE was excluded with a sensitivity of 80%, and a specificity of 70%. And again the combination of both diagnostic tests – end-tidal alveolar dead space fraction and D-dimer – increased the sensitivity to 98%, therefore ruling out acute or subacute PE without further diagnostic testing.

Despite its noninvasiveness and rapid availability, measuring $ETCO_2$ gradient for assessing alveolar dead space has not been regularly performed. Technical limitations and the lack of validation together with rather difficult data acquisition and a weak diagnostic performance were the main obstacles. Last but not least the strategy used by Yucel et al.,[1] is a non-invasive method without using radionucleids and radiation. This is very important in patients who may suffer PE during pregnancy which is quite common and very often overlooked condition for which patients do not receive appropriate therapy as and when needed.

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COMMENT

Helmet continuous positive airway pressure and prone positioning: A proposal for an early management of COVID-19 patients

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Introduction

In late December 2019, clusters of patients with interstitial pneumonia of unknown cause were reported by some local health facilities in Wuhan (China). The Chinese Centre for Disease Control conducted an epidemiologic and etiologic investigation, leading to the identification of a novel coronavirus (SARS-CoV-2).[1,2] On March 11th, the World Health Organization (WHO) declared the novel coronavirus disease (COVID-19) a pandemic. In the area of Wuhan, COVID-19 mainly affected male patients (around 60%), with a median age of about 50 years; 40% of patients developed Acute Respiratory Distress Syndrome (ARDS) 5% requiring intensive care. The mortality rate was around 2%.[3,4] However, Grasselli et al. found that the mortality was 26% in ICU. The death rate was higher among those who were older.[5]

In a more recent report from Italy including 22512 patients, COVID-19 has infected 2026 healthcare workers, with a total case fatality rate of 7.2%. Patients were predominantly older than 60 years, 46.1% had mild severity, while 24.9% severe disease.[6]

To date (April 16th) the cases are 1991562 with more than 130 000 deaths.[7] In a certain percentage of patients, COVID-19 is a viral interstitial pneumonia[8] characterized by fever, dry cough, dyspnoea, and bilateral ground-glass opacities,[9] with about 67% of patients evolving to a severe pneumonia.[10,11]

However, preliminary observations reported that COVID-19 patients, compared to conventional ARDS, are characterized by moderate to severe hypoxaemia despite a relatively high pulmonary compliance.[12,13] A potential mechanism may be loss of hypoxic vasoconstriction, explaining the observed severe hypoxaemia and the effect of very high levels of positive end-expiratory pressure (PEEP) on oxygenation not depending on lung recruitment.[13] High levels of PEEP may adjust redistribution of perfusion diverting flow towards high ventilation-perfusion (Va/Q) areas increasing arterial

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oxygen tension (PaO_2); however, over-distension of the healthy lung areas and an increased right cardiac afterload is possible.[13]

In patients with mild to moderate ARDS, with a PaO_2 to inspired oxygen fraction (PaO_2/FiO_2) >150, different modalities of non-invasive respiratory support (NIRS) might be attempted in order to avoid intubation.[14,15] However, NIRS could potentially lead to intubation delay and cause a self-inflicted lung-injury (SILI),[16] due to the high transpulmonary pressures. SILI in turn would lead to a severe decrease in lung compliance.[17] Continuous Positive Airway Pressure (CPAP) is a form of NIRS during which a fixed level of PEEP is applied to the airways, while the entire work of breathing is generated by the patient's respiratory muscles (i.e. no pressure assist is provided during inspiration). This would reduce the likelihood of generating high transpulmonary pressure and tidal volume compared to non-invasive intermittent positive pressure ventilation.[18]

Due to the enormous number of COVID-19 patients with acute respiratory failure and to the shortage of ICU beds and ventilators, helmet CPAP (hCPAP) is widely used in Italy.[5,19]

In particular, in a scenario of a discrepancy between facilities and a large number of casualties, as with COVID-19 pandemic, the application of hCPAP might be useful as an ''easy to perform'' supportive strategy.

Prone position sessions may adjust pulmonary perfusion diverting flow towards high Va/Q areas, and allowing a redistribution of aerated and non-aerated areas whenever present.[20,21] Furthermore, as opposed to non-invasive intermittent positive pressure, hCPAP does not necessarily need a ventilator (potentially in short supply in case of mass casualties) and it is not affected by patient-ventilator asynchrony, a determinant of discomfort and treatment failure.[22–24]

The hypothesis is that in case of a pandemic, selected COVID-19 patients may benefit from the combination of early hCPAP and prone position sessions, in order to reduce the need for intubation and invasive mechanical ventilation, ''buying time'' for the disease to heal.

Evaluation of the hypothesis

Prone position

Prone position was first described in 1976 in patients with ARDS.[25] First, prone position modifies respiratory mechanics. In particular, the ventral chest wall cannot expand, because it is in contact with the firm surface of the bed.[26] In patients with ARDS, the lung weight increases by 4–5 times, pulmonary tissue becomes stiffer and compliance decreases, in association with compression atelectasis.[26,27] During prone position, decreased chest wall compliance improves the redistribution of lung density from dorsal to ventral areas, and increases lung aeration from ventral to atelectatic dorsal regions, improving gas exchange.[28] Nowadays, the application of prone position is recommended in most severely ill patients. Guerin et al. showed that, in patients with severe ARDS, the application of prolonged (17 h) prone position sessions for approximately 4 days reduced the absolute mortality risk by 17% and the relative risk by 50%.[29] However, other studies have not shown outcome benefits of prone position.[30–33]

These differences might be explained by the fact that patients included were not so severely ill, periods of use were shorter and the use of protective ventilation strategies were less strictly enforced.[34] Early application of prone position for prolonged (up to 16 h) periods has been also demonstrated to improve the survival rate[29] in other clinical settings.

It has been suggested that prone position in COVID-19 patients may lead to overwork of professionals with scarce clinical efficacy in terms of recruitment.[13] However, preliminary data suggest that COVID-19 patients undergoing CPAP may benefit from this treatment with even the most severe forms of hypoxaemic respiratory failure characterized by a refractory hypoxaemia (i.e. $PaO_2/FiO_2 < 150$).[5]

Our hypothesis is that, selected COVID-19 patients may benefit from the combination of early hCPAP at moderate levels of PEEP (i.e. 10 cmH_2O) and prone position, to avoid overdistension of the healthy lung areas thus slowing the progression of the disease and allowing patients to ''buy time'' to heal. Indeed, in these instances, hCPAP is likely be effective by keeping the lung open[20] and reducing venous admixture by diverting flow towards better high Va/Q areas.[21]

Non-invasive respiratory support

Although life-saving, invasive mechanical ventilation is associated with side effects and complications leading to increased morbidity and mortality. Therefore, alternative strategies have been proposed, especially for those patients with less severe forms of ARDS. Among these strategies, NIRS might play a role in reducing intubation rate.[14] Application of positive pressure to the airway may open collapsed alveoli, increases functional residual capacity and improve the Va/Q match and lung compliance. As a result, oxygenation and respiratory workload improve, with the potential benefit of avoiding intubation and invasive mechanical ventilation.[14] More recently, the combination of non-invasive intermittent positive pressure with prone position was shown to prevent the need for intubation in up to half of the patients with moderate to severe ARDS. In addition, patients failing NIRS and requiring intubation were more severe, as compared to those succeeded.[35]

The use of CPAP may provide the application of a stable level of positive airway pressure throughout the entire respiratory cycle. Therefore, it may result in effective recruitment of closed alveoli, with an increase in the functional residual capacity and improvement of oxygenation.[36,37] During NIRS, comfort is one of the determinants of treatment success or failure.[38] CPAP may be delivered through different interfaces, such as masks or helmets. Compared to masks, helmets are more comfortable,[39] they allow longer continuous application of the treatment and lower complications correlated to the interface (i.e. eye irritation, gastric distension and skin necrosis).[39] As during NIRS, comfort is one of the determinants of treatment success or failure[38,39] it is important to note that unintentional leaks are kept to a minimum during hCPAP.[40–42]

The ''helmet bundle'' in COVID-19 patients has recently been published to optimize treatment.[19]

Precautions when using NIRS

It is worth noting that the recent guidelines on the use of NIRS in *de novo* hypoxaemic acute respiratory failure do not provide any recommendation, due to uncertain and conflicting evidence.[43] Very recently, the Surviving Sepsis Campaign has provided some guidelines on the management of critically ill COVID-19 patients.[44] The panel of experts suggested a trial of NIRS, recommending close short-interval monitoring for worsening of respiratory status and early intubation in a controlled setting if worsening occurs,[44] although the main risk of using NIRS in *de novo* ARF is delay in intubation[44] with the risk of developing SILI.[16,17]

NIRS in the era of COVID-19

Non-invasive intermittent positive pressure requires the use of mechanical ventilators, of there is currently a shortage due to the pandemic COVID-19.[3,6] Furthermore, non-invasive intermittent positive pressure may also worsen patient-ventilator interaction and synchrony, which might be detrimental for patients' comfort, leading to treatment failure.[22–24] For these reasons, CPAP might be a valid alternative. In addition, the use of an interface such as the helmet may be advantageous, compared to a facial mask.[45–47] In fact, the helmet improves comfort of the patient, assures prolonged continuous application of the treatment and it is characterized by very low air-leaks,[40,45–48] limiting the spread of the virus in the environment. Interestingly, when a patient coughs, he/she generates a peak cough flow up to 400 L/min, theoretically creating less contamination for the operators and environment. High flow nasal therapy could be also combined with hCPAP.[49,50] However, experimental studies of exhaled air dispersion by mannequins have demonstrated greater exhaled air dispersion with conventional low flow nasal cannula at 5 l/min, compared with HFNC.[51] Furthermore, the helmet's ports can be protected with two antimicrobial filters, further reducing air dispersion. This is of utmost importance in cases of infections transmitted by aerosolization, such as COVID-19.[41]

Based on these facts, we have hypothesized that, in the current COVID-19 pandemic emergency, an attempt to combine early hCPAP and prone positioning sessions might improve oxygenation in selected patients. Criteria to attempt hCPAP (8–12 cmH_2O) and prone position in fully collaborating symptomatic patients are listed in Table 1. The presence of dyspnoea, as defined by a Borg scale >3,[52] is not deemed necessary because dyspnoea is not always clinically evident in these patients. Patients with chronic obstructive pulmonary disease or with an arterial partial pressure of carbon dioxide >50 mmHg will be excluded.

Settings for CPAP in prone position

Prone position during hCPAP requires some precautions, in order to avoid discomfort, skin and eyes lesion and treatment failure. First, the use of helmet without armpit braces is preferable, although not mandatory, since in the literature it has been reported to be more comfortable.[48,53] Another important precaution is to prevent the rigid collar from generating skin lesions by direct pressure on skin due to ischaemia or shearing forces and mechanical stress to the neck. Interestingly awake patients during hCPAP may assume prone position with minimal assistance. Fig. 1 shows one patient switched from supine to prone position using hCPAP and continuous tidal volume measurement using a dedicated software built into a turbine driven ventilator.[54]

Table 1 Inclusion and exclusion criteria.

Inclusion criteria	Esclusion criteria
Cough, fever, sign of interstitial pneumonia on chest X-Ray, lung ultrasound and/or CT-scan	Chronic obstructive pulmonary disease
History of previous contact with COVID-19 patients	Arterial partial pressure of carbon dioxide >50 mmHg
Patients with a PaO_2/FiO_2 between 200 and 300, while breathing in room air or through Venturi mask measured after 1 h from hospital admission	Pregnancy
Pulse oxymetry (SpO_2) <95% in room air	Contraindication to CPAP
Dyspnoea, as defined by a Borg scale >3	

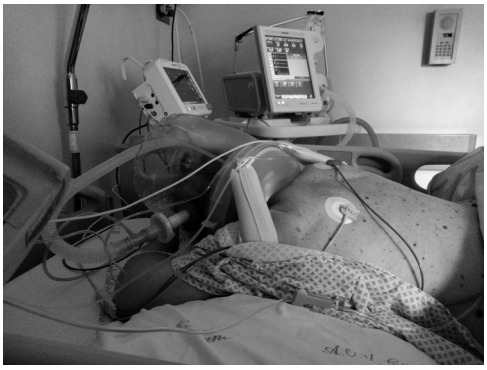

Figure 1 The figure shows a patient in prone position receiving hCPAP. One small pillow is positioned under the chest and another one under the head, to raise the head and to leave some free space around the neck.

Consequence of the hypothesis and discussion

This is the first proposal of a study aimed at investigating the possibility of combining hCPAP and prone position in order to avoid deterioration of gas exchange and intubation in patients affected by COVID-19 pneumonia.

The application of early sessions of pronation in patients with mild-to-moderate ARDS might improve gas exchange without further increasing PEEP.[26,27] This experimental plan has several strengths. First, a thorough literature review and straight-forward protocol definition will guarantee the best possibilities for the intervention. The experimental treatment has notable possibilities of being effective and helpful, in particular in a setting of mass-casualties happening now in Italy and rest of Europe. Second, the ability to limit the

treatment to selected patients may amplify the potential benefits reducing the failure rate. Third, if the combination of hCPAP and prone position reduced the intubation rate, the health care system could improve the allocation of ICU beds, granting better treatment to all patients needing ventilatory assistance.

Furthermore, our preliminary results (Gregoretti et al., unpublished data) from an ongoing pilot study in COVID-19 patients, measuring tidal volume during hCPAP,[54] showed that a low mean tidal volume coupled with high pulmonary compliance and a low respiratory rate, which suggests that transpulmonary pressure is kept low.

Our hypothesis has also some major limitations. First of all, the real effect of hCPAP from the pathophysiological point of view in this disease is unknown. In healthy patients, CPAP in prone position causes a Va/Q mismatch for a more uniform ventilation distribution, despite a higher perfusion in dependent parts of the lung.[33,55] CPAP may increase alveolar pressures and resistance in small vessels of the lungs (zone 1)[56] especially in nondependent lung regions, explaining the higher perfusion in dependent parts when the subject is prone. This finding suggests the redistribution of perfusion could improve oxygenation in patients lacking hypoxic vasoconstriction. Second, inclusion criteria for this treatment are untested; in addition, time in prone position from our preliminary data is shorter than in sedated patients. Third, strict monitoring by trained personnel, in a step-down unit or in a monitored unit, would be required to early identify a treatment failure and avoid any intubation delay. Lastly, patient's tolerance may play a fundamental role in the treatment. In addition, the lack of patient-ventilator asynchronies during CPAP together with the use of the ''helmet bundle'' should ameliorate tolerance.[41]

In conclusion, if our hypothesis is valid, physicians may reduce the need for endotracheal intubation and invasive mechanical ventilation, shortening the hospital length of stay and improving survival rates. Furthermore, the need for ICU beds may be reduced, in favour of sub-intensive beds. This setting does not exclude the need of implementation in areas where prompt intubation can be easily performed. In addition, this strategy may also be an adjunctive tool for those patients who are not recommended for endotracheal intubation and care is limited to hCPAP as ''ceiling of treatment''.

Otherwise, patients treated with hCPAP presenting with clinical signs of excessive inspiratory effort, should be promptly intubated to avoid too injurious transpulmonary pressure leading to SILI.[16]

Conflicts of interest

Dr. Navalesi's research laboratory has received equipment and grants from Maquet Critical Care, Draeger and Intersurgical S.p.A. He also received honoraria/speaking fees from Maquet Critical Care, Orionpharma, Philips, Resmed, MSD and Novartis. Dr. Navalesi contributed to the development of the helmet Next, whose licence for patent belongs to Intersurgical S.P.A., and receives royalties for that invention. Dr. Longhini and Dr. Navalesi contributed to the development of a new device, whose patent is in progress (European Patent application number EP20170199831). Dr. Cortegiani, Dr. Accurso, and Dr. Gregoretti declare a patent pending, in association with the University of Palermo – Italy (No. 102019000020532 – Italian Ministry of Economic Development) related to the content of this manuscript. Dr. Gregoretti received fees for lectures by Philips, and received payments by Philips for consultancies in the developing process of the EVO Ventilator and fees for lectures or consultancies from Resmed, Vivisol and Air Liquide not related to the present work. The remaining authors have no conflict of interest to disclose.

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ORIGINAL ARTICLE

The combined use of end-tidal carbon dioxide and alveolar dead space fraction values in the diagnosis of pulmonary embolism

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KEYWORDS
Pulmonary embolism;
Clinical prediction rules;
$ETCO_2$;
AVDSf

Abstract
Background: Several studies have reported that computed tomography pulmonary angiography is the best method for diagnosing pulmonary embolism (PE). This study, however, aimed to predict or exclude PE using the end-tidal carbon dioxide ($ETCO_2$) value and alveolar dead space fraction (AVDSf) together.
Methods and Materials: One-hundred patients were included in the present study. Patients with suspected PE were evaluated using clinical prediction rules proposed by the Wells and the Modified Geneva scoring systems. PE was ruled out in patients with normal D-dimer concentrations (< 0.55 mg/dl). Patient $ETCO_2$ values were recorded using time versus waveform capnography before performing imaging studies. Capnography was performed for 2 min; however, the average $ETCO_2$ values measured over the final 1 min were recorded in ''full continuous'' mode. Arterial puncture was performed simultaneously for arterial blood gas analysis. Additionally, AVDSf was calculated according to the Bohr equation.
Results: PE was detected in 36 % of patients. Patients were classified into high-, moderate, and low-risk groups according to the Wells and Modified Geneva scores. PE was excluded in 95 % and 100 % of patients with low Wells and Modified Geneva system scores, respectively, when $ETCO_2$ was > 28.5 mmHg. The diagnosis of PE was excluded in 100 % of patients with low Wells and Modified Geneva scoring system scores with AVDSf < 0.128. High wells and Modified Geneva system scores were helpful in diagnosing of PE (100 %) when AVDSf was > 0.128.
Conclusion: It was possible to exclude/predict PE based on $ETCO_2$ and AVDSf values calculated using capnography when evaluated with clinical prediction rules and D-dimer test using an algorithm.

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Introduction

Pulmonary embolism (PE) is one of the most common thromboembolic disorders, with complications ranging from mild symptoms to severe clinical conditions such as life-threatening right heart failure. Due to the nonspecific clinical presentations of PE, an incorrect approach to the work-up may be harmful to the patient or may result in recurrent thromboembolic events, bleeding, or death.[1]

Age adjusted D-dimer concentration can rule out PE in patients with low risk scores according to the Wells criteria.[2] The remaining patients often undergo computed tomography (CT), which is costly and time-consuming, and may yield a false-positive result and pose a risk for contrast-associated allergic reaction, nephropathy, and radiation-associated solid tumors.[3]

In recent years, the use of capnography—a simple, non-invasive, rapid, and practical technique based on simple physiopathology—for diagnosing PE has been investigated as a potentially useful method.[4,6]

Pulmonary vascular obstruction is indirectly reflected by the alveolar dead space fraction (AVDSf) and end-tidal carbon dioxide ($ETCO_2$). Because capnography can be used to evaluate these parameters, it has been recommended as a valuable tool to exclude PE. In PE, the lung compartment is ventilated but non-perfused. The AVDSf prevents sufficient gaseous exchange and decreases the alveolar carbon dioxide (CO_2) content, which can be measured using a bedside capnograph. Clinical presentation of conditions, such as angina, is similar to that of PE, but does not exhibit increased AVDSf. Conditions that increase AVDSf, such as chronic obstructive pulmonary disease, are easily distinguished from PE. AVDSf, which is estimated using the partial pressure of arterial CO_2 ($PaCO_2$) – $ETCO_2$ gradient, reflects the proportion of the lung that is ventilated but not perfused.[7]

The aim of this study was to exclude or predict PE using an algorithm to evaluate capnographs, clinical prediction rules, Wells and/or Modified Geneva scores, and D-dimer assays without using advanced imaging modalities because patients may not always be suitable for these modalities and, moreover, they are not availabile in all centers.

Methods

Ethics committee approval was obtained from XX University in May 2016 (GO 16/341-08). Written informed consent was obtained from all participants. A prospective observational study was performed between November 2016 and May 2017 in the Emergency Department of XX University, in Ankara, Turkey.

Patients with suspected pulmonary thromboembolism were included in the study. The 2014 European Society of Cardiology (ESC) PE guidelines were followed for investigating PE. Individuals < 18 years of age, those who refused or were unable to participate, and those with a contrast allergy according to the 2014 ESC guidelines were excluded. In addition, those with low-risk clinical prediction rules that met all the PE rule-out criteria (PERC) or negative D-dimer assay results and moderate-risk clinical prediction rules with negative D-dimer assay results, were also excluded.

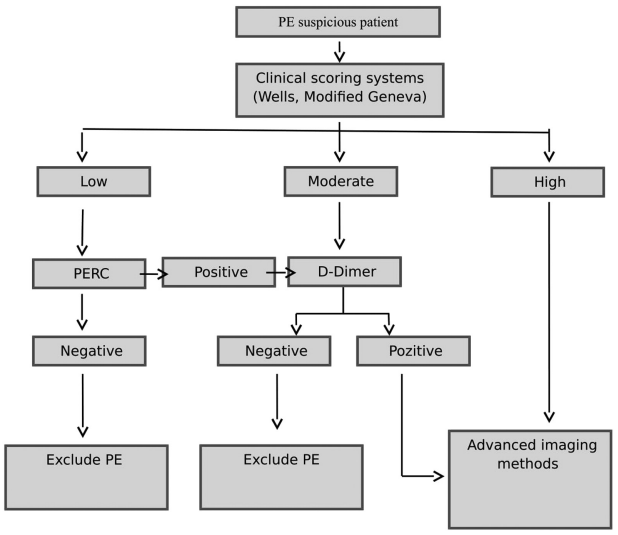

Fig. 1 Algorithm for diagnosis of pulmonary embolism (PE).

A capnography device (Covidien, USA), provided by the scientific research project unit of the authors' university, was used.

Study design

Age, sex, and PE-associated symptoms (dyspnea, pleuritic chest pain, cough, substernal chest pain, fever, hemoptysis, syncope, unilateral leg pain, and deep venous thrombosis [DVT]) of each patient were recorded. Patients with suspected PE were evaluated using clinical prediction rules and the Wells and Modified Geneva scoring systems (low, moderate, or high risk) (Fig. 1). According to the 2014 ESC guidelines, patients classified as low-risk based on clinical prediction rules, but not PERC, underwent a rapid quantitative ELISA plasma D-dimer test. Moderate-risk patients underwent D-dimer testing, while high-risk patients underwent further evaluation using advanced imaging methods without the D-dimer test. PE was ruled out in patients with normal D-dimer concentrations **(< 0.55)**; these patients were not included in the study.

Capnographs and arterial blood gas samples were first evaluated in patients who were chosen to undergo advanced imaging. All high-risk patients identified based on positive D-dimer test results or clinical prediction rules were evaluated using advanced imaging methods. Patients requiring advanced imaging modalities underwent CT angiography, ventilation/perfusion (V/P) lung scintigraphy or echocardiography, and lower extremity venous doppler ultrasonography (USG). Based on the results of these advanced imaging examinations, patients were divided into two groups according to the presence of PE.

Diagnostic studies

Capnographic measurements

In the present study, a side-stream capnograph (Covidien, USA) was used. The capnograph was calibrated before each use, as recommended by the manufacturer. Patients who were not intubated underwent slow and proper breathing

training before the data were recorded using the capnograph. Data were recorded in ''full continuous'' mode. $ETCO_2$ was recorded as a time waveform. A single-use O2/CO2 nasal filter line (Microstream) was used in patients who were not intubated, and a Microstream FilterLine Set was used in patients who were intubated during recordings. Capnography was performed for 2 min; however, the average $ETCO_2$ values measured over the final 1 min were recorded. Arterial puncture was performed simultaneously for arterial blood gas analysis. Additionally, AVDSf was calculated using the following formula derived from the Bohr equation:

$$(PaCO_2 - PETCO_2)/PaCO_2$$

Advanced imaging methods

CT was the first choice in patients with suspected PE. CT angiography is performed only when a patient is not pregnant and exhibits normal renal function. A radiologist performed CT angiography. Based on the results of CT angiography, patients were divided into two groups according to the presence of PE. Patients with a glomerular filtration rate < 50 % were evaluated using V/P lung scintigraphy or echocardiography, and lower extremity venous doppler USG. A nuclear medicine specialist performed V/P lung scintigraphy and reported the presence or absence of high suspicion for PE. Patients who were pregnant first underwent echocardiography and lower extremity venous doppler USG. A cardiologist performed echocardiography and reported the corresponding results. Findings suggestive of PE (increased pulmonary artery pressure, septum flattening, septum paradoxical movement, findings of right ventricular loading, and McConnell's sign) were recorded using echocardiography. Evidence of DVT was detected using bilateral lower extremity venous doppler USG by radiologists. Patients with DVT and exhibiting signs of PE based on echocardiography were considered to have PE.

Statistical analysis

Categorical and numerical data were subjected to kikarke and *t*-test or Mann-Whitney test, respectively. Receiver operating characteristic (ROC) analysis was performed using software to determine optimal cut-off points, and $P < 0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

From the 200 patients with suspected PE, 100 were included in the study, of whom PE was detected in 36 % (n = 36).The mean age of patients diagnosed with PE (66 years) was older than that of those without PE (59 years) ($P = 0.04$). Sixty percent of the patients were female, and 56 % of those diagnosed with PE were female ($P = 0.64$).

Clinical Prediction Rule: The distribution of patients according to clinical prediction rules and Wells and Modified Geneva scores is shown in Table 1. While Wells clinical prediction rule was not found to be significant in determining PE ($P = 0.05$), the Modified Geneva score was significant ($P = 0.01$)

Table 1 The distribution of the patients according to the gender and PE diagnosis.

PE diagnosis	Femalen	Malen	Totaln
PE (+)	20	16	36
PE (-)	40	24	64
Total	60	40	100

Diagnosis of PE

Eighty percent of the patients (n = 80) underwent CT angiography, with PE detected in 32.5 % (n = 26). Seventeen percent (n = 17) of the patients underwent lung V/P scintigraphy, with PE detected in 58.8 % (n = 10). Three percent of the patients underwent echocardiography only and Doppler USG, and PE was not detected in this group.

Capnographic measurements

Patients with PE ''24'' exhibited lower $ETCO_2$ values than those without PE ''31'' ($P = 0$). The area under the ROC curve (AUC) for $ETCO_2$ was 0.758. The ROC curve for $ETCO_2$ for diagnosing PE is shown in Fig. 2. The optimal cut-off value for $ETCO_2$ was 28.5 mmHg, with a sensitivity of 75 %, a specificity of 64.1 %, a negative-predictive value (NPV) of 82 %, and a positive-predictive value (PPV) of 54 %.

Patients diagnosed with PE exhibited significantly higher mean AVDSf values (0.217) than those without PE (0.098). The AUC for AVDSf was 0.734. The ROC curve of AVDSf for

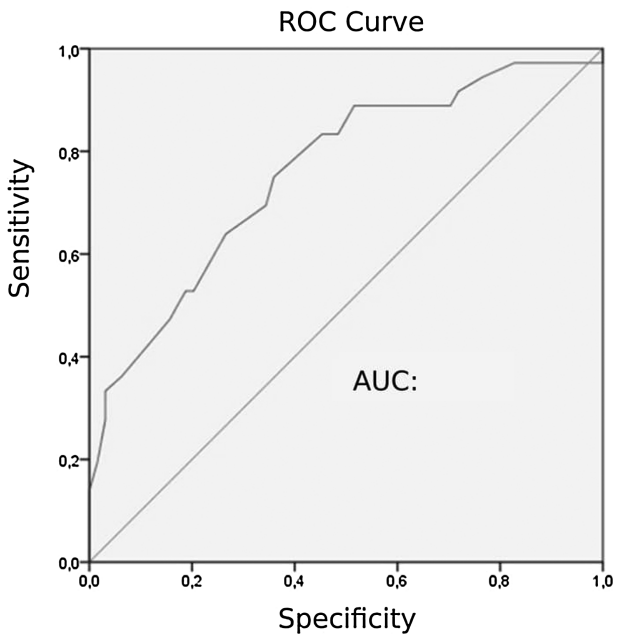

Fig. 2 Receiver operating characteristic (ROC) curve for end-tidal carbon dioxide ($ETCO_2$) in diagnosing pulmonary embolism (PE).

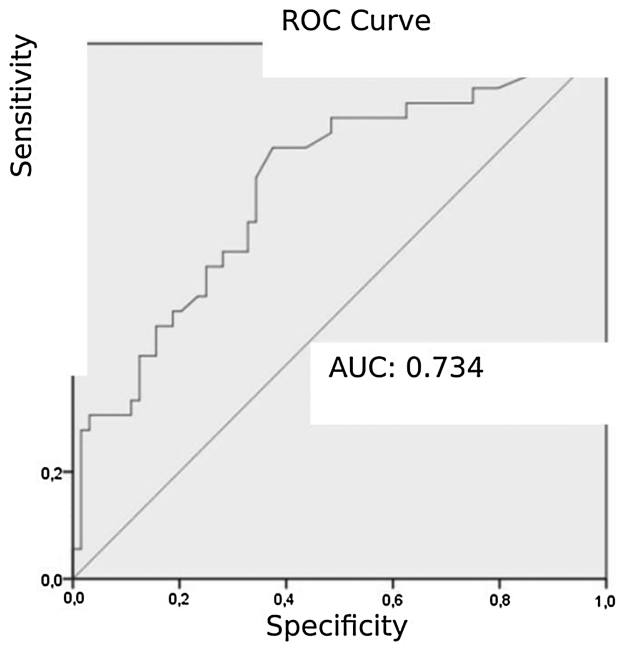

Fig. 3 Receiver operating characteristic (ROC) curve for alveolar dead space fraction (AVDSf) in diagnosing pulmonary embolism (PE).

diagnosing PE is shown in Fig. 3. The optimal cut-off value for AVDSf was 0.128, with a sensitivity of 80.6 %, a specificity of 62.5 %, an NPV of 85.1 %, and a PPV of 54.7 %.

Combined results of capnography and clinical prediction rules

Classification of the patients into high-, moderate-, and low-risk groups according to Wells and Modified Geneva scores was helpful in diagnosing PE, with PPV values of 71.4 %, 44.8 % and 64.3 %, and 80 %, 51.4 % and 50 %, respectively, when $ETCO_2$ was < 28.5 mmHg. When $ETCO_2$ was >28.5 mmHg, the corresponding NPV values for the exclusion of PE were 33.3 %, 77.8 % and 95 %, and 40 %, 80 % and 100 %, respectively (Fig. 4).

Classification of patients into high-, moderate-, and low-risk groups according to Wells and Modified Geneva scores was helpful in diagnosing PE, with PPV values of 100 %, 46.7 % and 55.6 %, and 100 %, 46.3 % and 66.7 %, respectively, when AVDSf was > 0.128. When AVDSf was < 0.128, the corresponding NPV values for the exclusion of PE were 60 %, 80.8 % and 100 %, and 75 %, 76.9 % and 100 %, respectively (Table 2).When $ETCO_2$ and AVDSf were combined in patients with low risk according to the Wells or Modified Geneva system, PE could be excluded. Furthermore, by using these parameters in patients with a high risk for these scoring systems, the diagnosis of PE could be 100 % confirmed.

Discussion

In our study, the mean age of the patients diagnosed with PE was 66 years, which was significantly older than those who were not diagnosed with PE. Similar results were observed by Ioannou et al., who found that the mean age of patients diagnosed with PE was 61.76 years.[8] Among the patients diagnosed with PE, 55.6 % were female, and no significant difference was observed in sex distribution. Similar results were observed in the study by Ioannou et al., who reported that the sex ratio (male:female) of patients diagnosed with PE was 1:1.04,[8] and PE was detected in 36 %. In a review by Manara et al., in which 14 studies including 2991 patients with suspected PE were analyzed, 608 were diagnosed with PE.[5] The frequency of PE varied from 5 % to 69 %, with an average of 20 %. The incidence of PE in the current study was within the range reported in these earlier studies (5–69 %).[5]

Among the patients diagnosed with PE in the current study, the proportion of those classified as low-, moderate-, and high-risk was 27.8 %, 52.8 %, and 19.7 %, respectively, according to Wells score, and 11.1 %, 69.4 %, and 19 %, respectively, according to Modified Geneva score. Similarly, in a previous study[160], 24 %, 54 %, and 22 % of the patients diagnosed with PE were classified as low-, moderate-, and high-risk according to the Wells scoring system, respectively, and 17 %, 64.4 %, and 17 % were classified according to Modified Geneva scoring system.

In our study, the Modified Geneva score was found to be significant in detecting PE, while the Wells score was not. Yetkin et al. found both the Wells and Modified Geneva scoring systems to be significant in detecting PE; however, these two clinical scoring systems were not found to be significant by Wong et al., Penaloza et al. and Shen et al., who found the Wells scoring system to be superior in detecting PE, although both the clinical scores were found to be significant.[9–12] The literature contains examples of significance and insignificance of both scoring systems in detecting PE.

Based on capnography, the mean $ETCO_2$ was found to be 24 mmHg, and was statistically significant in patients with PE. Similarly, Riaz et al. reported a mean $ETCO_2$ of 25.1 mmHg in patients diagnosed with PE and 33.1 mmHg in patients not diagnosed with PE.[6] This result is physiological due to the presence of ventilated but non-perfused lung compartments, $ETCO_2$ is lowered, which leads to PE.

Hemnes et al. reported an optimal $ETCO_2$ cut-off value of 36 mmHg, with a sensitivity of 87 %, a specificity of 53 % and an NPV of 97 %, with an AUC of 73.9 %. Riaz et al. determined an $ETCO_2$ cut-off value of 32.3 mmHg, with 100 % sensitivity, 68 % specificity, and 100 % NPV, with an AUC of 84 %.[6,13] Bonderman et al. established an $ETCO_2$ cut-off value of 36 mmHg, with an NPV of 96.6 %.[14] In the current study, the $ETCO_2$ cut-off value was found to be 28.5 mmHg, which is lower than the value reported by other studies, but with a lower NPV. Although Manara et al. included 14 studies in their review, the ideal cut-off value could not be determined due to differences among the studies.[5] Therefore, more studies with a larger number of patients are needed to calculate the ideal cut-off value.

Kurt et al. found the mean AVDSf value (0.174) to be higher in patients diagnosed with PE than in those not diagnosed with PE (0.136); these findings were similar those of the current study. The same researchers reported a cut-off value of 0.09, with a sensitivity of 70 %, a specificity of 61.1 %, a PPV of 80 %, and an NPV of 47.8 %.[15] In the current study, the cut-off value for AVDSf was found to be within the range

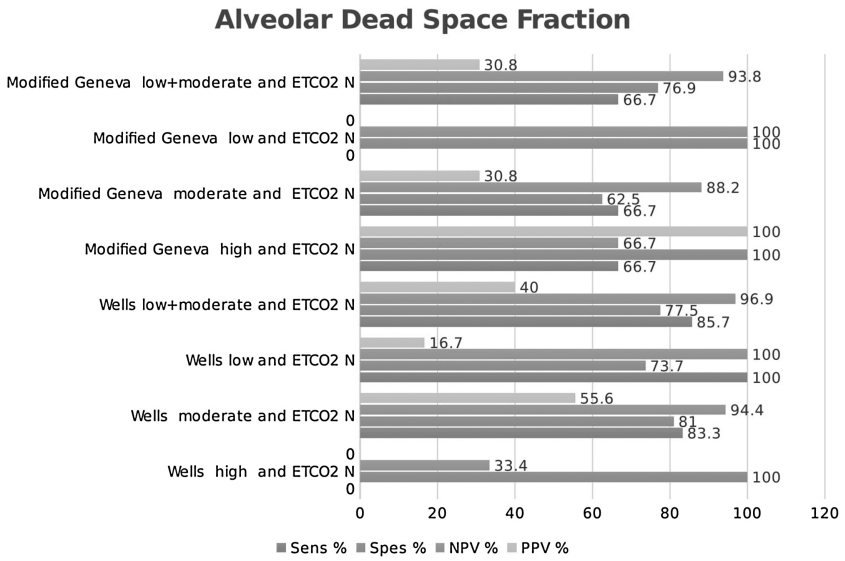

Fig. 4 The comparison of using together $ETCO_2$, AVDSf and Wells, Modified Geneva clinical prediction rules for diagnosing PE.

Table 2 The distribution of patients according to Wells and Modified Geneva clinical clinical prediction rules.

			High	Modarete	Low
Wells Clinical Prediction Rule	PE (−)	Number	3	37	24
		Percentage	4.7	57.8	37.5
	PE (+)	Number	7	19	10
		Percentage	19.4	52.8	27.8
	Total	Number	10	56	34
		Percentage	10	56	34
Modified Geneva Clinical Prediction Rule	PE (−)	Number	3	42	19
		Percentage	4.7	65.6	29.7
	PE (+)	Number	7	25	4
		Percentage	19.4	69.4	11.1
	Total	Number	10	67	23
		Percentage	10	67	23

of values reported in previous studies. Manara et al. could not suggest an ideal cut-off value for AVDSf because various studies had been included in their review, and the AVDSf measurement methods differed among them.[5]

In a previous study by Yoon et al., D-dimer test positivity and the results of capnography in patients with suspected PE decreased CT requirements to 55 % in low- and moderate-risk patients. Studies have shown that a normal $PaCO_2$ − $ETCO_2$ gradient does not exclude PE with a sufficient safety margin.[16] In the current study, when $ETCO_2$ was < 28.5, $ETCO_2$ alone had an NPV of 82 % in the diagnosis of PE, and NPV increased to 95 % and 100 %, respectively, in low-risk patients when evaluated using the Wells or Modified Geneva scoring system. In a study by Bonderman et al., capnography excluded PE in 96.6 % of patients when $ETCO_2$ was ≥ 36 mmHg and 93.8 % in patients with a Wells score < 4. Using the Wells score (< 4) and $ETCO_2$ (≥ 36 mmHg) value, PE was shown to be excluded in 97.6 %.[14] $ETCO_2$ has a high NPV for excluding PE, and the NPV was higher when combined with the Wells scoring system. In a meta-analysis by Ceriani et al., the prevalence of PE was reported to be < 10 % in patients with low clinical risk according to commonly used Wells and Geneva clinical prediction rules.[17] When capnography is used along with these prediction rules, PE can be safely excluded in patients with low clinical risk. Manara et al. discussed the possible diagnostic role of capnography in patients with a probability of PE < 10 % after a positive D-dimer test result.[5] In the current study, capnography safely excluded PE compared with the low risk Wells or Modified Geneva scoring systems and $ETCO_2$ after a positive D-dimer test result. In the current study, when an AVDSf value of < 0.128 was considered in low-risk Wells or Modified Geneva patients, PE was excluded with 100 % sensitivity. In a study by Verschuren et al., patients with low clinical risk, low AVDSf, and positive D-dimer test result showed 96 % sensitivity and 92 % NPV.[4] This study suggested that the use of capnography may decrease the necessity of CT or lung scintigraphy in patients with suspected PE. In a study by Yoon et al., PE was excluded in patients with low AVDSf values, low/moderate clinical risk, and positive D-dimer test result.[16] Prediction of PE with the combination of high clinical risk and AVDSf value (≥ 0.15) demonstrated 100 % specificity and 31.5 %

sensitivity. PE was excluded at similar rates when evaluated using clinical prediction rules and AVDSf values in the current study. In our study, high clinical risk for suspicion of PE had 100 % sensitivity and 100 % PPV in cases with AVDSf > 0.128. This result suggests that diagnosis of PE can be made safely without the use of advanced imaging techniques, in addition to indicating the possibility of early treatment.

Conclusions

It is possible to exclude or predict PE based on $ETCO_2$ and AVDSf values calculated using capnography when evaluated with clinical prediction rules and D-dimer test results using an algorithm. According to the results of our study, when $ETCO_2$ and AVDSf values were used together, PE could be excluded in 100 % of patients with a low risk score on the Wells and Modified Geneva systems. On the other hand, PE may be predicted in 100 % of patients with high risk score on the Wells and Modified Geneva systems. More similar studies with larger sample sizes are needed to determine the standard cut-off values for $ETCO_2$ and AVDSf. As a result, capnography may be used routinely and safely along with the algorithm for diagnosing of PE without the need for advanced imaging modalities.

Conflict of interest

All authors declare no conflict of interest.

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ORIGINAL ARTICLE

Obtaining spirometric reference values when height is not available – comparison of alternative anthropometric measures

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Spirometry;
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Abstract
Introduction: Height is one of the variables used to derive reference values for respiratory function but it is not always available. To fulfil this need, different formulas are described in literature.
Aim: To understand which method best estimate height in order to obtain Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1st second (FEV1) reference values.
Methods: The true stature (TS) and five alternative anthropometric measures that estimate height [arm span using a regression equation (ASR), arm span using a fix correction factor (ASF), half arm span, knee height and ulnar length] were measured for all patients. To assess the differences between the TS *versus* the estimated heights and the respective reference values of FVC and FEV1, T Student Test and Wilcoxon test were used. Agreement was evaluated by Intraclass Correlation Coefficient and by Bland-Altman plot.
Results: A total of 160 subjects were recruited but 14 patients were excluded due to skeletal deformities. The predicted FVC and FEV1 using all alternative anthropometric measures were statistically different from those calculated by TS, except for ASF. The limits of agreement were wide for all alternative measures. With the exception of ASF, predicted FVC and FEV1 were overestimated when using all other alternative measures.
Conclusions: For the purpose of replacing height in order to obtain predicted values of FVC and FEV1, the ASF was shown to be the most accurate and recommendable method. However, we must be aware there is a possible degree of error.

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Introduction

Since the invention of the spirometer by John Hutchinson the impact of the decrease of pulmonary function values on morbidity and mortality has been recognized.[1] Nowadays, pulmonary function tests fulfill a pivotal role in respiratory medicine. They are not only used as auxiliary diagnostic tools but also to assess the degree of respiratory incapacity of patients with pulmonary diseases.[2,3]

Lung function tests are usually interpreted by comparing measured values in an individual with reference values obtained from healthy individuals. To standardize interpretation, in 2012 the Global Lung Function Initiative (GLI) defined prediction equations for spirometric indices based on age, sex, race and height.[4] To the best of our knowledge, there are no specific reference equations for the Portuguese population, except for the six-minute walk test and for the incremental shuttle walk test.[5,6] However, for the assessment of true stature (TS) demanded by GLI, an individual is required to have no musculoskeletal abnormalities and should be able to stand up straight unaided without constraints. With certain medical conditions this measurement is not reliable, such as, axial skeletal deformities, neuromuscular weakness or extreme debility. In such cases, alternative anthropometric measurements have been proposed to estimate height to fulfill this need.[7] These, however, may introduce some degree of error leading to incorrect interpretation of lung function.[8]

The impact that alternative measures can have in spirometric indices is not yet fully understood. To date, few studies have sought to clarify this impact. Sancho et al. proposed an evaluation of such impact and showed poor agreement between different alternative measures.[9]

Under such circumstances, arm span (AS) has been chosen as one of the main surrogate measurements for estimating height. It can be calculated either by application of a fixed correction factor or by using regression equations.[7,10,11] The half arm span (HS) allows measurement of a single limb and has also been used to estimate height.[12] Another surrogate is knee height (KH) which is easy to obtain and may be useful in people with limb amputations. It has traditionally been used in nutrition.[13,14] Ulnar length (UL) is another alternative measure already studied in the field of pulmonary function.[15] Ulna is an accessible bone and its length is not usually impaired by joint deformities and it is less affected by the aging process.[16,17]

We hypothesized that substitution of TS by estimated height calculated from alternative anthropometric measures is likely to introduce only a tiny error in the predicted pulmonary function indices in individuals who cannot obtain a reliable measurement of TS.

Material and methods

Study design and participants

This is a cross-sectional study conducted in a public hospital in the north of Portugal.

The study was conducted on a sample population of adult subjects aged 18–95 years of either sex, referred to the respiratory laboratory of our hospital for pulmonary function assessment. Study subjects were consecutively recruited by systematic sampling over a 2-month period. In order to be included in the study, all participants signed the informed consent form. The study was approved by the hospital ethics committee.

A brief medical history, physical examination and spirometry were carried out on each person enrolled in the study. Subjects for whom height or alternative anthropometric measures could not be correctly measured were excluded. Exclusion criteria were specifically: neuromuscular diseases, axial or appendicular skeletal deformities, limb amputations, osteoporosis, previous orthopedic surgery, contractions or deformities of the shoulder, elbow or wrist joints, swelling of the knee or ankle and extreme debility that would not allow participant to stand up without constraints. Participants older than 95 years were also excluded because GLI does not define prediction equations for spirometric indices above this age.

Measurement of height and alternative anthropometric measures

All the measurements were made in the pulmonary function laboratory, using the same anthropometric apparatus. Prior to data collection, researchers were taught about anthropometric measurement techniques in order to obtain a standardization of the process. Anthropometric data used in our analyses were: true stature, arm span, half arm span, knee height and ulna length. Descriptions of the measurement techniques used to collect these data are documented below. All measures were obtained in centimeters to the nearest 0.5 cm. Two other measurements were taken and the median of the three measurements calculated. The three measurements had to be within 1 cm of each other, if not a fourth measure was taken and the median of the three closest values was recorded.

TS was carried out using a stadiometer that was placed on a level even surface and against a wall that was at a 90° angle to the floor. The patient had to be able to stand steady and upright, unaided. Shoes were removed and the patient was asked to look straight ahead with the *Frankfort* plane horizontal. The arms were relaxed at the sides, legs were close together and feet were flat with the heels together on a hard floor surface. Then a sliding head board was placed on to the vertex of the participant and the stature was read.

AS and HS were measured using a flexible measuring tape. The participants were asked to stand against the wall with their arms outstretched in a horizontal plane in relation to the floor and palms facing outwards. The arms had to create a 90° angle with the participant's body. To assess AS, the distance between the ends of the middle fingers of both hands was recorded. To measure HS, the distance between the midpoint of the suprasternal notch and the distal phalanx of the left middle finger was measured by passing a flexible, inelastic measuring tape parallel to the clavicle.

KH was measured with the subject in the sitting position and the knee and ankle joints of the left leg at 90° angles. A flexible measuring tape was placed next to the leg in line with lateral malleolus and the head of the fibula. The distance from the plantar surface of the left foot (heel) to the top of the thigh immediately above the condyles of the left femur was measured.

The UL was measured with a flexible metal measuring from the elbow's tip (olecranon process) to the tip of the styloid process. UL was measured in the left arm of the patient, folded in front of the patient's chest, with fingers pointing to the opposite shoulder.

Equations

The alternative anthropometric measurements obtained from data collection were inserted into different equations in order to predict height. The equations were applied accordingly and values were calculated to one decimal place.

Height estimation based on AS was calculated either by application of a fixed correction factor (according to Portuguese Directorate-General of Health (DGS) guidelines) and by using regression equations (recommended by American Thoracic Society/European Respiratory Society (ATS/ERS)).[7,10,11] The respective equations were:

DGS:

$$\text{Males}: Height(cm) = AS/1.03$$

$$\text{Females}: Height(cm) = AS/1.01$$

ATS/ERS:

$$\text{Males}: Height(cm) = 68.7363 + 0.63008AS - 0.10190age$$

$$\text{Females}: Height(cm) = 33.1453 + 0.79499AS$$

The equation for estimating height from HS was[12]:

$$Height(m) = [0.73 \times (2HS)] + 0.43$$

The equation for estimating height based on KH was[13]:

$$\text{Males}: Height(cm) = 78.31 + (1.94KH) - (0.14age)$$

$$\text{Females}: Height(cm) = 82.21 + (1.85KH) - (0.21age)$$

To predict height based on UL, a standardized table was used.[18]

Based on prediction equations defined by GLI[4] the predictive values of Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) were calculated. Six sets of values based on TS and others based on height estimated from AS (one obtained by application of a fixed correction factor (ASF) and another by using regression equations (ASR)), HS, KH, and UL were generated for each subject.

Statistical analysis

A statistical software program (SPSS version 20; SPSS Inc., Chicago, IL, USA) was used for data analysis. All reported p values are two-tailed, with a p value of 0.05 indicating statistical significance. Sample size was determined based on G*Power (version 3.1.9.3), for a power of 80%.

Categorical variables were presented as frequencies and percentages. Continuous variables were presented as means ± standard deviations, or as medians and interquartile ranges for variables with skewed distributions. The normality of data distribution was assessed with Kolmogorov–Smirnov tests. P-value greater than 0.05 indicates normal distribution of data.

Predicted pulmonary function values obtained from alternative anthropometric measures were compared with those based on TS, with the use of Student's *t*-test for paired data or the Wilcoxon test.

The concordance was analyzed by intraclass correlation coefficient (ICC), taking TS as the standard method. ICC estimates and their 95% confident intervals were calculated using SPSS.[19] ICC values were interpreted as excellent (>0.90), good (0.75–0.90), moderate (0.50–0.75) or poor (<0.50).

Agreement analysis as described by Bland & Altman[20] was used to further investigate how closely the alternative measurements could estimate height, and FVC and FEV1, subsequently. Agreement was assessed by plotting the difference between the two measurements, against the mean of the two measurements, for each individual. The limits of agreement were defined as the mean difference ± 1.96 standard deviation (SD). These limits showed by how much the tested measurement may vary from the standard method.

Table 1 Comparison between the measured TS with height estimated by all alternative anthropometric measures.

	Mean (cm)	SD (cm)	p
TS	162.86	8.05	
ASR	166.43	7.68	<0.001
ASF	162.90	8.29	0.908
HS	164.29	6.92	<0.001
KH	166.39	8.13	<0.001
UL	170.44	7.91	<0.001

Table 2 Comparison of predicted FVC and FEV1 values obtained using TS with those obtained using each alternative anthropometric measure.

		Mean (L)	SD (L)	p
Predicted FVC	TS	3.70	0.77	
	ASR	3.87	0.79	<0.001
	ASF	3.69	0.77	0.644
	HS	3.75	0.72	0.005
	KH	3.89	0.84	<0.001
	UL	4.10	0.84	<0.001
Predicted FEV1	TS	2.96	0.67	
	ASR	3.09	0.68	<0.001
	ASF	2.96	0.66	0.712
	HS	3.00	0.62	0.001
	KH	3.11	0.73	<0.001
	UL	3.26	0.71	<0.001

Results

A total of 160 subjects were recruited. Of these, fourteen individuals were excluded because they had one of the following exclusion criteria: scoliosis (n = 3), osteoporosis (n = 3), neuromuscular disease (n = 2), kyphosis (n = 2), previous spine surgery (n = 2), Madelung deformity (n = 1) and fingers amputation (n = 1). 146 individuals were included in the final analysis, 86 (58.9%) were male. The average age of the sample was 53.2 ± 17.0 years with an age range of 18–91 years (first quartile was 43, median quartile was 55 and third quartile was 66). The mean TS was 162.9 ± 8.1 cm; according to gender was: males 166.9 ± 6.31 cm and females 157.1 ± 6.6 cm.

Means of height estimated from different anthropometric measures were described in Table 1. There were significant differences between the averages of TS and those estimated from ASR, HS, KH and UL. The only exception was that estimated by AS, using a fixed correction factor (ASF).

Regarding the predicted values of FVC and FEV1, those calculated from ASF were the only ones without statistically significant difference when compared with those obtained from TS (Table 2). When analyzed by gender, in the subgroup of males ASF remained the only without statistically significant difference. However, in females either predicted values of FVC and FEV1 calculated from ASF as HS showed no statistically differences from those obtained from TS (Table 3).

The ICC for predicted FVC and FEV1, taking into account each of the alternative anthropometric measures used, are shown in Table 4. The degree of reliability associated with each ICC is given in the same table.

Assuming TS as the standard measurement to compare the estimates against, Bland-Altman analysis of agreement was carried out comparing the FVC predicted using the five surrogate measures with FVC predicted using TS. The limits of agreement were wide with all five surrogate measures. The Fig. 1A shows Bland-Altman analysis comparing predicted FVC using ASF with predicted FVC using TS. Another Bland-Altman analysis was performed comparing, this time, predicted FEV1 using five alternative measures with predicted FEV1 using TS. With the exception of ASF, when used all other alternative measures to estimate height, predicted FVC and FEV1 were overestimated; whereas on average ASF estimates it more closely (mean difference = -0.01 litres for predicted FVC; -0.01 litres for predicted FEV1).

Discussion

GLI identified height as the main determinant of pulmonary function,[4] so the correct value must be obtained to minimize the errors in prediction equations for spirometric indices. However, a reliable measurement of height is frequently not available. In order to overcome this limitation, the possibility is to estimate height using alternative anthropometric measures or by constructing reference equations for pulmonary function directly using the alternative measures.[8,15]

As far as we know, only the study conducted by Sancho-Chust et al.[9] proposed evaluating the impact of the use of some alternative anthropometric measures to estimate height for the purpose of predicting pulmonary function. This study was conducted before the publication of GLI equations and Sancho-Chust et al. found that using all alternatives measures the predicted values of FVC and FEV1 were overestimated, introducing a certain degree of error. The KH was the measurement with greatest agreement and so they propose its use in cases where obtaining height is impossible.[9]

In our study, the authors sought to understand this impact on our population after the introduction of GLI equations and using the most commonly anthropometric measures. Our study showed that the predicted values of FVC and FEV1 obtained using the TS or alternative anthropometric measures only did not show a statistically significant difference for the ASF. When analyzed by gender, our study continued to show that in the subgroup of males ASF is the only one that predicts FVC and FEV1 values with no statistical difference, but in subgroup of females HS also showed no statistical differences. Nevertheless, by Bland-Altman analysis we observed that even using the ASF the limits of agreement are wide. Taking the upper and lower limits of agreement of ASF, predicted FVC may be overestimated by 0.48 litres or underestimated by 0.50 litres, respectively. These values are higher than the limit of 0.15 litres used as repeatability criteria.[21] As such, this may have an impact on the spirometric evaluation of patients. In this analysis it was assumed that the differences did not vary in any systematic way over the range of measurements of FVC or FEV1. In fact, when we analyze Fig. 1A and B we find that the scatter plot of the differences remains the same as predicted FVC and FEV1 increase. Therefore, ASF could be used for individuals who are unable to stand but on understanding that the agreement is not optimal.

All the other alternative anthropometric measures tend to overestimate the predicted values of FVC and FEV1, especially UL (mean difference: 0.40 and 0.30 litres, respectively). Taking the upper limits of agreement of UL, predicted FVC may be overestimated by 1.09 litres. Thus, using these alternative measures (ASR, HS, KH and UL), we must be aware that it may lead to interpretation errors. In particular, by classifying more cases as probable restrictive abnormalities or by reclassifying in more severe degrees cases of restrictive or obstructive abnormalities.

Agreement between measurements was excellent as we can see from the ICC results obtained.

A limitation that may be pointed out to this study is that the authors did not provide correction factors for the height estimated by all alternative anthropometric measures. However this should be done in a healthy population. In this study, the authors used a sample population of adults referred to the respiratory laboratory mainly due to suspected respiratory diseases. As such, the creation of correction factors was not feasible.

Despite the widespread use of the GLI 2012 reference values, applying it to specific populations remains controversial. For instance, Fasola et al.[22] and Backman et al.[23] concluded that the use of GLI reference values in their population could produce a bias on airway obstruction prevalence. This means physicians should be careful to test reference values prior to their use in a local area. In fact, the authors did not test the applicability of GLI 2012 reference values to the Portuguese population prior to this study. This could be another possible weakness of this study.

Table 3 Comparison by gender of predicted FVC and FEV1 values obtained using TS with those obtained using each alternative anthropometric measure.

			Mean (L)	SD (L)	P
Males	Predicted FVC	TS	4.05	0.69	
		ASR	4.25	0.72	<0.001
		ASF	4.01	0.73	0.212
		HS	4.11	0.63	0.023
		KH	4.25	0.75	<0.001
		UL	4.52	0.77	<0.001
	Predicted FEV1	TS	3.21	0.64	
		ASR	3.35	0.67	<0.001
		ASF	3.18	0.66	0.197
		HS	3.25	0.59	0.025
		KH	3.35	0.69	<0.001
		UL	3.55	0.69	<0.001
Females	Predicted FVC	TS	3.19	0.57	
		ASR	3.33	0.53	<0.001
		ASF	3.23	0.57	0.157
		HS	3.24	0.49	0.060
		KH	3.37	0.69	<0.001
		UL	3.51	0.52	<0.001
	Predicted FEV1	TS	2.61	0.54	
		ASR	2.72	0.51	<0.001
		ASF	2.64	0.53	0.164
		HS	2.65	0.48	0.072
		KH	2.76	0.65	<0.001
		UL	2.86	0.52	<0.001

Table 4 ICC and degree of reproducibility for predicted FVC and FEV1 for each alternative measure.

		ICC	95% CI	Degree
Predicted FVC	ASR-TS	0.96	0.88–0.98	Good to excellent
	ASF-TS	0.97	0.96–0.98	Excellent
	HS-TS	0.98	0.96–0.98	Excellent
	KH-TS	0.96	0.85–0.98	Good to excellent
	UL-TS	0.89	0.24–0.96	Poor to excellent
Predicted FEV1	ASR-TS	0.97	0.91–0.99	Excellent
	ASF-TS	0.98	0.97–0.99	Excellent
	HS-TS	0.98	0.97–0.99	Excellent
	KH-TS	0.97	0.89–0.99	Good to excellent
	UL-TS	0.92	0.34–0.97	Poor to excellent

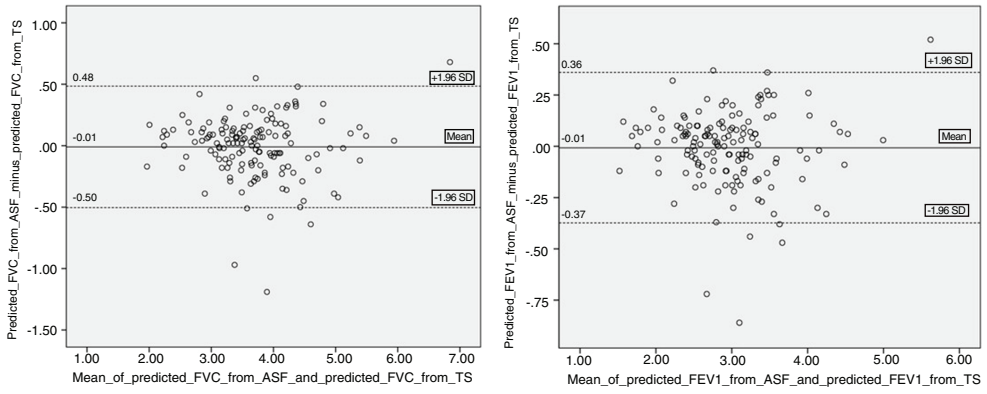

Figure 1 ''Bland-Altman plot – analysis of agreement. (A) Difference in predicted FVC between ASF and TS *versus* mean. (B) Difference in predicted FEV1 between ASF and TS *versus* mean''.

The study did not include individuals under 18 years-old. In most cases, these patients were not accompanied by their parents to the pulmonary function laboratory which would have made it more difficult to obtain the informed consent form. Another potential limitation is the use of measuring tapes that can overestimate the results by 1.03 cm.[9]

To sum up, our study emphasizes the importance of using appropriate anthropometric measures in order to obtain the predicted values of FVC and FEV1 of individuals for whom it is not possible to measure height. For this purpose, the ASF was shown to be the most accurate and the most recommendable method. Nevertheless, we must be aware of the possible degree of error introduced in predicting pulmonary function values.

Conflicts of interest

The authors have no conflicts of interest to declare.

Author contributions

Miguel Guimarães and Daniel Vaz conceived the idea. Nuno China, Daniel Vaz, Cristiana Martins and Joana Gomes collected the data. Nuno China wrote the manuscript and did the statistical analysis. All the authors have reviewed and edited the final version.

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REVIEW

Medical masks and Respirators for the Protection of Healthcare Workers from SARS-CoV-2 and other viruses

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Abstract The use of medical masks and respirators as personal protective equipment is pivotal to reducing the level of biological hazard to which healthcare workers are exposed during the outbreak of highly diffusible pathogens, such as the recent novel coronavirus SARS-CoV-2. Unfortunately, during this pandemic, supplies are rapidly running out worldwide, with potential consequences for the rate of occupational infections. Also, knowledge about specific characteristics of respirators is of utmost importance to select the proper type according to the clinical setting. A wide variety of literature is available on the topic, but mostly based on Influenza viruses infection models. Clinical evidence on the use of respirators is poor and interest in the topic has not been constant over time. A better understanding of SARS-CoV-2 transmission is needed, together with high-quality clinical data on the use of respirators or alternative devices. Moreover, healthcare workers, regardless of their level of experience, should receive specific training. This review aims to summarize the available evidence on the use of medical masks and respirators in the context of viral infections, especially the current coronavirus disease 2019 (COVID-19).

Abbreviations: COVID-19, Coronavirus disease 2019; ECDC, European Center of Diseases Control; FFR, Filtering facepiece respirators; MERS, Middle East Respiratory Syndrome; PPE, Personal protective equipment; SARS, Severe Acute Respiratory Syndrome; WHO, World Health Organization.

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Introduction

The outbreak of highly diffusible pathogens, such as the recent pandemic of SARS-CoV-2 infection, can increase the level of biological hazard to which healthcare workers are exposed thus requiring the use of personal protective equipment (PPE). Healthcare institutions should also plan the early isolation of sources and provide training program on the appropriate use of PPE.[1] PPE, defined as 'equipment worn to minimize exposure to hazards that cause serious workplace injuries and illnesses', includes masks and respirators.[2] The use of PPE and the application of other safety measures, especially in the context of a public health emergency of international concern, is regulated by international and national authorities that issue indications for healthcare workers and general population, according to the characteristics of transmission and the different levels of exposure to risk.[3] Unfortunately, in the case of a pandemic, the supply of PPE can be insufficient or heterogeneously distributed around the world, due to centralized production hubs, transport difficulties, lack of stockpiles, panic buying and appropriate heavy use.

Fig. 1

RNA viruses, such as SARS-CoV-2, SARS-CoV-1, Ebola and MERS virus, are examples of pathogens causing infectious diseases with zoonotic origins and human-to-human transmission, where spread can be restricted by the appropriate use of PPE. To date, the transmission of SARS-CoV-2 is reasonably supposed to be mediated by respiratory droplets and contact routes.[4,5] Recommendations about the appropriate use of PPE have been controversial and at times conflicting,[6] and continuous updates have been released during the current SARS-CoV-2 pandemic,[7] with a rising demand for incontrovertible and clear data.

The importance of the availability of an adequate supply of PPE and the training level of healthcare workers in its correct use in the healthcare setting has been evident during the current Coronavirus diseases 2019 (COVID-19) since a high proportion of healthcare workers have been infected. [8,9]

The aim of this review is to summarize the available evidence on the use of medical masks and respirators in the context of viral infections, with a specific focus on COVID-19.

Methods

Search strategy

For the purpose of this review, we searched PubMed, EMBASE, and MEDLINE for pre-clinical and clinical studies on the use of medical masks or respirators in the context of viral infections up to 3 April 2020. Our search included the keywords 'mask', 'respirator', 'ffp', 'droplet', 'aerosol', 'coronavirus' and 'viral infection' as exact phrases and also a combination of broad subject headings according to databases syntax. After exclusion of duplicates and abstracts, two authors (MI, AC) independently screened full-text papers to include the most relevant on the topic. Snowballing search on the references of selected articles was also performed.

Medical masks and respirators

Personal protective equipment includes medical masks or respirators, used to protect the wearer from droplets, airborne particles and body fluids potentially contaminating the face. [10,11]

The term 'respirators', in the context of personal protective equipment, should be intended as filtering media, usually in the form of half-face or full-face masks, used as protection for healthcare workers exposed to pathogens.

Types of device and characteristics

The main performance characteristics of medical masks and respirators are summarized in Table 1.

Medical masks are loose-fitting and disposable. They are meant to reduce the spread of the wearers' respiratory droplets to other people and the environment and to provide a general protection of the wearer from large droplets, usually generated by cough or sneezing, and body fluid splashes. Type I medical masks are generally used for patients with the aim of controlling the source, and Type II or Type IIR by healthcare workers in operatory room or procedural settings. The main difference among the types is according to their bacterial filtration efficiency, i.e. the efficiency as a barrier to bacteria penetration. The protection from splashes is only provided by Type IIR medical masks, where R stands for 'resistant'. [10–12]

Filtering facepieces respirators (FFR) are tight-fitting and disposable protective devices, designed to filter airborne droplet nuclei (defined as non-oil based particles < 5 μm in diameter [13]) they are registered as inhalational protective devices. They are differently labelled on the basis of their filtration properties and of the national regulations defining the standard conditions they were tested at.[14] As an example, the European label 'FFP2' refers to a respirator able to reduce a specific aerosol concentration of at least 94%, while 'FFP3' corresponds to a filtration performance of at least 99%. National regulatory standards have similarities around the world and recommendations usually refer to a specific class and its foreign equivalent models. Examples of FFP2 equivalents are N95 (United States), KN95 (China), P2 (Australia/New Zealand), DS (Japan) and Korea 1st class (Korea).

Worth noting, FFR are tested at a high flow-rate (85-95 L/min) and with test aerosol of around 0.3-0.5 μm in diameter. As a consequence, their real-life performances should be better than the tested one. Filtering performance strongly depends on fitting, and healthcare workers should test different devices to find the best fitting model and size for their face. Filtering face-piece respirators are not intended to be one-size-fits-all. For example, the presence of a beard can alter the sealing, and shaving is required. A fit test with an indicator aerosol should be used to evaluate the presence of leakages and to confirm the choice of the respirator model and size. Inhalation and exhalation seal checks will be then performed before every use, to tighten the device properly and confirm that it was put on properly. Filtering facepiece respirators are also available in versions with an expiratory valve, which make them more comfortable for long-time wearing. The valve, in fact, opens during

Table 1 Characteristics of surgical masks and respirators.

Name or Respirator class EU-OSHA [a]	Fit-test [b]	Splash protection [c]	Type of protection	Filter performance [d]	Inward leakage [e]	Equivalent classes [f]	Notes
Medical mask	Not needed	Type IIR	Droplets	Variable	Variable	NA	Loose-fitting; not protective for inhalation
FFP1	Needed	Type IIR	Droplets and airborne particles	≥ 80%	< 22%	NA	Expiration valve version available*
FFP2	Needed	Type IIR	Droplets and airborne particles	≥ 94%	< 8%	N95/P95/R95	Expiration valve version available*
FFP3	Needed	Type IIR	Droplets and airborne particles	≥ 99%	< 2%	N100/N99/P100/ P99/R100/R99	Expiration valve version available*
Elastomeric respirator	Needed	Provided	Droplets and airborne particles	Interchangeable filters	Interchangeable filters	NA	Re-usable; expensive; half or full face
PAPR	Usually not needed	Provided	Droplets and airborne particles	Interchangeable filters	Interchangeable filters	NA	Powered; re-usable; expensive; hood or loose-fitting; extended working hours
SAR	Needed	Provided	External uncontaminated source of breathing air	External uncontaminated source of breathing air	External uncontaminated source of breathing air	NA	Powered; re-usable; expensive; continuous or on demand flow; self-contained or airline source of breathing air

The table provides a summary of the main characteristics of medical masks and respirators.
Data were retrieved from ECDC and OSHA documents. [10,11]

[a] The common name of the device or the respirator class, according to EU-OSHA classification, is reported.

[b] A fit test with an indicator aerosol should be performed before first use of a model/size. If the test is positive, the respirator is leaking, and another model or size must be chosen.

[c] Protection from body fluid splashes. If the device is not certified as splash-proof, a separate hood should be used for this purpose.

[d] Filter performance measures the reduction in concentration of specific test aerosols passing through the filter. It is calculated at specific standard conditions that can vary according to national regulations. Minimal variations can occur among equivalent classes around the world.

[e] Inward leakage measures the amount (%) of a specific aerosol allowed to enter the device in a test chamber.

[f] Respirators performance characteristics are tested at national regulatory standard conditions. These standards have similarities around the world; thus recommendations usually refer to a specific class and its foreign equivalent models. Examples of FFP2 equivalents: N95 (United States), KN95 (China), P2 (Australia/New Zeland), DS (Japan), Korea 1st class (Korea).

[*] The presence of an expiratory valve results in a more comfortable breathing, offering less resistance to exhalation. The valve also reduces goggles fogging. Valved respirators are usually not certified as splash-proof.

EU-OSHA: European Agency for Safety and Health at Work; FFP: Filtering facepiece; NA: not available; N-: tested with NaCl filter loading; R-: tested with dioctylphthalate filter loading; P-: tested with dioctylphthalate at maximum filter degradation; PAPR: Powered Air-purifying respirator; SAR: Atmosphere-supplying respirator

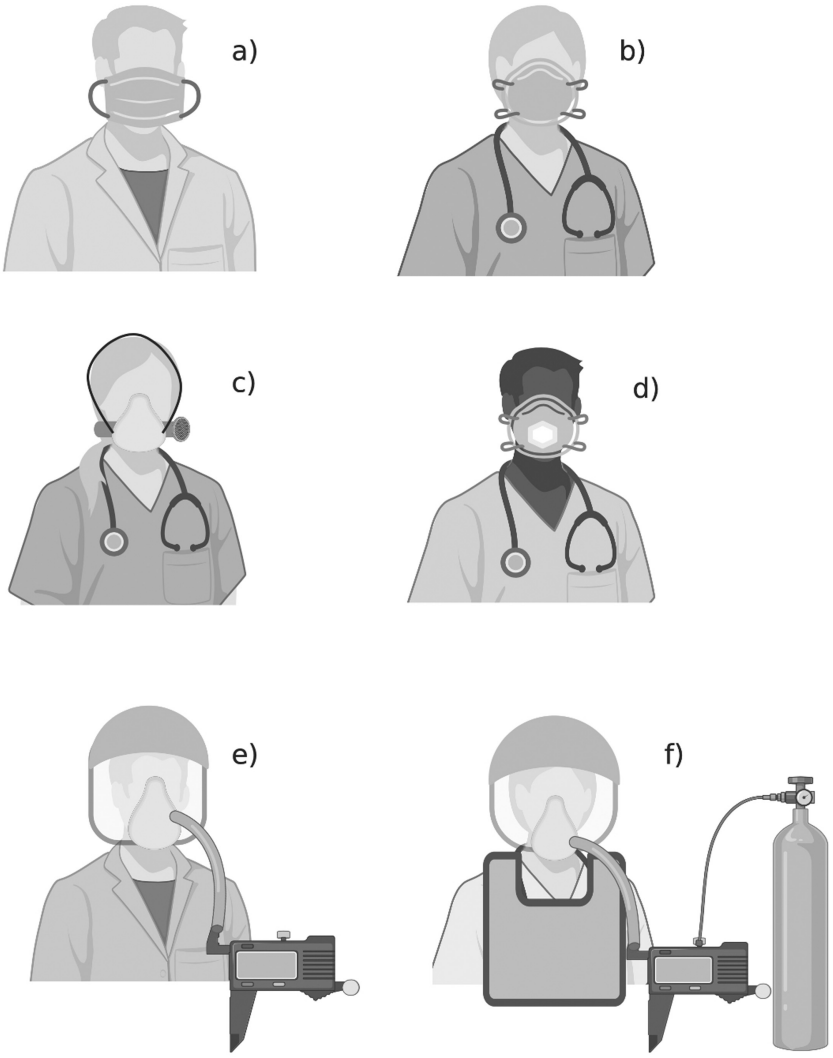

Fig. 1 Medical mask and respirators
The figure shows the available types of medical masks and respirators: a) medical mask; b) filtering facepiece respirator; c) elastomeric respirator; d) filtering facepiece respirator with expiratory valve; e) powered and supplied air respirator; f) atmosphere-supplying respirator. The figure does not show other PPE elements (gloves, gown, goggles, face shield, boots).

the expiratory phase of the wearer's breathing, allowing the exhaled air to flow-out. The protection from body fluids and splashes is rarely guaranteed by valved FFR, and has to be confirmed by the label ''Type IIR'', as for medical masks. The presence of an expiratory valve also reduces goggles fogging.[10,11] The nominal protection factor is an important index of a respirator performance. It is measured as the ratio between external concentration of contaminant and its concentration measured on the inner side of the device (Cout/Cin). If we assume Cout to be 1, with Cin = (1 - filtration performance), we can easily calculate the nominal protection factor. As an example, a respirator with a 94% filtration performance, will have a nominal protection factor of 16. In this case, the value means that the contaminant is 16 times less concentrated inside the device than in the external environment. Another parameter to be known is the threshold limit value, a threshold level of concentration, specific for each contaminant, which must not be exceeded if the safety of the wearer is to be guaranteed. The real-life protection given by a respirator, in fact, depends on its assigned protection factor, an index that depends on the protection factor provided by the respirator, but also by the ratio between the concentration of the contaminant and its threshold limit value.[11] In the case of some biological contaminants, such as the case of SARS-CoV-2, a threshold limit value is not known, and so the assigned protection factor of the respirator remains unknown. However, a reasonable estimate of assigned protection factor, intended as real-life protection guaranteed by the device, can be given by the respirator protection factor or by its filtration performance, if other measures are used to minimize Cout to the farthest level from the threshold limit value. Thus, especially in the context of an unknown contaminant, these concepts and common sense make clear the importance of a safety program including different measures (use of PPE, room ventilation, social distancing, source control).

In the cases of insufficient supplies or if required for specific characteristics of contaminant, disposable FFR can

be substituted by alternative types of respirators, not usually common in the healthcare settings, such as elastomeric respirators and powered air-supplying respirators. Atmosphere-supplying respirators are intended for particularly hostile environments.

The elastomeric respirators are re-usable devices, made of synthetic materials that can be disinfected and have interchangeable filters. [10,11]

The powered and supplied air respirators are battery-powered reusable respirators composed of hoods or loose-fitting masks, provided with interchangeable and disposable filters, such as high-efficiency particulate air filters. An essential part of the correct use of re-usable PPE, typically used in labs setting, is an accurate cleaning/disinfection procedure. Another device is the atmosphere-supplying respirator, which delivers air to the wearer from an external uncontaminated source. This feature becomes relevant in highly toxic environments or in the case of oxygen deficit. Concerns about the clinical use of re-usable PPE are: difficult communication, due to the noise generated by the power-unit, the need for electricity or batteries and the exposure of personnel in charge of disinfection to an additional biological risk.[10,11,15] Healthcare workers should follow their local regulations to select the best device.

Viral infections

Viruses are frequently causes of occupational infections. Personal protective equipment is considered a pivotal part of safety programs for healthcare personnel at risk of exposure especially when no effective therapies or vaccines are available. [7,16,17]

Influenza viruses are among the most commonly studied pathogens. They are RNA viruses and belong to the *Orthomyxoviridae* family. Their transmission is mostly mediated by droplets through coughing or sneezing, but also by airborne droplet nuclei or by contact, although the importance of the airborne route is controversial. Coronaviruses share some characteristics with Influenza viruses, such as RNA genome. They belong to the *Coronaviridae* family, known as cause of common cold, but also of other respiratory tract infections, such as severe acute respiratory syndrome (SARS). Their transmission happens through large droplets or by touching contaminated surfaces and fomites, with uncertainties about airborne route.[18] A recent study has detected NL63, OC43 and HKU1 coronaviruses RNA in airborne droplets nuclei contained in four participants' exhaled breaths, out of ten samples. [19]

The recent pandemic spread of the novel coronavirus SARS-CoV-2 has pushed the scientific community to a better understanding of the transmission routes. To date, the human-to-human transmission of SARS-CoV-2 is reasonably caused by respiratory large droplets and contact route, but data are insufficient to exclude airborne droplet nuclei transmission. [20]

Inward protection: protecting the wearer from the environment

Filtering facepiece respirators provide inward protection, defined as the capacity to reduce the concentration of airborne particles from the environment to the inner side of the device that is in contact with the upper airways of the wearer. Their protection consists of limiting the inhalational transmission of droplets and aerosols, potentially containing pathogens. While FFR are specifically produced for this purpose, medical masks are registered as medical apparel, for general protection of the wearer.[10,11] Moreover, respirators are more expensive than medical masks and healthcare facilities do not usually have stockpiles, thus creating more interest about the detailed differences among these devices, especially during epidemics or pandemics.

The most recent indications of World Health Organization (WHO) about the use of PPE during COVID-19 pandemic, recommend the use of respirator N95 or equivalent FFP2 only in the context of aerosol-generating procedures performed on patients with COVID-19, while medical masks are recommended for the general care of patients with COVID-19 provided that they are wearing a medical mask. [21] Aerosol-generating procedures are currently intended for cardiopulmonary resuscitation, tracheal intubation or suction, tracheotomy, manipulation of oxygen masks, bronchoscopy, non-invasive ventilation or, although controversial, use of high flow nasal cannula. [21–23] Worth noting, collecting diagnostic respiratory samples (e.g. nasopharyngeal swab) should be considered as aerosol-generating procedures, because it can cause coughing and/or sneezing. Thus, the healthcare worker in charge for these procedures should wear FFR. [7]

In its latest technical report, The European Center of Diseases Control (ECDC) stated that healthcare workers in contact with a suspected or confirmed COVID-19 case should wear a medical mask or, if available an FFP2 respirator. [7]

Most of the evidence about the use of PPE in viral infections is based on Influenza models. Despite the known similarities in term of transmission, they should be considered with caution in the context of SARS-CoV-2 infections. A recent systematic review and meta-analysis evaluated the effectiveness of N95 respirators versus medical masks for the prevention of influenza. It included six randomized clinical trials for a total of 9171 participants. No significant differences were found between the use of N95 respirators and medical masks for the outcomes of laboratory confirmed respiratory viral infections (RR = 0.89, 95% CI 0.70-1.11), laboratory-confirmed influenza (RR = 1.09, 95% CI 0.92-1.28), laboratory-confirmed respiratory infection (RR = 0.74, 95% CI 0.42-1.29) or influenza like illness (RR = 0.61, 95% CI 0.33-1.14). One of the trials included was actually done in a household setting. The authors concluded suggesting that N95 respirators should not be recommended for the general public and healthcare workers performing low-risk procedures. [24]

Specific evidence regarding SARS-CoV-2 is ongoing. A randomized multicentre controlled trial (NCT04296643) in Canada is underway to compare the use of either medical masks or N95 respirator in 576 nurses involved in the care of patients with COVID-19. The primary outcome is laboratory confirmed COVID-19 among the participants.

In addition to FFR, a PPE ensemble usually includes boots, gowns, gloves, hoods and goggles or face-shield. [21] These components seem to provide an additional inward protection, despite the amount of extra protection given by goggles

or face-shield remaining controversial, especially in the case of lengthy exposure to airborne droplet nuclei. [25]

For household settings, WHO has recommended the use of medical masks, gowns, gloves and eye protection for healthcare workers providing home care to patients with COVID-19, and medical masks for both caregivers and patients. [21,26]

Literature exists about the use of masks in household setting, but showing no significant reductions in household transmission, except for some benefit in the case of early application after the onset of the index patient's symptoms. These findings may be partially explained by the lack of compliance with the intervention. [27–29]

An interesting pilot study has evaluated N95 respirator and medical masks in the setting of home care.[30] The participants were three nurses, involved in healthcare assistance at a patient's home. The workplace protection factor was the primary outcome of the study, defined as Cout/Cin, i.e. the ratio between the aerosol concentrations inside (Cin) and outside (Cout) the device. The measurement of workplace protection factor was repeated twice for each participant, one with N95 respirator and one with medical mask. N95 respirators provided higher respiratory protection in comparison to medical masks, but the protection factors varied on an individual basis, also depending on the activity performed, with a greater risk in specific tasks like tracheal suctioning or nebulizer treatments. [30]

Van der Sande et al compared three types of masks (home-made masks, medical masks and FFP2) in their study conducted on healthy volunteers. The performance of the three devices was evaluated, at first, on 28 volunteers, including children, for 10-15 minutes. Then, another group of 22 volunteers wore the masks for 3 hours during the execution of common activities. Protection factor remained stable over time, not dependent on activity or on changes in the respiratory rate. Although hand-made masks have shown to provide some protection, FFP2 respirators had better protection factors over both medical masks and hand-made masks. [31]

Outward protection or source barrier: protecting the environment from the wearer

Medical masks are meant to provide an outward protection, thus witnessed by the recent indications about the use of medical masks in COVID-19 patients and symptomatic people visiting a healthcare setting [21,26]. Diaz and Smaldone were the first to evaluate the role of medical masks in respiratory source control.[32] In a bench study, they found that applying a medical mask on the source could significantly reduce the exposure of the receiver to a radiolabeled aerosol, providing a higher protection than a N95 respirator worn by the receiver. The study was conducted in a chamber designed with 6 air exchanges per hour to permit both dilution and deflection of exhaled particles, and the effect was lost at 0 air exchange per hour. Since the effectiveness of respirators is strongly dependent on their capacity to seal to the face, a more recent bench study has used modern and more fitting mannequins ('Resusci Anne' – Laerdal) and confirmed the role of medical masks for source control.[33] The role of medical masks for the source control of SARS-CoV-2 infected patients is controversial. A recent study showed a lower seasonal coronavirus RNA detection rate in droplets and aerosol samples collected from participants wearing a medical mask, compared to participants not wearing a mask.[19] In contrast with these findings, a study has been conducted on four patients with COVID-19 invited to cough onto a petri dish. Each participant repeated the experiment with no mask, a medical mask and a cotton-mask. Differences in SARS-CoV-2 viral loads on the petri dishes were not significant across the combinations and the virus was detected on the external surfaces of the masks, thus demonstrating a potentially insufficient outward protection. [34]

Lack of supplies and re-use

The tragic conditions of a pandemic can increase the demand for PPE, potentially exceeding its availability. On 19th of March 2020, WHO confirmed that ''The current global stockpile of PPE is insufficient, particularly for medical masks and respirators; the supply of gowns and goggles is soon expected to be insufficient also'', as already stated also in the precedent versions of its document 'Interim guidance on COVID-19'. [21]

WHO has recommended an extended use of PPE, i.e wearing the same respirator for repeated close contacts in the case of cohorted patients with COVID-19. [21] However, no recommendations were released about the re-use or decontamination of disposable PPE. The hypothesis of the re-use has been evaluated by several bench studies over time and interesting data about residual efficacy and performance post decontamination of disposable respirators are available.

The U.S. Center for Disease Control and Prevention has provided a summary of the evidence available on decontamination procedure of disposable FFR. It is clearly stated that the use of a decontaminated FFR should be a part of a crisis capacity strategy. Vaporous hydrogen peroxide, ultraviolet germicidal irradiation, and moist heat are listed among the methods that may preserve filtering performance. A recommendation is made against the use of autoclave, 160 °C dry heat, 70% isopropyl alcohol, microwave irradiation, bleach and soap and water, because they could affect the filtering performance. [35]

In 2012, Lore et al. examined the effectiveness of three energetic decontamination methods (ultraviolet germicidal irradiation, microwave-generated steam, and moist heat) on two models of N95 respirators, previously contaminated with H5N1.[36] Post decontamination viral load results decreased with all the methods. Filter performance was also tested, and no alterations were registered. These findings were in line with data on six respirators with H1N1 contamination.[37] Other studies have observed physical degradation of respirator materials such as the fibers composing the body material, which is probably less resistant than the filters.[38] Thus, the decontamination should balance the need for inactivation of the specific pathogen, even from the interior layers of the respirator, and the need to preserve the filtering performance, the structure of the respirator and its fitting characteristics. Further studies are needed to clarify the safety profiles of re-using procedures of disposable PPE. Meanwhile, if re-use is needed, the user should check that

the decontamination tests have already been performed on the specific model of FFR.

The use of cloth-masks in comparison with medical mask and usual protection, has also been investigated by a multicentre cluster randomized trial, including 1607 healthcare workers. The trialshowed a significantly higher rate of ILI in the cloth-mask intervention group (RR = 13.00, 95% CI 1.69 to 100.07) compared with the medical mask intervention group and with the entire control group, where healthcare workers wore their usual protection (including N95 respirator, no mask, medical mask, cloth mask or a combination of medical and cloth mask). [39]

Performance of healthcare workers using PPE

Although necessary, the use of PPE can also influence the performance of healthcare workers, as observed in studies on cadaveric models, where a higher difficulty rate and a lower success rate of tracheal intubations were registered.[40] In contrast with these findings, a clinical study conducted during SARS outbreak, found no significant differences in the overall tracheal intubation-related complication rate comparing the periods pre-SARS, during SARS and post-SARS. [41]

With the aim saving on supplies, extended use of PPE has been recommended, but healthcare personnel may experience intolerance to wearing a respirator for the entire work shift, even with interposed break periods.[42] Wearing a medical mask over the FFR has also been proposed, to enhance the duration of FFR, but concerns exist regarding negative effects on the wearer. [43]

Filtering facepiece respirators are used for several uninterrupted hours (about 8 hours) in non-healthcare settings. The maximum length of use in healthcare settings is typically dictated by other factors, such as contamination occurring, wearer intolerance or need to use the rest period, rather than by a predetermined duration. [44]

The need to reduce the exposure time and to use the smallest possible number of PPE reinforces the restriction on the number of healthcare personnel caring for the infected patients. This is of outmost important during aerosol-generating procedures, especially airway management, which should be performed by the most skilled available operators.[45] The downside of this approach is the reduced exposure of junior doctors to these procedures. This phenomenon has been already observed during SARS outbreak, and continued in the immediate post-outbreak periods, with concerns about training quality and preparedness of young personnel in the management of future similar situations. [41]

Finally, although equipped with protective clothing and even being experienced for the required tasks, healthcare workers can also be contaminated by improper removal of PPE,[46] thus regular training should be implemented to guarantee the best protection. Filtering facepiece respirators should be removed after the removal of the other components of PPE, just before removing of the gloves. The anterior part should not be touched during removal.[47] It is important to note doffing is done at the end of a shift, when an already fatigued worker can easily make mistakes during the procedure. A lot of human and organizational risk factors can co-exist, and appropriate knowledge of the procedure, plus the presence of a doffing partner are suggested.

Conclusions

In general, clinical evidence on the use of FFR is poor. The use of appropriate PPE, such as FFR, is of pivotal importance for the healthcare workers involved in the care of patients with viral infections, such as the currently pandemic, COVID-19. Unfortunately, supplies are rapidly running out worldwide. Moreover, knowledge about specific characteristics of FFR is of utmost importance to select the proper type according to the clinical setting. Direct evidence on the effectiveness of FFR in the prevention of SARS-CoV-2 infection is low and still underway, with concerns about the generalizability of other virus models. Available literature seems to reflect the alternating of periods of peak interest, coinciding with epidemics, with periods of lack of interest towards the topic. There should be a more constant research effort which also addresses the need for periodical training of healthcare workers.

Authors' contribution

MI conceived the content, drafted the manuscript, approved the final version to be submitted. FV, CG, GA, PI, AG helped in writing the manuscript and revised it critically for important intellectual content, approved the final version to be submitted. AC conceived the content, drafted the manuscript, approved the final version to be submitted.

Competing interests

All authors declare no competing interests.

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SPECIAL ARTICLE

COVID-19 pandemic and non invasive respiratory management: Every Goliath needs a David. An evidence based evaluation of problems

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Acute respiratory failure

Abstract
Background and aim: The war against Covid-19 is far from won. This narrative review attempts to describe some problems with the management of Covid-19 induced acute respiratory failure (ARF) by pulmonologists.
Methods: We searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and reviewed the references of retrieved articles for additional studies. The search was limited to the terms: Covid-19 **AND**: acute respiratory distress syndrome (ARDS), SARS, MERS, non invasive ventilation (NIV), high flow nasal cannula (HFNC), pronation (PP), health care workers (HCW).
Results: Protection of Health care workers should be paramount, so full Personal Protective Equipment and Negative pressure rooms are warranted. HFNC alone or with PP could be offered for mild cases (PaO2/FiO2 between 200–300); NIV alone or with PP may work in moderate cases (PaO2/FiO2 between 100–200). Rotation and coupled (HFNC/NIV) strategy can be beneficial. A window of opportunity of 1–2 h is advised. If PaO2/FIO2 significantly increases, Respiratory Rate decreases with a relatively low Exhaled Tidal Volume, the non-invasive strategy could be working and intubation delayed.
Conclusion: Although there is a role for non-invasive respiratory therapies in the context of COVID-19 ARF, more research is still needed to define the balance of benefits and risks to patients and HCW. Indirectly, non invasive respiratory therapies may be of particular benefit in reducing the risks to healthcare workers by obviating the need for intubation, a potentially highly infectious procedure.

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''You are coming to fight against me with a sword, a spear and a javelin. But I'm coming against you in the name of the Lord who rules over all. He is the God of the armies of Israel. He's the one you have dared to fight against''
1 Samuel 17

Introduction

While the world is racing to contain the spread of COVID-19 and updated/real time medical information has reached high ranked journals faster than ever, there are still a lot of questions unanswered. The huge efforts made by some countries have allowed us to gain critical time for better preparation and increase our awareness.

In fact some reflections could help pulmonologists tackle the current pandemic. Reports from China suggest that 81% of COVID-19 are mild, 14% are severe and that 5% require intensive care.[1] Mortality rate in the series published from China, Italy and US,[2–16] ranges from 1.4% in hospitalized[6] to 61.5% in critically ill patients.[10]

In this frame the role of pulmonologists is increasing. This narrative review tries to describe some problems with the management of Covid-19 induced acute respiratory failure (ARF) by pulmonologists, remaining aware that the overflow of new information may make all reports rapidly obsolete.

Data sources and search strategies

We searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, from 2010 to April, 15th 2020, with no language restriction. We also reviewed the references of retrieved articles for additional studies. The search was performed using the terms: Covid-19 **AND**: acute respiratory distress syndrome (ARDS), non invasive ventilation (NIV), high flow nasal cannula (HFNC), pronation, chest physiotherapy, health care workers, severe acute respiratory syndrome (SARS), influenza A H1N1, Middle East respiratory syndrome (MERS).

Protection of health care workers

One of the most relevant, and unfortunately neglected (at least at the beginning) problems is the protection of professionals involved in high-risk interventions such as nebulizer therapy, HFNC, oxygen therapy, NIV, patient pronation, chest physiotherapy. According to the available reports, 3.8% of Chinese health care workers were infected,[1] 63% of cases occurring in Wuhan; In Italy the figures are worse with 14% of cases.[17] How can we reduce the impact on these professionals? The fundamental defense is to wear effective protective personal equipment such as N95 masks, gowns hair covers, gloves, eye and face shields.[18] The use of more efficient respirators (Powered Air Purifying Respirators) for high risk aerosol generating procedures (like respiratory therapies) has been proposed[19] (Fig. 1).

Non invasive ventilation and high flow nasal cannula

The ERS/ATS clinical practice guidelines recommend (not firmly) NIV as a preventive strategy for avoiding intubation in hypoxemic ARF[20] only when performed by experienced teams in highly selected cooperative patients with community-acquired pneumonia or early ARDS without any associated major organ dysfunction.

In patients with de novo ARF under NIV, large expiratory tidal volumes (VTE) may be generated in assisted pressure controlled modes by the ventilator pressure and the one generated by the respiratory muscles. Therefore reliable monitoring of VTE and unintentional leaks would be of outmost importance. When using an ICU ventilator driven by high pressures in the double limb configuration, leaks are computed as the difference between inspired tidal volume and VTE. As a consequence, the amount of tidal volume that the patient gets is usually quantified as VTE.[21] In the majority of patients with ''de novo'' moderate-to-severe hypoxemia, a targeted VTE of 6–8 mL/kg was impossible to achieve by NIV with humidified masks and ICU ventilators.[22] A higher VTE was independently associated with NIV failure. In the subgroup of patients with an arterial oxygen tension to inspiratory oxygen fraction (PaO_2/FiO_2) ratio up to 200, a mean VTE higher than 9.5 mL/kg over the first four cumulative hours of NIV accurately predicted NIV failure.[22] A higher VTE was independently associated with NIV failure. In the subgroup of patients with an arterial oxygen tension to inspiratory oxygen fraction (PaO_2/FiO_2) ratio up to 200, a mean VTE higher than 9.5 mL/kg over the first four cumulative hours of NIV accurately predicted NIV failure.

In a recent randomized controlled trial, Patel et al.,[23] found that NIV delivered via helmet reduced intubation rates in patients with ARDS more significantly, compared to NIV delivered via facial mask (from 61% to 18%, respectively). As the helmet seems a more effective and tolerable interface in this setting, it would make sense to evaluate how it stands compared to HFNC.[24] Indeed, very recently, a physiological randomized cross-over study,[25] concluded that in patients with PaO_2/FiO_2 <200, high-PEEP helmet NIV could be preferred over HFNC to optimize oxygenation and mitigate the inspiratory effort, especially in most severely hypoxemic patients and in those exhibiting intense inspiratory effort during HFNC. Caution is needed in patients with low inspiratory effort during HFNC, because they can experience increases in dynamic transpulmonary driving pressure while on NIV with the helmet.

A recent systematic review[26] shows that compared to conventional oxygen therapy HFNC decreases risk of requiring intubation without impacting mortality. The authors pointed out that flow rates were variable between the studies and also, duration of treatment was not analyzed. A physiologic randomized controlled study[27] showed that the higher (60 L min^{-1}) the flow, the better the physiologic response.

Pronation

Adding prone positioning to HFNC, Riera et al, Riera et al.,[28] demonstrated, in healthy subjects, that it leads to a more

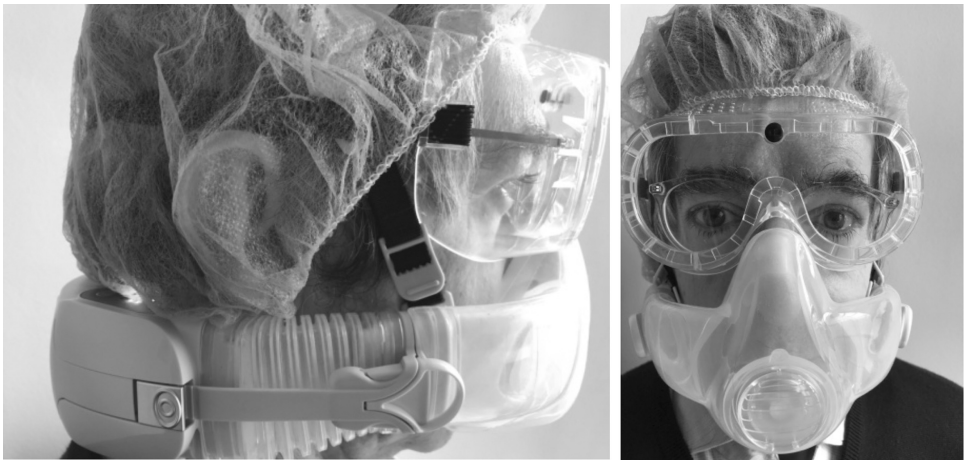

Figure 1 Powered Air Purifying Respirator (CleanSpace Halo®, CleanSpace Technology Pty Ltd, Artarmon, NSW Australia, NIOSH (US) and ATEX (Europe) approved).

homogeneous distribution of end-expiratory lung impedance possibly translating into better oxygenation.

In awake, non-intubated, spontaneously breathing patients with hypoxemic ARF (majorly immunocompromised) Scaravilli et al.,[29] showed a significant improvement in PaO_2/FiO_2 with prone positioning. More recently, early prone positioning added to HFNC or NIV avoided the need for intubation in up to half of the patients with moderate to severe ARDS including those with viral pneumonia.[30] No health care professional was infected during this study carried out in isolation negative pressure rooms. Other authors report similar results[31] and a randomized controlled trial is ongoing.[32]

Combination of both NIV and HFNC

Frat JP et al.,[33] in patients with PaO_2/FiO_2 <300, studied the effect of sequential application of sessions of HFNC and NIV. Intubation was required in 36% of patients, including individuals with ARDS. Authors concluded that due to the good tolerance and efficacy on oxygenation, HFNC could be a good option to be used between NIV sessions to pursue a coupled non invasive strategy of ventilation without a marked impairment of oxygenation.

NIV and HFNC in a pandemic context. Lessons learned from SARS, H1N1 and MERS

In 2003, NIV was tried in Hong Kong in patients with ARF (initial mean PaO_2/FiO_2 137) secondary to SARS outbreak. The treatment was carried out in isolation/negative pressure rooms, with a Bi-Level ventilator in spontaneous/timed mode, oro-nasal masks and single circuit with the filter before the expiratory valve. Endotracheal intubation was avoided in 70% of cases and one month after the outbreak no health care worker (wearing fully fledged protective personal equipment, including Powered Air Purifying Respirators) was infected.[34] Non invasive ventilation was also used in patients with ARF due to influenza A H1N1 infection, with success rates ranging between 15% and 25%.[35,36]

More recently, during the MERS outbreak Alraddadi et al.,[37] showed that NIV as first line intervention, although modestly effective was not associated with increased 90 day mortality. No data was available on potential risks of transmission to health care professionals. Considering the usage of HFNC in the pandemic context, Rello et al.,[38] reported cases of ARF due to the pneumonia 2009 influenza A/H1N1v, with a success rate of 39%, and no secondary infections in health care workers (even without negative pressure rooms). Moreover reports from China in MERS show the effectiveness of HFNC with apparently no transmission reported to the professionals.[39,40]

Risk of different interventions

Before choosing the best respiratory support for patients with ARF, we need to understand the risks of different interventions. A systematic review concluded that the most consistent association with increased risk of SARS transmission to professionals was tracheal intubation; mask ventilation was also positively associated (only 2 studies) but data were not considered sufficiently robust to establish firm conclusions.[41]

As shown in Table 1, bench studies showed that dispersion of exhaled air is different depending on the respiratory therapies and interfaces (nasal cannula, oro-nasal mask or helmet).[42–46] Oxygen delivered at 6 L/min in a mild lung injury model had maximum dispersion distance of 0.22 m from the mask.[42] When the experimental setting analyzed the performance continuous airway positive pressure (CPAP) with the Quattro Air mask (ResMed®) there was no significant leakage when pressures up to 20 cmH2O were applied. In fact, exhaled air dispersed evenly via the vent holes located circularly around the elbow connection point in all directions at very low normalized smoke concentration <20%.[43] With Nuance Pro Gel (Philips-Respironics®) and Swift FX (ResMed®) nasal pillows there was a significant increase in exhaled air dispersion distance for both nasal pillows with increasing CPAP (0.19–0.21 m).[43]

Regarding the performance of Bi-Level modes, substantial exposure to exhaled air occurs within a one

Table 1 Exhaled air dispersion according with modalities and interfaces.[43–46]

Interfaces and pressures (in cmH20)	Maximum exhaled air distance (in meters)
ResMed Ultra Mirage mask IPAP/EPAP cmH_2O	
10/4	0.40
14/4	0.42
18/4	0.45
ResMed Quattro Air mask (with anti-asphixia valve closed)	
CPAP 10–20 cmH20	Negligible
Respironics Total Face IPAP/EPAP cmH20	
10/5	0.61
18/5	0.81
Helmet StarMed CaStar R IPAP/EPAP cmH20	
IPAP from 12 to 20/EPAP 5	Negligible

Abbreviations: CPAP, continuous positive airway pressure; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

meter region, from patients receiving NIV through oro-nasal masks with integrated expiratory valves or oro-nasal masks attached to an expiratory valve, with more diffuse leakage from the latter, especially at higher IPAP.[44] A different oronasal mask with integrated expiratory valve located on the upper part of the mask (Ultra Mirage Medium; ResMed®) led to substantial exposure to exhaled air occurring within a 0.5-m radius of patients receiving NIV.[45] With the Philips-Respironics® total face mask early model, exhaled air jet through the integrated exhalation port could reach a distance of 0.92 m when NIV was applied using single circuit.[46]

With the StarMed CaStar R Helmet, leakage of exhaled air was negligible when NIV was applied with a double limb circuit, filters and a good seal at the neck-helmet interface, whereas leakage at the neck interface could reach a maximum radial distance of 0.27 m through another helmet (Sea-Long model) without a tight seal in the interface.[46]

Using a real human model (with healthy controls, subjects with coryzal symptoms and patients with infective COPD exacerbations) Simonds et al.,[47] showed that NIV using a vented mask produced droplets in the large size range (>10 μm) compared with the baseline droplet counts (without any intervention). This increase in large droplets was not seen using the NIV circuit modification (with non-vented mask and exhalation filter). Oxygen therapy did not increase droplet count in any size range.

From these studies, we might conclude that NIV through the helmet with double limb circuit and a good seal at the neck-helmet interface would be a safe option for managing infectious patients with hypoxemic ARF. As alternative, the Quattro Air mask (ResMed®), or a non-vented oro-nasal mask with a bacteriologic filter at the circuit's expiratory valve could be the more efficient alternatives.

High flow nasal cannula

Studies coming from the above mentioned laboratory,[43] showed that with HFNC (model Airvo 2; Fisher & Paykel®) exhaled air mean distances increased from 65 to 172 mm when flow was increased from 10 to 60 L min^{-1}, a shorter distance than that from application of CPAP through the commonly used nasal pillows. Moreover air leakage to 620 mm occurred laterally when HFNC and the interface tube became loose.[43] In another experiment with a manikin and no negative pressure room, 10 min of HFNC at 60 L/min of flow, caused no dispersal of water yeast in areas >60 cm away from the face. Manual repositioning of cannula slightly increased dispersal.[48]

In critically ill patients with Gram negative Pneumonia, in single occupancy negative pressure rooms, there was no difference in bacteria count between HFNC and Venturi Mask at 0.4 m and 1.5 m plates.[49] In an experiment with healthy volunteers to simulate a patient coughing while using HFNC to assess the maximum distance of droplet dispersion, Loh et al.,[50] showed that while wearing a well-fitting nasal cannula at 60 L min^{-1} flow, cough generated droplets spread up to a distance of 4.50 m. To circumvent some of the risks of HFNC, some authors propose that the patient wear a surgical facemask on top of the nasal cannulas.[51] A recent simulation of HFNC along with a surgical facemask in place over the cannula, confirms that, at 40 L min^{-1}, the surgical mask captured 83.2% of particles, at the expense of a moderate reduction in CO2 clearance.[52] This may require increasing flow rate of HFNC if the patient is displaying increased work of breathing.

NIV and HFNC usage in the current COVID-19 pandemic

Analyzing current trends in NIV and HFNC usage in all published series in major journals shows the following,[2,15,16] mean NIV usage in hospitalized patients in China was 20.1% (from 4.9 to 56%; higher in series including only critically ill,[10] moderate to severe[14] and in one series of Pneumonia cases[11]); in Italy 11%[15]; and in USA from 0 to 19%.[12,13] Mean HFNC usage in China was 22.8% (raging from 0 to 63.5% and higher in series including only critically ill[10] and moderate to severe[14]), in Italy[15] 0%, and in the USA from 4.8% to 42% (higher in Critically ill in Seattle[13] than in Washington-[12]). In a real world study in two Chongqing hospitals in China[53,52] of the patients experiencing severe ARF, 63% of patients were treated with HFNC as first-line therapy, 33% were treated

Table 2 Respiratory non-invasive therapies for COVID-19: recommendations from scientific societies.

Scientific society (country), ref nr	Non-invasive respiratory therapy first option
SEPAR (Spain)[56]	HFNC
AIPO (Italy)[57]	Helmet CPAP
ESICM/SCCM (EU/US)[58]	HFNC
SPP (Portugal)[51]	HFNC or CPAP
NHS (UK)[59]	CPAP
WHO[60]	HFNC or NIV
CTS (China)[61]	HFNC
ANZICS (Australia/New Zealand)[62]	HFNC
Multiple Societies (Germany)[63]	Helmet NIV

Abbreviations: SEPAR-Sociedad Española de Patologia Respiratória; AIPO-Associazone Italiana Pneumologi Ospedalieri; ESICM-European Society of Intensive Care Medicine; SCCM-Society of Critical Care Medicine SPP-Sociedade Portuguesa de Pneumologia; CTS-Chinese Thoracic Society, ANZICS-Australian and New Zealand Intensive Care Society.

with NIV and 4% were treated with invasive ventilation. Of the HFNC patients, 41% experienced failure, failure rate being 0 in patients with PaO_2/FiO_2 >200 and 63% in those with $PaO_2/FiO_2 \leq 200$.

One important issue about HFNC is that the amount of condensation in the circuit increases when the ambient temperature decreases. At present, the condensed water can become an important source of infection for COVID-19 so, avoidance or reduction in condensation may be very important when HFNC is used. Bacterial contamination of the inner surface of circuits after termination of HFNC has been shown in 16.1% of cases, mainly occurring at the interface end. This figure is as high as for anesthetic breathing circuits, but can be decreased by circuits fitted with heating wires, which greatly reduce condensation.[54]

Although the evidence from the recent series is lacking (with no single mention of transmission to professionals through these techniques), there are authors that do not recommend NIV or HFNC until the patients is cleared of COVID-19.[55] However some other experiments from China suggest that early intervention with HFNC and NIV associated or not with prone positioning can lead to lower mortality, less than 1% of cases needing intubation (versus 2.3% of National average).[53]

Potential strategies and perspectives

Options differ between Scientific Societies[56–63] (Table 2), countries and different environmental factors.[64] In fact, lack of facilities, ICU beds, experienced personnel,[65] or equipment[66] may have a role in selecting these therapies and ultimately will have an impact in clinical outcomes.

Effectiveness of NIV or HFNC as first line needs a deeper evaluation, and also whether the early use of invasive ventilation can really improve prognosis. Two different phenotypes of patients have been hypothesized[67]: more than 50% of COVID-19 pneumonia with Berlin criteria of ARDS have normal lung compliance, with ''silent'' hypoxemia (the so called Type L phenotype); these patients when non dyspnoeic should just receive supplemental oxygen; if dyspnoeic, should be offered HFNC, CPAP or NIV. If the patient shows significant increase in work of breathing, we should proceed to intubation and invasive mechanical ventilation.[67] A clear analysis of NIV/HFNC time before invasive mechanical ventilation is most important. Indeed some authors that NIV has a role in self inflicted lung injury (SILI) and the risk of impacting in a change in ARDS phenotype (Paolo Pelosi, personal communication, Webinar ESICM). The extended effect of heated and humidified oxygen in HFNC to avoid mucosal injury, improve secretion clearance, reduce transpulmonary driving pressure, should also be looked at in this setting.[68] Its role in preventing injury and accelerate recovery if initiated early in the clinical course should be also analyzed.

Non invasive ventilation and HFNC can be reserved for patients with mild ARDS, with close monitoring, airborne precautions, and preferably in single rooms. In patients with suspected or diagnosed COVID-19 requiring NIV, helmets may be the best solution for CPAP or NIV, because of minimal or no dispersion from leaks, easy to filter/scavenge exhausted gas. Due to the scarcity of this interface it is probable that traditional oro-nasal masks will be the most commonly used. In this case suboptimal NIV set-up, with interface with inappropriate seals and improper circuitry will not be tolerable. If NIV is the option, try ''protective-NIV'' with lower tidal volumes between 6 and 8 mL/kg.[69]

This simple description of some problems of this narrative review elicits the need for innovative strategies[70] in addition to medical therapy and vaccination campaigns.

Conclusion

All respiratory therapies represent a risk of aerosol generating procedures during the care of patients with COVID-19. Personal Protective Equipment and Environmental Control/Engineering should be the initial concern and consideration when managing patients with COVID-19. Given the current circumstances it is not likely that there will be randomized controlled trials to confirm which non invasive respiratory support is better to reduce the need for intubation in the context of COVID-19 pandemic. Manufacturers should be urged to create safer interfaces, viral proof circuitry and ''new generation'' non invasive ventilators with integration of different therapies, specific monitoring and necessary safety features. It is our impression, that this will be a marathon not a sprint, and like David we must beat Goliath.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Telemonitoring systems for respiratory patients: technological aspects

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Abstract This review introduces the reader to the available technologies in the field of telemonitoring, with focus on respiratory patients. In the materials and methods section, a general structure of telemonitoring systems for respiratory patients is presented and the sensors of interest are illustrated, i.e., respiratory monitors (wearable and non-wearable), activity trackers, pulse oximeters, environmental monitors and other sensors of physiological variables. Afterwards, the most common communication protocols are briefly introduced.

In the results section, selected clinical studies that prove the significance of the presented parameters in chronic respiratory diseases are presented. This is followed by a discussion on the main current issues in telemedicine, in particular legal aspects, data privacy and benefits both in economic and health terms.

Introduction

Telemonitoring consists in the transmission of physiological and other non-invasive data and aims at reducing hospitalisations, improving self-care and enhancing Health-Related Quality of Life (HRQL) of patients.[1] Recent advances in sensors, miniaturised processors, body area networks (BANs) and wireless data transmission technologies permit the assessment of environmental, physical and physiological parameters in different environments, without restriction of activity. Specifically, BANs are systems composed of a network of wearable devices that can be implanted, attached in fixed positions or carried by the person[2]; wireless BANs (WBANs) perform measurements and transmit the obtained values via wireless communication networks.[3] This review introduces the main technologies available to perform telemonitoring on respiratory patients. As of today, there is no commercially available telemonitoring system for respiratory patients allowing a complete analysis, although the single elements are technologically ready and need therefore to be integrated together.

The aim of the review is to present (1) the technological opportunities that pave the way to future developments

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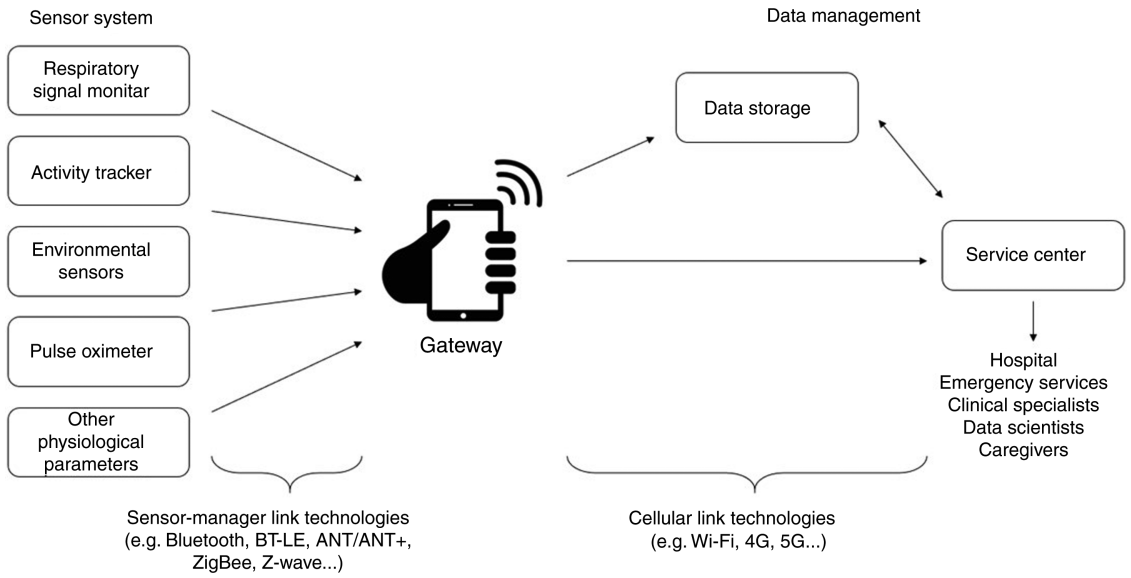

Fig. 1 Telemonitoring system with a two-hop data transmission architecture.

of respiratory telemonitoring, explaining (a) the signals of interest and the available methods to measure them; (b) the existing communication methods. Furthermore, this review illustrates (2) selected clinical studies that have proven the significance of the presented parameters in chronic respiratory diseases.

Methods

Telemonitoring systems for chronic respiratory patients may include several elements, as shown in Fig. 1. Systems generally follow the so-called two-hop architecture, i.e. data coming from sensors are transmitted to a gateway with sensor-manager link technologies and then from the gateway to the data management section with cellular link technologies. In this review, sensors are grouped into the following categories: respiratory monitors, pulse oximeters, activity trackers, environmental sensors and monitors of other physiological variables.

Respiratory monitors

Several types of sensors can be used for respiratory monitoring, with different measured parameters and levels of invasiveness. Some pathologies for which this signal is of particular interest are obstructive or restrictive respiratory conditions, sleep disorders and cardiac diseases.

Spirometers

Among the large commercial offer of different models of spirometers, handheld spirometry devices are those that are most suitable for telemonitoring applications. Modern models are connected to a gateway, usually a smartphone. The main drawbacks of these devices are that only spot assessments (e.g., once per day) are possible; furthermore, these devices require patient collaboration and analyze specific maneuvers, not spontaneous breathing. In general, assessment of breathing through a flowmeter is not feasible for continuous monitoring as it requires the use of a mouthpiece, a mask or a tube, therefore it is uncomfortable to wear and not usable for a prolonged time outside of clinical or laboratory settings.[4]

Forced oscillation technique

Forced oscillation technique (FOT) is a noninvasive method to assess lung function during normal breathing by using a small pressure oscillation (equivalent to the one exerted by 2 cm of water) imposed on regular quiet breathing to ''force'' a small quantity of air to move in and out the respiratory system. Thanks to this, the mechanical properties of the lung can be measured without supervision and also in home contexts; from resistance and reactance measurements, information on the breathing pattern can be obtained.[5] A product that can be used in home settings is Resmon Pro Diary by Restech, which was used in a clinical trial on COPD patients.[6]

Systems for continuous monitoring of breathing

Another approach for measuring breathing consists in deriving breathing parameters from body surface (namely, chest wall) motion detection, i.e. by inferring changes in thoracic volume from geometrical changes at discrete locations on the torso. Systems for continuous monitoring of breathing can use either wearables (e.g., respiratory inductance plethysmography, resistance-based sensors, capacitance-based sensors, inertial measurement units, fiber optic sensors...) or non-wearable devices (e.g. mechanical ventilators, long-term oxygen therapy, polysomnography...).

a Systems using wearable devices

Respiratory Inductance Plethysmography (RIP). RIP involves the use of two transducer bands placed around the subject to monitor excursions of the chest and abdomen over time. As the subject breathes, the volumes of the two compartments change, and these changes are reflected in

alterations in the self-inductance of the coils. One drawback is that slippage of bands can be a problem in RIP, leading to inaccurate readings. This technique also requires direct contact with the subject during placement and positioning of the bands.[7] The LifeShirt® by Vivometric® was an example of device that included RIP to measure ventilatory parameters,[8] but nowadays is no longer produced. Hexoskin®, on the other hand, is currently available on the market and bases its respiratory rate and minute ventilation measurements on the use of RIP. This device was validated in multiple studies that involved tests in different postures and with incremental levels of exercise; Hexoskin® volume measurements have low variability and good agreement and consistency.[9]

Resistance-based wearable sensors. Several wearable sensors are based on the principle that the resistance measured varies with the movement of the torso. An example is L.I.F.E.'s medical compression garment composed of 12 electrodes for ECG monitoring, 5 respiratory strains sensors and 1 accelerometer. The respiratory sensors are based on the variation of the resistance and are positioned on the anterior external surface of the garment as follows: two are thoracic, one is central and two are abdominal.[10] Another wearable respiratory monitor is AirGo™, which measures the thoracic circumference changes with a stretchable knitted matrix of nylon and spandex with a built-in silver coated yarn. The system takes the form of an electrically conductive chest band that encircles the lower chest and ribs of a patient or individual. The on-board microprocessor is also equipped with a three-axial accelerometer for motion detection.[11] There are also some recent projects with a quantitative estimation of volumes from wearable sensors. In one study, measurements of respiratory rate and tidal volume using a disposable Band-Aid®-like sensor have been evaluated. This sensor allows us to derive the two aforementioned parameters by simply measuring the local strain of the ribcage and abdomen during breathing.[12] While devices like L.I.F.E.'s garment and AirGo™ are both placed around the torso, this type of sensor has the advantage of being a patch, hence less invasive and obtrusive.

Capacitance-based wearable sensors. Another field of research and development regards sensors based on variations of capacitance. In a study, the variations in electrical capacity between two conductive wires integrated in an elastic garment was employed to obtain the respiratory pattern.

Approaches to the design of portable devices for non-contact monitoring of respiratory rate by capacitive sensing have also been developed: this technology is based on the measurement of the capacitance existing between two electrodes between which the thoracic tissue acts as a dielectric material. The mechanical changes produced by breathing cause variations in the capacitance, which can be correlated with the respiratory rate.[13] Respiratory sensors with a single electrode have been studied, but are not yet validated and must be considered as future developments: in this case, the capacitance is constructed between one electrode attached on the skin and another constituted by the electrolytes inside, i.e., the conductive body fluid. At exhalations, the body volume decreases and the skin contrasts increasing its thickness, therefore the capacitance changes; the same principle can be applied to analyse inhalations.[14]

Inertial measurement units. The processed information captured by an accelerometer can be used to derive the respiratory rate from the movements of the rib cage; several studies with this type of solution can be found.[15] An example of this type of device is RespirHò, composed of three IMU-sensor units communicating via Bluetooth with a smartphone. Two units record chest-wall respiratory-related movements and are placed on the thorax and on the abdomen; the third sensor unit is placed on a body area that is not involved in respiratory movement.[16,17]

Fiber optic sensors. Recently, smart textiles based on fiber optic sensors have shown promising results in the field of respiratory monitoring. Especially fiber Bragg grating (FBG) sensors have been used to monitor the respiratory rate by integration of the sensing elements in patches or garments.

The deformations of the thorax and the abdomen can indirectly estimate the contribution of the thoracic and abdominal compartments on the tidal volume, because the reflected wavelengths sensed by the FBGs are affected by strain and temperature. As an example, a research group in Rome has recently developed a garment based on 12 FBGs placed in specific body landmarks.[18]

a Systems using non-wearable devices

Typically, continuous monitoring of breathing is performed with unobtrusive wearable devices, however there are specific cases in which measurements can be performed with more cumbersome techniques. In the case of Long-Term Oxygen Therapy (LTOT), there are commercial devices that calculate the respiratory rate via sensors that detect pressure changes in the oxygen line. Another case is polysomnography (PSG), which consists of a simultaneous recording of multiple physiologic parameters related to sleep and wakefulness. In standard PSG, at least seven signals are required: electroencephalography (EEG), electrooculography (EOG), chin electromyography (EMG), ECG, an airflow measurement using thermistors and nasal pressure transducers, pulse oximetry and respiratory effort (thoracic and abdominal).[19] In some studies on sleep disorders, portable testing can be limited to ECG or heart rate, oxygen saturation and at least two channels of respiratory movement or respiratory movement combined with airflow.[20] Finally, non-invasive mechanical ventilation (NIV) can be performed with Home Care Ventilators (HCVs), where a monitoring system can be embedded. In ventilators, directly measurable variables are the pressure at the airways opening and the flow; subsequently, other parameters are derived from the analysis of these signals. The accuracy of these measurements is reduced by the presence of leaks, which may be intentional or unintentional, and may cause discomfort and a decrease in compliance. Some ventilators allow continuous pulse oximetry monitoring and even end-tidal carbon dioxide ($ETCO_2$) monitoring. In particular, $ETCO_2$ is referred to as capnography and has been clinically demonstrated to provide an early indicator of respiratory distress.[21]

Some models of HCV are equipped with built-in software to download and analyse data over the previous weeks, providing compliance, estimation of leaks, tidal volume, minute ventilation, respiratory rate, apnoea and apnoea-

hypopnea indexes and percentage of inspirations triggered by the patient (or by the ventilator).[22]

a Contactless methods

A promising field of study is the development of telemonitoring techniques that do not require contact, even though a main drawback is that these devices are usually in fixed positions, as is further illustrated in the section dedicated to activity recognition, and therefore their range of utilization is limited. For instance, Doppler bio-radars have the ability to monitor physiological signals that depend on the Doppler effect. Electromagnetic waves can travel to the surface of the chest cavity and the reflected wave contains information on chest displacement, mainly caused by breathing.[23]

Pulse oximeters

Low blood oxygen concentrations (hypoxemia) increase the risk of respiratory exacerbation, while exacerbations can also induce hypoxemia. Hypoxemia can also lead to long-term adverse effects such as pulmonary hypertension and systematic inflammation, reducing quality of life. Oxygen levels are routinely measured noninvasively by pulse oximetry, which provides continuous peripheral O_2 saturation (SpO_2).[24] Using a spectrophotometric methodology, pulse oximeters measure oxygen saturation by illuminating a portion of skin at two wavelengths, 660 nm (red) and 940 nm (infrared), and measuring light absorption, which depends on the levels of oxygenated (oxyhaemoglobin) and deoxygenated blood (deoxyhaemoglobin). Conventional pulse oximeters use transmission sensors in which the light emitter and detector are on opposing surfaces of the tissue bed. A photo-plethysmography (PPG) waveform is produced, from which both SpO_2 and heart rate (HR) can be derived.[2,25] Finger pulse oximeters are uncomfortable to wear for prolonged time intervals, but the same measurement can be performed in different body parts (wrist, head, ear/earlobe, thigh, leg, ankle), thus allowing continuous measurements. The Oxitone 1000 wrist pulse oximeter is an example of a device that can be used for continuous monitoring without losing reliability. In fact, it was demonstrated to be accurate and precise for SpO_2 and pulse measurements during daily activities of pulmonary patients and not inferior to standard devices for spot checking and short period examinations.[26]

Another trend is non-contact PPG, also called imaging PPG (iPPG). Photoplethysmographic imaging using a cellular phone or computer camera is designed to operate without specialized hardware; there are various proposed techniques in this field, for instance DigitalPPG.[27] This technique only requires an area of the skin to be placed in front of the camera lens for several seconds as consecutive images are captured. Signals such as HR, respiratory rate, heart rate variability and SpO_2 are obtained. This technology is non-contact, inexpensive and pervasive; furthermore it is particularly suited for home applications[28] as it belongs to the emerging field of non-contact vital signs measurements.

Activity monitors

Physical activity can be defined as any body movement that uses skeletal muscles and results in energy expenditure. Objective methods to quantify activity are based on the measurements of physiological parameters, such as metabolic cost (total energy expenditure, or TEE), heart rate, body temperature and biomechanical effects, like acceleration, velocity and displacement.

Activity trackers include algorithms for the automatic recognition and allow for example to monitor whether a patient is compliant to a rehabilitation protocol or to assess whether the lifestyle of chronic patients is sedentary.[2] While there are several studies in which the lung function has been tested before and after a rehabilitation protocol,[29] telemonitoring would allow to evaluate the whole process rather than specific moments in time.

The current wearable technologies that can be used to implement human activity recognition (HAR) can be sensor-based, vision-based and radio-based.

Sensor-based recognition systems

Linear accelerations and angular/rotational velocities can be detected via micro-electro-mechanical systems (MEMS), which measure either capacity changes or the deflection of magnetically excited comb structures.

Accelerometers. At present, movement registration with body-fixed motion sensors offers the best alternative for physical activity assessment. Their use is based on demonstrated relationships between accelerometer output and energy expenditure in studies on gait analysis and ergonomics. Miniaturized accelerometers are able not only to quantify activities like walking, running, cycling and exercising, but also to recognise the time spent under sedentary conditions and distinguish different postures through the detection of gravity acceleration.[30] There are several activity monitors that are solely based on accelerometers and commercially available, for instance the ones produced by Philips Respironics, ActiGraph LLC (current models are CentrePoint Insight Watch, Actigraph GT9X Link, WGT3X-BT[31]; other monitors combine accelerometers with other type of sensors such as heat flux, galvanic skin response and skin temperature, like the SenseWear Armand by Bodymedia.[32]

Gyroscopes. In several studies, researchers combined accelerometers with gyroscopes to perform fall detection, gait analysis and gesture recognition. In most circumstances, the accelerometer acts as the lead sensor while the gyroscope functions as the supplementary sensor. Activities such as standing and sitting are better recognized from accelerometer data, while walking upstairs and downstairs are activities better recognized from gyroscopic data. For walking, biking and jogging activities accelerometer data performs slightly better than gyroscope data.[33]

Magnetometers. While accelerometers and gyroscopes are the most common types of sensors used in HAR, the possibility of using magnetometers has been studied. Starting from the information of the orientation of the magnetic field, the angular velocity in each direction is derived.

The main drawback of this technology is that there are magnetic disturbances caused by electrical appliances and metallic objects in the environment.[34]

Barometric pressure sensors. Barometric pressure sensors can be useful in activity recognition, for instance to detect falls due to a sudden pressure increase or to recognize if a subject is going up or down the stairs. In fact,

although current activity monitors based on inertial sensors are accurate in recognizing dynamic activities (walking and running), their abilities to classify static postures (standing vs. sitting or sitting vs. lying) remain limited as there is no estimation of the elevation, which on the other hand can be obtained from barometric pressure.[35]

Video-based recognition systems

Video-based recognition systems are a useful tool for activity monitoring. Common in-camera types include RGB video, depth video and RGB-D video; their software is capable of recognizing complex gait activities. However, such strategies restrict the movement of the user within a specific range, depending on how many 2D/3D cameras are employed. Furthermore, outputs are easily influenced by lighting variability and other exogenous factors.

Radio-based recognition systems

Radio-based recognition systems employ radiofrequencies to detect positions and activities; the most common technologies are RFID, Wi-Fi, ZigBee and infrared light. There are recent studies on other strategies, like the Doppler radar system, which can also be used to detect information on chest displacement.[23] In terms of radio-based HAR systems, the base stations must be prearranged and the tags are often attached to a person's wrist, ankle, head, or other parts. By observing that different activities cause different wireless communication patterns between the attached tags and the base station, activities can be recognized. However, these technologies only work within a specific range of distances from the base stations.[33]

Environmental monitors

Outdoor environmental monitoring

According to the World Health Organization, air pollution exposure is responsible for 7 million premature deaths every year. Thanks to wearable devices that monitor air quality in real time, environmental data can be transmitted to the Internet to create maps of air quality using a GPS. There are devices that can be clipped to the clothes, for instance TZOA, AirBeam or the Lapka Personal Environment Monitor. A recent trend is to create specific clothes with embedded environmental sensors, such as the WAIR scarf, also equipped with a filter that blocks particulates ($PM_{>0.1}$), pollen, gases and bacteria.[2]

Indoor environmental monitoring

Household air pollution is ranked as the 9th largest Global Burden of Disease risk and derives from a range of sources. The most important ones are combustion for heating, tobacco smoke, cooking, building materials, paints and varnishes. Indoor air pollution using biomass fuel in low-income countries has also been found to contribute to the prevalence of COPD.[36] Using modern sensor technology, it is possible to measure online not only the climatic parameters but also the concentrations of polluting substances.[37] There are several commercially available devices that measure environmental parameters of interest in respiratory research; examples are uHoo[38] and Foobot,[39] among others.

Main parameters of interest

Several environmental parameters have been found to be particularly significant in the case of respiratory patients. Concentrations of CO_2 higher than 800 ppm cause a broad range of diseases and symptoms, related to the upper and lower respiratory tract, eyes and skin and include headache, fatigue and difficulty in concentrating. With rising values of CO_2 in the atmosphere, symptoms worsen up to unbearable dyspnoea, vomiting, disorientation, hypertension and loss of consciousness for concentrations above 100,000 ppm.[40] Carbon monoxide (CO) reacts with haemoglobin to form carboxyhaemoglobin: reversible binding occurs on the same heme site where oxygen binds, thus preventing the transport of oxygen to the tissues.[41] Among other causes, it has been found that CO concentration increases if there is no ambient ventilation after smoking.[42] Chemical and microbiological volatile organic compounds (VOCs) influence the air quality in an indoor space and are primarily generated by humans. Internal sources are derived from human activities such as cooking or smoking and from building materials, as well as metabolic and biochemical processes.[43–46] Evidence has been found that nitrogen dioxide (NO_2) has a causal role in mortality and in the development of chronic respiratory diseases. Some epidemiological studies suggest associations of long-term NO_2 exposures with respiratory and cardiovascular mortality and with children's respiratory symptoms and lung function.[47] Ozone (O_3) is a strong oxidant agent with a variety of effects including lung inflammation,[48] alveolar epithelial damage and changes in chemical composition of lung lavage fluids, as well as reduction in lung function.[49,50] Fine particles ($PM_{2.5}$) have small diameters but large surface areas and may therefore carry toxic agents, because, through the nose filtration, they reach the end of the respiratory tract with airflow and accumulate there by diffusion, then enter the circulation.[51] $PM_{2.5}$ causes asthma and respiratory inflammation, jeopardizes lung functions and even promotes cancers.[52] In scientific literature, excessive cold temperatures have been linked to increases in the mortality and morbidity of COPD patients.[48] The interactions between temperature and humidity have also been studied: humidity itself is not associated with patients' symptoms, but there is an interactive effect between temperature and humidity.[53]

Monitors of other physiological parameters

$PaCO_2$ and $tcpCO_2$ monitors

CO_2 and O_2 are the gases exchanged between the blood and the inhaled air during respiration, with CO_2 diffusing approximately 20 times faster than O_2. A high level of $PaCO_2$ (hypercapnia) causes symptoms such as mild headaches, lethargy, and confusion, or severe ones with a hypnotic effect and acidosis with subsequent organ dysfunction, which can lead to coma and death. $PaCO_2$ can be estimated with transcutaneous CO_2 measurements ($tcpCO_2$) sensors, which are non-invasive, continuous and cause no sleep disturbance. However, this measurement is nowadays performed by electrochemical sensors requiring a temperature increase, which causes burns in long-term monitoring. Another drawback is the approximate 2-min lag time for the $PaCO_2$ changes to be reflected in the $tcpCO_2$. The problem of burns caused by electrochemical sensors may be overcome

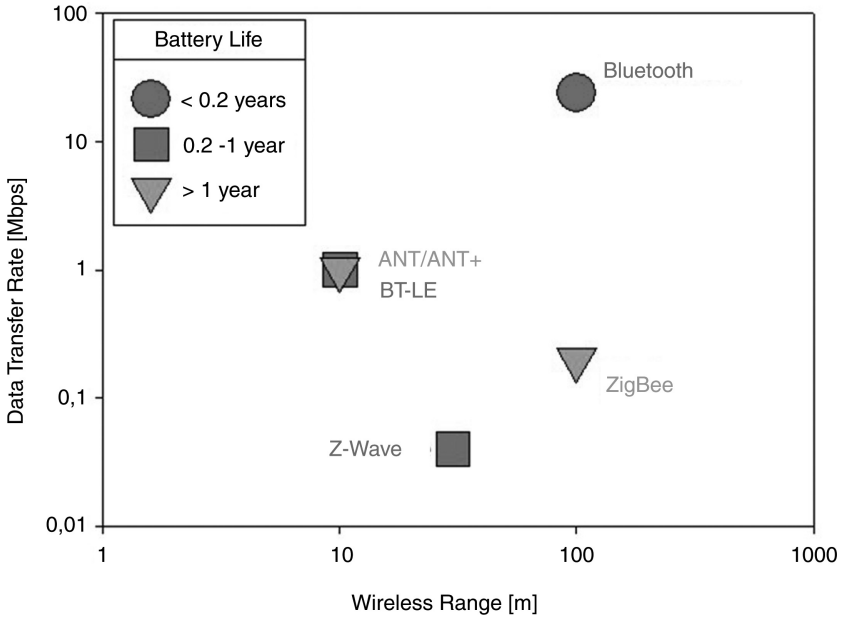

Fig. 2 Main characteristics of common mHealth sensor-manager link technologies. The wireless range, the data-transfer rate and the battery life are represented.

by using optical sensors able to determine CO_2 by measuring its optical absorption in the evanescent wave of a waveguide integrated in their surface.[54] Various devices offer the possibility to simultaneously monitor the level of oxygenation and CO_2, combining either SpO_2 with $tcpCO_2$ (e.g., SenTec™, Therwil, Switzerland, and TCM Tosca™, Radiometer, Neuilly Plaisance, France) or transcutaneous $tcpO_2$ with $tcpCO_2$ (e.g., TCM Combi MTM, Radiometer, Neuilly Plaisance, France).[24]

Electrocardiographs

Holter monitors are traditionally used for ECG acquisitions in remote settings, but they are being surpassed by wireless bipotential patch devices. The patch ECG (PECG) sensors are unobtrusive, wire free and can record from weeks to months, which helps detection of long-term malignant arrythmias. Examples are the Savvy monitor, ZIO® XT Patch by iRhythm Technologies, Inc. and SEEQ™ MCT patch device by Medtronic, Inc.[24] The previously cited L.I.F.E. device includes a wearable ECG, as it features 12 electrodes located on the internal surface of the garment.[10] Even more recently, very short-term (seconds to minutes) handheld smartphone-enabled systems (AliveCor®, ECG Check) have been developed. They require attachment of an electrode-embedded module to a smartphone that detects electrical impulses from the user's fingertips and transmits signals to the mobile device to generate continuous single-channel ECG for the duration of the contact between the fingers and the sensor.[55]

Arterial blood pressure measurement methods

The arterial blood pressure can be noninvasively measured by the auscultatory method with an inflatable cuff, a manometer measuring the pressure in the cuff and a stethoscope placed over the brachial artery in the elbow. With the oscillometric method, on the other hand, the cuff is inflated to a point above systolic blood pressure and slowly deflated while oscillations are detected by a pressure sensor. Oscillations begin approximately at systole and continue below diastole with maximal oscillations occurring at mean arterial pressure.[56] There are also continuous, noninvasive arterial pressure-monitoring devices that measure in real time without cuffs, but their precision is yet to be proved.[24]

Thermometers

Normal body function depends on a relatively constant body temperature. Body temperature increases in infections, malignancy and many inflammatory conditions; a value above 38.5° can indicate a severe exacerbation in COPD patients. The most common sites used to obtain body temperature readings with medical thermometers are the anus, the mouth, under the arm and the ear; approaches for continuous monitoring of the temperature have been reported in the literature.[24]

Communication systems

Sensor-manager link technologies

The main sensor-manager link technologies[57] are shown in Fig. 2.

Bluetooth and Bluetooth Low Energy (BT—LE)**.** The Bluetooth technology operates at unlicensed ISM (Industrial, Scientific, and Medical) 2.4 GHz frequency band, which is currently being used by Home RF, Wi-Fi networks, cordless telephones, baby monitors, walkie-talkies, garage door operators and other applications, so it is subject to interference. Bluetooth transmits both data signals and voice signals over a short distance of up to 100 m.[58] In contrast to Bluetooth, Bluetooth Low Energy (BT—LE) has a longer battery life at the price of reducing the wireless range and the data transfer rate, therefore it is an appropriate substitute for applications in which the amount of data sent is low but

there is the need to reduce costs and improve the autonomy of the device.

ANT and ANT+. ANT is a protocol for ultra-low-power, short-range wireless communications in sensor networks. It ensures low power consumption by using low data rate, short delay cycles, and deep-sleep mode and can operate for longer periods of time (more than a year). It operates in the 2.4 GHz ISM band and can communicate with multiple nodes over a single 1 MHz channel, switching channels if any interference occurs. ANT can be distinguished from other wireless protocols by its unique feature in which it acts as a master for one channel and slave for another channel. Like ZigBee, ANT supports multiple network topologies and also ensures coexistence with neighbouring ANT nodes. The maximum data rate achieved by ANT systems ranges from 20 to 60 kbps and there is a trade-off between data rate and low power consumption. A recent advancement in the ANT protocol, ANT+, uses application-specific device profiles to communicate between two devices, i.e. the set of network rules, parameters, data formats specific to a particular application. Furthermore, the ANT + protocol has the advantage of being interoperable with other ANT + devices having the same device profile.[59]

Z-Wave. Z-Wave is a wireless communication standard designed for remotely controlled application. Its data rate is 40 kbps at a transmission frequency of 915 MHz (900 MHz ISM band) and it can reach up to 30 m in the open air.[60] This technology is particularly optimized for low-overhead commands such as on-off (as in a light switch or an appliance) and raise-lower (as in a thermostat or volume control). As it does not interfer with other devices usually present in home environments, Z-Wave allows for a standardized low bandwidth control medium that can be reliable.[61]

ZigBee. One of the most widely used wireless technologies in WBANs is ZigBee (IEEE 802.15.4) because it is targeted at applications that require a low data rate and long battery life. In particular, this protocol is advantageous in real-time monitoring because of the low power consumption, large range (10−1500 m), limited data rate (250 kbit/s), low cost and flexibility in supporting multiple network topologies.[62] The working frequencies of ZigBee are 868 MHz (Europe), 915 MHz (Americas/Australia) and 2.4 GHz (worldwide) and transmits data over one, ten and sixteen channels respectively. In the last band, it is subject to interference with other devices sharing this band.[3] While Bluetooth and BLE only support peer-to-peer (P2P) and star topologies, ZigBee devices can be connected using P2P, star, tree and mesh network topologies. Prior to transmitting a packet, the ZigBee protocol assesses the communication link by using CSMA/CA (Carrier Sense Multiple Access with Collision Avoidance) protocol or by sending beacons to other nodes.[59]

Cellular-link technologies

Wi-Fi. Wi-Fi is a family of radio technologies that is commonly used for wireless local area networking (WLAN), which is based on the IEEE 802.11 family of standards, and designed to interwork with its wired sister protocol Ethernet. Devices that can use Wi-Fi technologies include desktops, laptops, smartphones, tablet, smart TVs, printers, digital audio players, digital cameras, cars and drones. Compatible devices can connect to each other via Wi-Fi through a wireless access point as well as to connected Ethernet devices. Such an access point (or hotspot) has a range of about 20 m indoors.

Wi-Fi uses the 2.4 GHz and 5 GHz ISM radio bands, which are subdivided into multiple channels, each time-shared by multiple networks.

Several sensing devices have embedded Wi-Fi modules and therefore can be connected to the Internet directly. This is advantageous when the sensors are in fixed positions, for instance in the case of home environmental sensors.

4G. The 4G (Fourth Generation) technology is a cellular technology which relies on an all-Internet Protocol (IP) based communication, IP telephony.

With the ultra-broadband internet service, 4G networks are projected to provide speeds of 100 Mbps while moving and 1 Gbps for stationary devices.

The mobile 4G network uses several frequencies, depending on the provider and the country, in the ranges of MHz and GHz. Several actions are possible thanks to this technology, such as broadband access in remote locations, seamless connectivity, interoperability, access to music and data and photo sharing.

5G. The 5G (Fifth Generation) technology provides real time success device-to-device communication (D2D). The frequencies covered are in the bands of 700 MHz, 3.5 GHz and 26 GHz and a speed of 10 Gbps can be reached. The main advantages of this technology are that the data are processed close to the final user thanks to the utilization of core Multi-Edge Computing (MEC) networks positioned close to the access network, which grants a low latency. Other differentiating characteristics are the high band capacity and number of connected devices. The 5G technology is based on a Multiple Input Multiple Output (MIMO) technology and multiple access is obtained with Orthogonal Frequency division: these traits are distinctive compared to previous technologies.[63] In fact, Massive MIMO utilizes extensive service antennas by spatial multiplexing. Overall, the 5G technology helps in concentrating energy into smaller areas, therefore high throughput and efficiency can be readily achieved on a large scale and with great momentum.[64] Nowadays, the 5G technology is mostly used only in wide networks, while local networks usually use sensor-manager link technologies.

Results (clinical studies)

In the literature, several works regarding clinical studies on chronic respiratory patients performed with monitoring of some parameters can be found, mostly dealing with COPD, asthma and cystic fibrosis (CF).[65] The main limitation that can be found in most studies is that they usually do not collect all the parameters of interest, but only a few of them. Furthermore, most clinical studies do not use a telemonitoring system, but rather collect data that are analysed offline; the advantage of a real-time telemonitoring system is that it not only allows us to monitor parameters, but also to perform timely interventions once a critical event is identified. In this field, there are studies that report significant variations of physiological parameters before a COPD exacerbation, some of which are reported in Table 1. In particular, the amount of studies of the respiratory rate is limited, with contrasting results. The studies from Martin

Table 1 Selected results of telemonitored parameters before a COPD exacerbation.

Reference	Parameters considered	Results
[66]	Heart rate; blood oxygen saturation; peak flow	The maximal change in SpO_2% and HR occurred two days into an exacerbation: SpO_2 had fallen by − 1.24 SD, HR increased by 3.09 SD
[69]	Respiratory rate	Mean respiratory rate raised 1–5 days prior to hospitalization (two days: 15% from the baseline; one day: 30% from baseline)
[67–68]	Heart rate; blood oxygen saturation; respiratory rate	Mean SpO_2% fell from 93.1% to 91.0% (4.6 SD) and mean HR increased from 77.8 to 84.2 min^{-1} (17.1 SD). There was no significant change in the respiratory rate.
[70]	Heart rate; blood oxygen saturation	There was an increase in HR (from 87 min^{-1} to 94 min^{-1}) at the onset of an exacerbation and the mean SpO_2 fell (93.6% to 92.4%) around the onset time.

Lesende et al. found no significant change in the respiratory rate, but this can be attributed to the low accuracy of the method of investigation used.[67,68] On the other hand, in the work by Yañez et al., based on a direct measurement of the flow, a statistically significant result on the respiratory rate has been obtained: specifically, the patients in this group were under LTOT and measurements have been performed with the VisionOx monitor.[69] There are also studies in which the alarm limits have been customized for each subject by previously monitoring his/her baseline in a period without exacerbations. In three studies, the magnitude of change in heart rate and SpO_2% reported was an increase of around 5 min^{-1} for heart rate and a fall by 1–2 % for SpO_2. Two studies reported an increase in the respiratory rate before the onset of am exacerbation or before hospitalization.[71] Continuous oxygen saturation measurements have already been performed in the TELEMOLD project with the pulse oximeter Avant 4000 (Nonin Medical) for one week. Concerning rest periods, only 2 patients out of the 35 participants were found with a desaturation > 30 % of the time. On the other hand, 87 % of our patients had important desaturation occurring during activity, with visible effects in the transition periods. In this study, more than 30 % of night-time with SpO_2 < 90 % (at least in 1 night) was considered as abnormal, and it was found in 27 % of the patients. However, desaturation was not detected on every night recorded so nocturnal oximetry performed in a single night may be insufficient to detect important sleep desaturation in some patients.[72] As symptoms during physical activity and physical inactivity are characteristic of chronic respiratory diseases, several studies can be found where activity monitoring is performed. Physical activity levels have been found to have a moderate to strong correlation with pulmonary function, exercise capacity, quality of life, and mortality and hospitalizations in patients with COPD, interstitial lung disease, pulmonary arterial hypertension and cystic fibrosis; many FDA-approved research-grade devices have been and are being used in worldwide clinical trials.[73] As an example, the objective of a study in Brazil was to determine whether there was an association between physical inactivity and pulmonary function, fatigue, dyspnea, functional status and exercise capacity in individuals with COPD on home-based LTOT and to investigate which of these variables could influence inactivity. Pulmonary function was assessed with a spirometer; fatigue, dyspnea and functional status were assessed with questionnaires; functional status was assessed again with an objective method (Timed Up and Go test); finally, exercise capacity was assessed using specific tests (6-Minutes Step test and 1-Minute Sit-To-Stand test). There was a significant correlation between number of steps/day and daily duration of LTOT (h/day), fatigue, functional status and capacity to exercise.[74] In this field, there was also a study on 1001 patients affected by COPD in which activity measures and hourly patterns were analysed based on data from a multi-sensor armband. Data mining methods were applied to physical activity measures to identify clusters. The most inactive clusters were characterised by higher BMI, lower FEV_1, worse dyspnoea and higher ADO (age, dyspnoea, obstruction) index,[75] however daily physical activity measures and hourly patterns were found to be heterogeneous in the cohort.[76]

Another field of application is on patients with CF, in which compliance with the therapy is a major problem. ICT can improve compliance and feed information back to the clinicians about the respiratory status (e.g. with pulse oximetry) and allows interceptions of respiratory exacerbations. There has been a pilot study on 71 patients, of which some of them were affected by CF, which showed a perceived improvement in clinical and ethical aspects, revealing neutral results from an economic point of view. The results of the data survey analysis showed the need for patients and caregivers to see which data that they are sending, in order to become more active and participative in the management of their condition.[77]

Tele-health has also been used to support self-management of long-term conditions such as asthma, with positive results. A systematic review and meta-analysis from three randomised controlled trials using different technologies showed an improvement of asthma control, though the clinical effectiveness varied.[78,79] As far as environmental parameters are concerned, substantial epidemiological evidence indicates that ambient $PM_{2.5}$ is a major detrimental risk factor for COPD: it is associated with an enhanced risk of COPD hospitalization, morbidity and mortality and also exacerbates and aggravates respiratory function and symptoms, such as shortness of breath, coughing and wheezing. It was found that prolonged chronic exposure to $PM_{2.5}$ resulted in decreased lung function, emphysematous lesions and airway inflammation.[80]

There are also more broad-spectrum studies that look at the effectiveness of monitoring techniques which include a data processing phase, like the built-in software of home ventilators. In fact, there have been validation studies to determine whether the signals and data recorded are reliable, with positive results; what still needs more research is what to expect from monitored patients in terms of normal/abnormal results. Understanding what parameters must be expected in different patient categories is a necessary step in order to give feedbacks and alerts in critical situations.[81]

Discussion

The field of telemonitoring is expected to bring benefits both from the point of view of quality of the care and of economic aspects. However, there are some open issues regarding legal responsibilities, privacy and adherence of the patients.

Socio-Economic considerations

By 2060, the European population aged > 65 years and those aged > = 80 years will rise to 30.0 % and to 12.1 % of the total population, respectively. Projections show that the EU average health expenditure may grow to up to 8.5 % of GDP, mostly due to age.[65] Among chronic respiratory diseases, COPD is of particular interest from the socio-economical point of view, as it is the third most frequent cause of death worldwide, according to the WHO. The health economics impact of the use of telehealth has been evaluated and experts indicate a €1060 average decrease of hospitalisation costs and additional €898 savings per COPD patient in 2013.[82] A pilot study in Germany demonstrated that telemonitoring of COPD patients is a viable strategy to reduce mortality, healthcare costs and utilisation at 12 months. A telemonitoring console was used to answer a disease-specific and general well-being questionnaire (three questions) at least twice a week. The analysis comprised 651 telemonitoring participants and 7047 individuals in the standard care group. Telemonitoring cut total costs by 895 €-value < 0.05) compared to COPD standard care, mainly driven by savings in COPD-related hospitalisations in severe COPD patients (-1056 €, p-value < 0.0001). On the other hand, costs for out-patients visits slightly increased.[83]

Improvements in health outcomes

In the literature, it was found that home telemonitoring appears to have a positive effect in reducing respiratory exacerbations and hospitalisations and improving the quality of life of patients, however the evidence of its benefits is still limited and results are controversial. In the previously cited pilot study in Germany., the mortality hazards ratio was lower in the intervention arm (HR 0.51, 95 % CI 0.30–0.86).[83] In another review from Cruz et al., nine studies were considered and significant differences were found in the hospitalisation rates between the standard care group and the telemonitored one.[84] As reported by Liu et al., there is evidence that older adults with COPD experience a lower rate of exacerbations and hospitalizations when wearing a Bluetooth wristband that telemonitored their vital signs.[85] In other studies, however, there was evidence that a home-health physiological monitoring system had no impact on the number of hospital admissions or hospital length of stay in older adults with COPD[85,86]; it is however suggested than telemedicine can partially substitute visits at respiratory outpatient clinics[87] and improve health-related quality of life and anxiety.[88]

Legal issues

Any application of telemedicine is considered a medical act; therefore, the legal principles of the traditional doctor-patient relationships remain valid. The relationship between the patient and other stakeholders must be governed by the ''informed consent'', which includes the patient's awareness of the technicalities, the potential risks, the required precautions and ensures the confidentiality, security and authenticity of the data.[65]

General data protection regulation (GDPR)

The General Data Protection Regulation (GDPR) takes into account the development of technology and regulates the aspects regarding not only personal data, but all sides of data management. The approach of GDPR is based on a balance between protection and free flow of data, which allows to obtain big data in the first place. Examples of security and privacy risks are data leakage or disclosure, data corruption or loss and user privacy breach.[89] There are many use cases in which data protection is particularly relevant and healthcare applications belong to this category.

Adherence and risk of dropouts

Another open issue is the non-adherence or partial adherence to intervention programmes and/or the withdrawal of participants over the course of several studies. Dropout rates for telehealth vary across trials; possible factors may be related to participant characteristics, interventional methods and the environment where the patient is telemonitored. The first attempts to review the literature and statistically analyse acceptance, adherence and dropout rates are ongoing[90]; the relevance of these studies is due to the fact that patient compliance and cooperation is necessary for successful telehealth solutions.

Conclusion

Telemonitoring of chronic respiratory patients is a promising solution both from the technical and the economic point of view, as it improves the quality of the care provided and at the same time allows for a better management of chronic diseases. In order to obtain a more complete information that might be relevant to this application, it is important to include all the sensors needed rather than focusing on only one aspect. Furthermore, most clinical studies involve the offline monitoring and subsequent analysis of parameters of interest, but do not have the architecture of a telemonitoring system. Integrating all the sensors needed in a system

that comprises the aspects of data collection, storage and analysis is the next step to obtaining a real-time telemonitoring system for respiratory patients. This will lead to large amount of data that can be transmitted with low latency and high reliability thanks to wireless communication technologies such as 5G. In order to extract meaningful and synthetic information from big data, cooperation between data analysts and clinicians is fundamental.

Conflicts of interest

The authors have no conflicts of interest to declare. Dr Aliverti has been consultant for L.I.F.E.

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BRIEF COMMUNICATION

Tuberculosis, COVID-19 and migrants: Preliminary analysis of deaths occurring in 69 patients from two cohorts

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KEYWORDS
TB;
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Abstract Little is known about the relationship between the COVID-19 and tuberculosis (TB). The aim of this study is to describe a group of patients who died with TB (active disease or sequelae) and COVID-19 in two cohorts.

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Mortality;
Migrants;
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Data from 49 consecutive cases in 8 countries (cohort A) and 20 hospitalised patients with TB and COVID-19 (cohort B) were analysed and patients who died were described. Demographic and clinical variables were retrospectively collected, including co-morbidities and risk factors for TB and COVID-19 mortality.

Overall, 8 out of 69 (11.6%) patients died, 7 from cohort A (14.3%) and one from cohort B (5%).

Out of 69 patients 43 were migrants, 26/49 (53.1%) in cohort A and 17/20 (85.0%) in cohort B.

Migrants: (1) were younger than natives; in cohort A the median (IQR) age was 40 (27–49) VS. 66 (46–70) years, whereas in cohort B 37 (27–46) VS. 48 (47–60) years; (2) had a lower mortality rate than natives (1/43, 2.3% versus 7/26, 26.9%; *p*-value: 0.002); (3) had fewer co-morbidities than natives (23/43, 53.5% versus 5/26–19.2%) natives; *p*-value: 0.005).

The study findings show that: (1) mortality is likely to occur in elderly patients with co-morbidities; (2) TB might not be a major determinant of mortality and (3) migrants had lower mortality, probably because of their younger age and lower number of co-morbidities. However, in settings where advanced forms of TB frequently occur and are caused by drug-resistant strains of *M. tuberculosis*, higher mortality rates can be expected in young individuals.

Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is causing a debate on preventive, diagnostic, and therapeutic strategies among scientists, clinicians, and public health experts.[1–3]

The current scientific evidence suggests that individuals with the disease are infectious, SARS-CoV-2 rapidly spreads within the community because of the lack of herd immunity,[4,5] it has high case-fatality rate among elderly and patients with co-morbidities and can stretch unprepared healthcare systems causing rapid collapse of intensive care units (ICU).[1,6]

Patients with COVID-19 may complain of cough, fever, tiredness, dyspnoea, and other signs and symptoms[1–3] similar to those of tuberculosis (TB) and of other respiratory infections.[7]

Little is known about the relationship between the COVID-19 and TB. Data from 49 cases (cohort A) reported elsewhere[7] show that COVID-19 can occur before, simultaneously, or after the diagnosis of TB. Furthermore, additional information from 20 hospitalised patients with TB and COVID-19 (cohort B) is available (Stochino C. et al, unpublished data).

The aim of this study is to describe for the first time a group of patients who died with TB (active disease or sequelae) and COVID-19 in the cohorts A and B.

Patients and methods

Data of both cohorts were combined to assess the mortality. Cohort A included 49 patients with TB and COVID-19 from 26 centres in Belgium, Brazil, France, Italy, Russia, Singapore, Spain, and Switzerland,[7] whereas cohort B included 20 cases admitted to a single reference hospital located in Northern Italy.

Both cohorts belong to nested studies of the Global Tuberculosis Network (GTN) large observational project monitoring adverse reactions to anti-TB drugs for which the coordinating centre in Tradate (Italy) has the ethical approval (and other participating centres according to the respective national regulations).[7–9]

All consecutive cases with a diagnosis of TB (at any time in the past, so as to include patients with TB sequelae, which may be a risk factor for mortality) and COVID-19 from cohorts A and B were included.

Demographic and clinical variables were retrospectively collected, including co-morbidities and risk factors for TB and COVID-19 mortality.

TB patients were microbiologically confirmed (Table 1), whereas SARS-CoV-2 infection was confirmed by molecular biology. The first COVID-19 diagnosis was made on March 12th, 2020; data were updated as of May 5th, 2020.

Continuous variables, if not otherwise specified, are presented as medians (IQR-Interquartile ranges). Categorical variables were described with absolute and relative (percentage) frequencies. Chi-squared and Fisher exact tests were used to compare qualitative variables when appropriate. A two-tailed p-value less than 0.05 was considered statistically significant.

The MuLBSTA (multilobular infiltration, hypolymphocytosis, bacterial coinfection, smoking history, hypertension, and age) clinical score used to predict 90-day mortality due to viral pneumonia, although not yet validated for COVID-19, was calculated.[10]

Results

Overall, 8 out of 69 (11.6%, 10.6%) patients died, 7 from cohort A (14.3%, patients 1–6.8) and one from cohort B (5%, patient 7) (Tables 1 and 2).

Table 1 Information on tuberculosis in 8 patients with COVID-19 who died.

#Case age	Gender	Country of origin	Co-morbidities/Risk factors	Type of TB case definition P/EP	Imaging at TB diagnosis (chest-X ray/CT)	TB drug-resistance pattern	TB course at time of COVID-19 diagnosis/microbiology
1 70 yrs	Male	Italy	Hypertension, prostatic hypertrophy	*M. tuberculosis* new, pulmonary	CT/C-X ray: bilateral pulmonary lesions with cavities	Pansusceptible	RHZ, SS ++, last culture positive
2 79 yrs	Male	Italy	Previous TURP, nephrectomy in 2011 for renal cancer, NHL diagnosed in 2017 and treated with R-CHOP regimen for 6 cycles (last cycle February 2020)	*M. bovis* new, pulmonary	CT/C-X ray: bilateral miliary lesions	Intrinsically resistant to Z	RE, TB diagnosis on BAL, C+/direct microscopy +; due to hepatotoxicity and prothrombin time prolongation TB drugs were stopped and re-challenge was ongoing. After COVID-19 diagnosis R stopped (due to drug–drug interactions) and H restarted
3 70 yrs	Male	Italy	HIV infection, liver cirrhosis HBV/HDV related, metastatic prostate cancer, smoke	*M. tuberculosis*, TB sequelae new, pulmonary	CT/C-X ray: unilateral infiltrate	Pansusceptible	Treated with HRZE, cured in 2017

Table 1 (*Continued*)

#Case age	Gender	Country of origin	Co-morbidities/Risk factors	Type of TB case definition P/EP	Imaging at TB diagnosis (chest-X ray/CT)	TB drug-resistance pattern	TB course at time of COVID-19 diagnosis/microbiology
4 45 yrs	Male	Italy (born in Moldova)	Alcohol, liver disease, smoke	*M. tuberculosis* new, pulmonary	CT/C-X ray: bilateral cavities, left hydropneumothorax with mediastinal emphysema.	Pansusceptible	HRZE, SS++++
5 82 yrs	Male	Spain	Alcohol, hypertension, renal failure, smoke	*M. tuberculosis* new, pulmonary	CT/C-X ray: miliary pattern	Pansusceptible	HRZE
6 66 yrs	Male	Spain	Alcohol, COPD, liver steatosis, smoke	*M. tuberculosis* new, pulmonary	CT/C-X ray: bilateral infiltrates	Pansusceptible	HRZE, C+/SS+
7 73 yrs	Female	Italy	Cachexia (BMI < 20), vomit and diarrhoea from 8 months, (possible underlying cancer), diabetes mellitus, hypertension, mental disorders	*M. tuberculosis* new, pulmonary	CT/C-X ray: bilateral excavated lung thickening, tree in bud (right lung)	Pansusceptible	HRZE Advanced pulmonary TB, SS− (7 days before death)
8 70 yrs	Male	Spain	Diabetes mellitus, hypertension, obstructive sleep apnea syndrome, renal failure, smoke	*M. tuberculosis* new, pulmonary	CT/C-X ray: bilateral infiltrates	Pending	HRZE, C pending/SS+

BAL: broncho-alveolar lavage; BMI: body mass index; COPD: chronic obstructive pulmonary disease; COVID-19: COronaVIrus Disease 19; CT: computed tomography; EP: extrapulmonary; HBV/HDV: chronic hepatitis B virus and hepatitis delta virus co-infection; HIV: human immunodeficiency virus; HRZE: isoniazid, rifampicin, pyrazinamide, ethambutol; NHL: non-Hodgkin lymphoma; P: pulmonary; SS/C: sputum smear/culture; TB: tuberculosis; TURP: transurethral resection of the prostate.

Table 2 Information on tuberculosis and COVID-19 in 8 patients who died.

#Case	Time between TB and COVID-19 diagnosis (no. of days)	COVID-19 symptoms/MuLBSTA score at diagnosis	COVID-19 therapy (antivirals, steroids, maximum oxygen flow received, ventilation, etc.)	Imaging during TB/COVID-19 course	Time between COVID-19 diagnosis and death; cause of death; hospital admission (no. of days)	Comments
1	121	None, MuLBSTA score 8	Hydroxychloroquine, parnaparine 4250 IU, oxygen through Venturi Mask 60% 12 l/min	Not done	10 days, respiratory failure 130 days at hospital	BCG vaccinated COVID-19 diagnosis after contact tracing due to a case in same ward. Patient developed fever and dyspnoea later.
2	19	None, MuLBSTA score 15	Hydroxychloroquine, lopinavir/ritonavir, enoxaparine 4000 IU, dexamethasone 8 mg × 2, oxygen through non-rebreather, 15 l/min	C-X ray: new bilateral pulmonary infiltrates	13 days, respiratory failure 31 days at hospital	BCG vaccinated COVID-19 diagnosis after contact tracing due to a case in same ward. Patient developed fever and dyspnoea later.
3	1205	Fever, MuLBSTA score: 5	Hydroxychloroquine, azithromycin, oxygen through face mask	CT/C-X ray: unilateral infiltrate	8 days, cachexia and respiratory failure 8 days at hospital	BCG status unknown COVID-19 major determinant of death, complicating the poor clinical conditions due to multiple and severe co-morbidities
4	7	Cough, dyspnoea, tiredness, MuLBSTA score:12	Hydroxychloroquine, oxygen through non-rebreather mask, 15 l/min	CT: unilateral crazy paving developing on pre-existing lesions	6 days respiratory failure 13 days at hospital	BCG vaccinated COVID-19 determinant of death

Table 2 (*Continued*)

#Case	Time between TB and COVID-19 diagnosis (no. of days)	COVID-19 symptoms/MuLBSTA score at diagnosis	COVID-19 therapy (antivirals, steroids, maximum oxygen flow received, ventilation, etc.)	Imaging during TB/COVID-19 course	Time between COVID-19 diagnosis and death; cause of death; hospital admission (no. of days)	Comments
5	12	Fever, cough, vomit, MuLBSTA score: 11	Hydroxychloroquine, oxygen through face mask, Hb saturation: 89% with 4 l/min	CT/C-X ray: miliary pattern	14 days respiratory failure 24 days at hospital	BCG status unknown COVID-19 aggravated general conditions and renal fail
6	75	Fever, MuLBSTA score: 9	Hydroxychloroquine, azythromycin. Hb saturation: 93%, room air	CT/C-X ray: bilateral infiltrates	8 days, respiratory failure 82 days at hospital	BCG status unknown, COVID-19 major determinant of death; COVID-19 acquired at hospital
7	26	Fever (up to 39 °C), severe dyspnoea with respiratory failure, MuLBSTA score: 9	Hydroxychloroquine. Oxygen supply from 2 to 10 l/min with reservoir.	C-X ray (at bed): bilateral excavated lung thickening, tree in bud (right lung)	6 days Respiratory failure 32 days at hospital	Not BCG vaccinated. COVID-19 accelerated death, although the patients was already very compromised since admission, COVID-19 acquired at hospital
8	4 days (COVID-19 diagnosed before TB)	Fever, cough, MuLBSTA score: 15	Hydroxychloroquine, lopinavir/ritonavir, azythromicin, piperacilin-tazobactam, Hb saturation: 99% with re-breather mask, 15 l/min, non-invasive ventilation performed	CT/C-X ray: bilateral infiltrates	12 days Respiratory failure 12 days	BCG: unknown COVID-19 accelerated death, although the patients was already very compromised since admission COVID-19 acquired at hospital

BCG: Bacillus Calmette-Guérin; COVID-19: COronaVIrus Disease 19; CT: computed tomography; C-X ray: chest radiography; Hb: hemoglobine; IU: international unit; MuLBSTA: multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hyper-tension and age; TB: tuberculosis.

All but one (patient 7) were males, with a median age of 70 (range 45–82) years, and had TB diagnosed before COVID-19; only patient 8 had almost simultaneous diagnosis of COVID-19 and TB. They showed from 2 to 5 co-morbidities, for two patients being cancer (haematological and prostatic, and for patient 7 underlying cancer could not be excluded, although the rapid decline and death prevented the possibility of diagnosing it); one patient was co-infected with HIV and HBV/HDV (chronic hepatitis B virus and hepatitis delta virus).

Out of 69 patients 43 were migrants, 26/49 (53.1%) in cohort A and 17/20 (85.0%) in cohort B.

Migrants were younger than natives: in cohort A the median (IQR) age was 40 (27–49) VS. 66 (46–70) years, whereas in cohort B 37 (27–46) VS. 48 (47–60) years.

Overall, migrants had a lower mortality rate than natives (1/43, 2.3% versus 7/26, 26.9%; *p*-value: 0.002).

Migrants had fewer co-morbidities than natives; in particular, 23/43 (53.5%) migrants had no co-morbidities versus 5/26 (19.2%) natives (*p*-value: 0.005).

Among the patients who died, 3 were vaccinated with Bacillus Calmette-Guérin (BCG); 4 were infected by pan-susceptible *Mycobacterium tuberculosis* strains and one by *Mycobacterium bovis*, which is intrinsically resistant to pyrazinamide. Except patient 3 who had TB diagnosed in 2016 and was declared cured (affected by post-treatment sequelae) and patient 8 (simultaneous diagnosis of COVID-19 and TB), the remaining patients had COVID-19 diagnosed between 7 and 75 days (median: 22.5 days) after the TB diagnosis. In 6/7 patients SARS-CoV-2 infection was nosocomial.

While only a single patient (patient 3) had unilateral infiltrates, all the others had bilateral lesions: patients 2 and 5 a miliary pattern, patient 4 crazy paving, and patient 7 a 'tree in bud' pattern (Tables 1 and 2). TB was treated using first-line drugs; five patients were treated with hydroxychloroquine for COVID-19. Four patients needed oxygen therapy through face mask and one underwent non-invasive ventilation. Death occurred after a median of 9 (range 6–14) days after COVID-19 diagnosis. COVID-19 was considered relevant in either causing death or accelerating its occurrence. Median (range) hospital stay was 27.5 (8–130) days.

The median MuLBSTA score found was 10 (range 8–15) with a theoretical predictive 90-day mortality of 9.33%.

Discussion

To the best of our knowledge this is the first report of patients dying with TB and COVID-19, including 69 patients from the two largest cohorts of co-infected patients available so far.

Although the case-fatality rate was rather high (overall 10.6%, but 14.3% in the first cohort) and still preliminary (it can increase over time within both cohorts), the results seem consistent with those observed in other cohorts of COVID-19 patients.[1–3] In general, all patients (except one) were aged >65 years, and were affected by >2 co-morbidities.

In all cases COVID-19 contributed to worsen the prognosis of TB patients and/or to cause death.

In the majority of patients who died, SARS-CoV-2 infection was nosocomial during early phases of the outbreak in Northern Italy and Spain. This highlights the importance of implementing strict infection control interventions for all hospitalised patients (and, particularly, for those at higher risk, e.g. elderly and patients with co-morbidities including TB), taking into account the risk of viral transmission from other patients, visitors, and healthcare workers.[4,5]

The MuLBSTA score has been developed for viral pneumonia[11] and has similar inputs to risk factors for mortality seen in the initial COVID-19 patient cohorts in China.[12] Age has a much stronger odds ratio for increasing mortality in COVID-19 patients than in other viral pneumonia patients. A score higher than 12 points is considered high risk (bacterial coinfection detected by sputum or culture - as for concomitant active TB counts 4 points.) In our patients it does not seem to predict mortality well: the median value is 10 and only 2 patients scored values higher than 12.

TB and COVID-19 seem to absorb relevant human and economic resources, although the relatively small size of the cohort prevents drawing specific conclusions.

The main limitation of this preliminary study is that the cohort, although likely to report the vast majority of cases with TB and COVID-19 in the countries surveyed, cannot be considered representative either of the European nor of the global situation.

The study findings show that: (1) mortality is likely to occur in elderly patients with co-morbidities; (2) TB might not be a major determinant of mortality and (3) migrants had lower mortality, probably because of their younger age and lower number of co-morbidities. However, in settings where advanced forms of TB frequently occur and are caused by drug-resistant strains of *M. tuberculosis*, higher mortality rates can be expected in young individuals.

However, as the study will continue prospectively with the inclusion of GTN countries where TB and COVID-19 patients have not been diagnosed until now, we wish to invite all interested clinicians and programmes to contact us and participate in the study.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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COMMENT

COVID-19 in Brazil

It has been ∼4 months since the first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, China including a total of ∼82,000 patients and 3,341 deaths. Until April 14th, 2020, COVID-19 has affected ∼1,950,000 patients in 210 countries and territories around the world and 2 international conveyances and caused ∼122,000 deaths in 162 countries/territories.[1] However, the epidemiologic data differs across countries. Although China showed the first case and a higher rate of morbidity and mortality than other sites, the number of new cases per day in China has been less than that elsewhere since February 26, 2020. Further studies and continued monitoring are needed to better understand the underlying mechanism of COVID-19. In addition, United States of America (USA) exceeded the number of cases observed in China on March 28th, 2020 with more than 590,000 COVID-19 patients and ∼24,000 deaths, followed by Spain (∼172,000 patients and ∼18,000 deaths), Italy (∼160,000 patients and ∼20,000 deaths), France (∼137,000 patients and ∼15,000 deaths), Germany (∼130,000 patients and ∼3,000 deaths), United Kingdom (∼94,000 patients and ∼12,000 deaths) and Iran (∼75,000 patients and ∼4,700 deaths) by April 14th, 2020. Several effective measures including restricting travel from China, controlling the distribution of masks, extensive research of COVID-19 spread, and government efforts to inform and educate the public were aggressively conducted in Taiwan.[2] This is probably the reason why there were only 39 cases (until February 29th, 2020) with a daily cumulative index of one case per day in Taiwan, which was much lower than that of nearby countries, such as Republic of Korea and Japan.[2]

In Brazil, the number of COVID-19 cases is increasing daily and by April 14th, 2020, 23,955 positive cases have emerged. The number of deaths has also increased to 1,361 COVID-19 patients in the country so far. Deaths are mainly located in São Paulo, which is the most populated state in Brazil.

China has managed to greatly reduce the SARS-CoV-2 virus transmission mostly with three effective measures (WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)[3]: (a) protect health professionals with personal protective equipment; (b) identify quickly symptomatic patients by real-time polymerase chain reaction (RT-PCR) test and isolate them; (c) identify the patients' close contacts and quarantine them. Italy has different demographics and social behavior than China and other countries like Germany that coped with the higher ratio of infection and it exceeded the capacity of the health system. Italy showed a lower testing capacity than China and other countries such as Germany during the first weeks of COVID-19 pandemic, but the capacity to perform RT-PCR has improved, giving better epidemiologic data of less severe cases and asymptomatic individuals carrying the SARS-CoV-2 virus in the population. However, as a final scenario, USA has shown the highest number of deaths related with COVID-19.

In Brazil, until April 14th, 2020, the mortality rate was 1,361/23,955 (5.68%). Italy was the first country to reach the mark of ten thousand COVID-19 related deaths as described by Boccia et al.,[4] which showed a 11.90% of mortality (13,155/110,574). As discussed by the authors, some conditions are closely related to the Italian situation such as the size of the aged population (23.1% of citizens from Italy versus 13.5% in Brazil), the presence of concomitant serious diseases such as chronic obstructive pulmonary disease, ischemic heart disease, smoking habit, number of intensive care units (ICUs) beds and sub intensive care beds along with the quality of the health service. In addition, characteristics of COVID-19 disease in Italy highlights the importance of increasing the number of diagnostic tests performed in the population, to encourage more healthy life styles of individuals who are subject to quarantine measures and ICU admittance, raising awareness about the seasonal flu that can maximize the number of patients visiting hospital and reaching the SARS-CoV-2 virus colonization acting as a vector, protecting medical personnel who could contribute to dissemination of the infection and avoiding simultaneous transmission which can cause momentary health system failure.[4]

The experience of dealing with COVID-19 in Brazil may give a new perspective since the country is dealing with many issues at the same time including social, political and genetics (admixed population with high variability at genome level) aspects, as follow:

(i) Brazil has many risk groups as described by World Health Organization (WHO) like those older than 60 years and with prognostic comorbidity, which may occur when diseases predispose the patient to develop severe COVID-19 symptomatology needing intensive care in ICUs. In addition, Brazilian population is comprised of ∼500,000 indigenous citizens with a genome composition and a different physiological response from other people and the indigenous genome and its response to SARS-CoV-2 virus infection is not well known. Moreover, the indige-

nous people like the rest of the population, has limited access to hospital for intubation when needed. Also, on April 2nd, the first case of COVID-19 was identified in the indigenous population. Now, Brazil has several indigenous cases with COVID-19 including three deaths: (a) 15-year-old Indigenous Yanomami boy from Roraima State without known previous diseases and/or comorbities; (b) 44-year-old Indigenous Kokama woman from Amazonas State with autoimmune hemolytic anemia; (c) 78-year-old Indigenous Tikuma man from Amazonas State with cardiac disease. The COVID-19 can be devastating for the indigenous population mainly because of their restrictions to access to medical care.

(ii) Brazil is a continental country with a population that is different in each region based on social behavior, genetics (each region has a different level of ancestral contribution of African, Caucasians and Indigenous genomes) and economic backgrounds raising the need for different medical and social managements in each area. All regions in Brazil have already seen COVID-19 cases and there is no medical support for all which takes into consideration particular state characteristics. In addition, Brazil does not have formal data on ICU beds and sub intensive care beds; besides that, the number of beds is distributed between private and public health systems. The number of patients needing the public health system is higher than for private health care. In the early stages of COVID-19 disease, before community infection, the number of hospitalizations in the private system was higher than in public health system conforming with the disease origin and type of infection and its placement. Between the Influenza virus subtype (H1N1) pandemic (2009) and COVID-19, Brazil lost ~34,500 hospital beds. In approximate the number of hospital beds in the country fell approximately from 460,920 to 426,380 in the interval between the two pandemics. The fall occurred in the Unified Health System (SUS), which lost 48,530 service spaces. In the same period, the private health service showed an increase of ~14,000 beds. However, Brazil gained 17,300 (from 42,400 to ~60,000–62,000 thousand) ICU beds in the same period. Brazil's ICUs are concentrated mainly in three states: São Paulo (~18,000 ICUs), Rio de Janeiro (~7,000 ICUs) and Minas Gerais (~6,000 ICUs). Moreover, most of the ICUs are located in the capital cities and in cases of adult ICU, and there is an occupancy rate of beds of ~90%. The WHO recommends 1–3 ICUs beds for every 10,000 inhabitants and Brazil has approximately 1 bed for every 10,000 inhabitants, but the number of ICUs beds is not equally distributed within different regions of Brazil, even including adjustment by the number of inhabitants in each state. In addition, the quantity of equipment such as respirators is scarce, there are, according to the government, ~65,000 respirators available in the country and, interestingly, in the H1N1 pandemic there were just over 35,000. To be noted, the Brazilian Federal Government and the Brazilian Health Ministry recommended the use of Hydroxychloroquine and Chloroquine in cases of COVID-19 after medical indication – the drugs can be used after case by case evaluation, even without scientific proof.

(iii) The studies about COVID-19 and its behavior in a tropical climate are scarce until now and Brazil has this climate with huge amplitude of temperature, air pollution, relative high humidity and environmental factors, which is mainly vegetation cover from north to south, east to west. Maybe, like other tropical countries, Brazil may have a different severity and/or disease progression considering the climate markers as discussed before. In addition, in our country, there is high amplitude of lethality among states varying from zero at Tocantins to 16% at Piauí. Also, São Paulo State represents the State with highest number of cases and a lethality of 6.8%. The lethality index will change after concluding the diagnosis by RT-PCR in mild, severe cases and deaths related with respiratory symptoms close to COVID-19. However, Brazil is testing only severe cases and the total number of patients is underestimated.

(iv) Brazil is formally an admixed population including African, Caucasians and Indigenous features. There is also a variability in the contribution of each offspring by region from the Brazil collaborating with genetic diversity that leads to a wide phenotypic expression. In those cases, the phenotype response to COVID-19 can diverge among regions and, concomitantly, genetics features behind each subpopulation from Brazil.

(v) There is a social and economic disparity among regions corroborating several issues related with COVID-19 pandemic such as availability of diagnostic tests, number of ICUs, access and understanding of information about the disease, and the decisions to control the pandemic.

(vi) Brazil presents great urban low-income conglomerates known as ''favelas'' where many people live in precarious condition with no access to health, social and financial support. Favelas comprise ~3.7% (Federal District) to 53.9% (Belem, capital of Pará) of people in some capitals. In addition, in São Paulo there are ~2 millions of people living in Favelas where the infection can be transmitted and without diagnostic confirmation before or after death. Also, it is estimated that ¼ of Brazilian population in São Paulo state has a poor adhesion to quarantine.

(vii) In Brazil, scientific research has been suffering from reduction in the financial support to research and scholarships. In addition, the Universities, mainly federal and public, experienced a setback in recent years. This whole process confounds the difficulties of dealing with the COVID-19 pandemic because Brazil has many University Hospitals which have financial limitations in terms of performing COVID-19 diagnosis and resources to deal with the disease. Some agencies are now making an effort to investigate COVID-19, but we will have a limited amount of funding for studies in other areas.

(viii) During recent years, the level of education of the Brazilian population has hugely improved; however, the quality is not totally proven. The academic levels corroborate the low understanding about the COVID-19 pandemic and the importance of social changes such as self-isolation at home.

(ix) Throughout the whole country there has only been genetic diagnosis in cases of severe COVID-19, leading therefore, to a very high number of undiagnosed patients. The undiagnosed patients relate to a higher

index of infection and dissemination within the population which negatively affects disease control, postpones quarantine, and has further negative effects on the economy. The use of RT-PCR to confirm the disease may be the best choice for isolating confirmed patients and giving time to treat severe patients at UTIs. In this context, the main issue in treating COVID-19 is when to start the treatment and to isolate the patients with positive RT-PCR even in the absence of clinical symptoms such as fever and cough. The country is not able to treat all patients correctly at the same time and due to that, Brazil is going through the first stages of the infection. Health professionals are worried about the next steps since the country is recording higher numbers of cases every day. Also, during the month of March, April and May, emerging new cases of bronchiolitis at pediatric age which need treatment, interventions and hospitalizations; in addition, the H1N1 and Dengue, both are a continuous health problem.

(x) In Brazil, as widely publicized in the media and declared in official interviews, the Brazilian Federal Government declared the need for a vertical quarantine model to mitigate the economic impact, highlighting an underestimation of the COVID-19 pandemic. There were some official declarations after a presidential visit to the American President Donald Trump accompanied by 20 individuals from Brazilian delegation, who were later diagnosed positive to COVID-19. At that time, some public demonstrations took place in favor of the Federal Government behavior. Despite that opportunity, members of the government did not agree with quarantine and greeted voters in front of the Republican Palace.

On March 29th, 2020, members of the government visited public places mitigating the measures stipulated by the Ministry of Health. Also, the Government included as a campaign measure the hashtag #OBrasilNãoPodeParar (#BrazilCannotStop). The campaign was removed from official media and the Government denied the disclosure of the advertisement.

The discordance between the members of government's speeches including the follow main issues: the efficacy of Hydroxychloroquine and Chloroquine and its use to treat COVID-19, the need to quarantine all citizens instead of restrictions for risk groups only, the severity of the COVID-19 disease and its capacity for dispersion among people, the beliefs about the exclusively affecting patients above 60 years old or with a comorbidity, quarantine as a measure to postpone the number of infected patients vs. avoiding the infection.

The Brazilian Health Ministry and the media are providing enough data, information and education for the public about the pandemic. Moreover, the population has a low adhesion to quarantine and Ministry Health recommendations. This may contribute to higher infection rates, high demand for ICUs and general collapse in health with many deaths that could be avoided. Brazilian population should have learned from Italy and other countries with high number of cases and lethality[5]; however, Brazil is heading toward an uncertain future.

As described by Boccia et al.,[4] Brazil should at least follow the lessons from Italy: ''(1) avoid admitting patients with suspected SARS-CoV-2 infection to the hospital, except when they clearly require hospital care; (2) maintain strict hygienic procedures in the hospital environment; and (3) act swiftly in case of exposure of medical personnel to avoid the loss of personnel capacity.'' Until now, Brazil is learning to follow the lessons. In addition, as discussed by Froes, we need to update our action plans and to learn from our mistakes during the pandemic.[6] Now, we are suffering the effects of the COVID-19 disease – the third global outbreak of coronavirus disease in the 21st century – and we cannot overestimate the potential of infectious diseases to change our habits as human living as civilization, but we can optimize the diagnosis time and efficacy, to achieve better adherence to infection control measures, to improve therapeutic and preventive options and to reduce the exposure to infectious agents such as SARS-CoV-2 virus.[6]

In conclusion, the SARS-Cov-2 virus cannot be allowed to insert itself among us and be just another agent responsible for the flu, because it has very high rates of transmission and its case-fatality is not low.[7] Further studies and continued monitoring are needed to better understand the underlying mechanism of COVID-19. In part, the Brazilian society is going along with the quarantine, but there is pressure from the Federal Government to return everyone who has been in vertical isolation. In addition, COVID-19 pandemic highlights the importance of Science, education and support for scientific advance. Science is the key to solving many problems; however, that key should be professionally used by society and government in order to resolve difficult and challenging situations.

Authors' contributions

All authors have approved the manuscript and agreed with its submission to the journal. Also, FALM and MMO wrote and revised the manuscript.

Conflict of interest

None declared.

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Sleep labs, lung function tests and COVID-19 pandemic – Only emergencies allowed!

Respiratory tract infections remain the top cause of morbidity and mortality worldwide from infectious diseases.[1] In January 2020, a novel coronavirus was identified, from the respiratory tract secretions of patients in China,[2–4] due to whole-genome sequencing. The disease was named COVID-19 (Corona-VIrus DIsease-2019) by the World Health Organization (WHO).[4] Afterwards, different investigation and research was undertaken and evidence was provided on human-to-human transmission in community, household and hospital settings.[5,6] Guidelines and recommendations were developed worldwide about prevention, diagnosis, control and management of COVID-19.

Public health measures targeting community infection control remain of primary importance and are still the only ones capable of buying time, flattening the infection incidence curve and causing a dramatic change in the course of the outbreak. Mankind has to make sustained and responsible changes in behaviour.[7] There still remain many unanswered questions concerning infection control measures inside the hospitals and clinics. In epidemic or pandemic situations like the one we are living through, sleep labs can configure increased risk of infection for patients and health care professionals and to the best of our knowledge, guidelines in this field are lacking.

Furthermore, patients under nocturnal ventilatory support including non invasive ventilation (NIV) combine an intrinsic high risk for respiratory infections and related complications and a very high potential risk of infection for care givers because of the high burden of droplets created by the ventilators (8). In fact, NIV using a vented mask in patients with acute respiratory failure can disseminate large droplets up to a distance of 1 m.[8]

Polysomnography level I (PSG I), the gold standard for sleep disorders breathing (SDB) diagnosis, takes place in sleep labs worldwide, using specific beds and under direct supervision of a sleep technician. Also PSG level II (domiciliary unsupervised) and PSG level III (domiciliary cardio respiratory study) are commonly performed. All these diagnostic approaches carry infection risks and in a pandemic situation, especially in the mitigation or suppression phases/strategies, sleep labs should no longer be working on diagnosis.

The belts used to fix the equipment to patients pyjamas or to patients' underwear are made of textile fibres which disable its disinfection. Also the manufacturers of the polysomnographers do not recommend them to be sanitized due to possible damage. So, this equipment is not safe to use in hospital or in patients' homes. Testing to clarify what kind of disinfection this equipment does resist without losing capability, and most of all, development of equipment that can be effectively disinfected in cases of respiratory infection due to highly contagious microorganisms are urgently needed.

At this point in this pandemic, sleep labs should avoid performing polysomnographies unless for hospitalized, acutely ill patients with a high probability of sleep disordered breathing that will impact negatively on the underlying disease(s). The equipment used in infected patients should undergo a quarantine period according to the material used by its manufacturer.

The working team of a sleep lab consisting of physicians, sleep technicians and respiratory physiotherapists or respiratory nurses should receive training in updated clinical knowledge of the COVID-19 pandemic, prevention tools and guidelines from the government, scientific societies and national authorities. Updates on this information should be provided as needed. Measures of prevention, protection and screening have been shown to be efficient in other settings.[9]

The healthcare team should respect some recommendations:

- check body temperature on arrival and departure to/from the sleep lab
- inform team leader if patient is presenting with *de novo* respiratory symptoms or in contact with a case
- use personal protective equipment (facial mask and gloves)
- use full personal protective equipment when dealing with confirmed cases of infection (protective gown, gloves, facial mask, goggles and cover boots)
- perform hand hygiene on arrival and departure from sleep lab and whenever needed

Medical doctors working in sleep labs have another great task and responsibility on their hands, that is the follow up of long term ventilated patients due to SDB and due to overlap of SDB and respiratory/pulmonary diseases. Keeping them free from respiratory exacerbations and away from health care resources must be a main objective.

Consequently, for those patients already diagnosed with SDB and under ventilatory support some approaches have to be initiated. Telemedicine is an interesting tool for following up patients who live far away from the health care structures, moreover these programmes can be of great value in public health emergencies, climate disasters and pandemic scenarios.[10] No telemedicine programme can be created overnight, but in patients who are chronically ventilated the medical community already have the technology allowing telehealth. Recent developments in modem-equipped ventilators software allow patients to be closely monitored,[11] providing data on compliance, leaks as well as residual apnea-hypopnea index. Also remote adjustment of ventilator parameters,[12] according to patient need and comfort, is possible, allowing prompt interventions, avoiding ineffective therapies and lack of adherence.[11,12] Furthermore, there are specific telemedicine applications designed for respiratory diseases,[13] offering a variety of possible evaluable parameters.

Patients under NIV infected by SARS-CoV-2 should be changed to non-vented masks, provided with filter in the circuit, and then the mask and humidifiers should be quickly retrieved, either if managed at home or in hospital. Also, after recovery, the ventilator equipment should go for a quarantine period of not less than 30 days as the virus can be viable for a long period in plastic.

There remain many uncertainties about the possibility of virus transmission when testing pulmonary function and the data are in evolution. Because of the potential for coughing and droplet formation, these procedures should be limited to spirometry, oximetry and arterial blood gases only if essential for immediate treatment decisions (for example in urgent preoperatory circumstances). Measures to protect both the staff and the patients should be put in place.[14,15] Personal protective equipment (long sleeved impermeable gowns, gloves, cover boots, mask, goggles and cap) that limits droplets acquisition should be used and the testing space has to be sanitized, including wiping down surfaces with appropriate cleaning materials.[14,15]

COVID-19 is a disease caused by a novel virus from the *coronaviridae* family, and at present it is a major global human threat which has become a pandemic. In these situations doctors should avoid unnecessary procedures that put patients and health care professionals at risk of infection and it is important especially that they adapt their clinical routine to be safe and efficient and postpone every non emergency diagnostic or therapeutic procedure.

Conflicts of interest

The author has no conflicts of interest to declare.

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Covid-19: Round and oval areas of ground-glass opacity

The World Health Organization has classified the COVID-19 situation as a pandemic. Patients infected with COVID-19 typically present with fever, cough, dyspnea, and myalgia, and the infection may cause severe pneumonia. Laboratory findings are unspecific. Although test results are normal for many patients, the predominant laboratory abnormalities include the elevation of inflammatory markers, such as C-reactive protein, lactate dehydrogenase, and the erythrocyte sedimentation rate. Additionally, lymphopenia is consistently present in more than 40% of patients.[1–3] Currently, real-time reverse-transcription polymerase chain reaction is the reference standard test for the definitive diagnosis of COVID-19 infection.

A 44-year-old man presented to the hospital (Centro Hospitalar do Porto, Porto, Portugal) on 7 March 2020 with a 6-day history of fever, cough, rhinorrhea, diffuse myalgia and fatigue. He had had close contact with a friend who had traveled to Milan, Italy, on 22–23 February 2020, during the COVID-19 pneumonia outbreak. On admission, the patient was in good general condition; he was tachypneic (respiratory rate of 30 breaths/min), his body temperature was 38.2 °C, and cardiac auscultation was normal, with no murmur or arrhythmia. Pulmonary auscultation demonstrated the presence of sparse bilateral crackles. Laboratory tests showed a normal blood cell count, erythrocyte sedimentation rate of 84 mm/h (normal = 0–10 mm/h), C-reactive protein level of14 mg/L (normal = 0.3–10 mg/L), and unremarkable lactate dehydrogenase, creatine phosphokinase, and liver function findings. Blood gas analysis yielded normal findings (O_2 saturation = 98%). The patient's respiratory rate returned to normal after the normalization of his temperature. Non-enhanced chest computed tomography (CT) showed multiple round and oval ground-glass opacities in both lungs, with a crazy-paving pattern (Fig. 1B–D). No mediastinal lymphadenopathy or pleural effusion was present. Real-time reverse-transcription polymerase chain reaction of a nasopharyngeal sample revealed positivity for 2019-nCov nucleic acid. Hydroxychloroquine and symptomatic medication were administered. The patient recovered uneventfully and was discharged after 16 days in an asymptomatic state.

Although our patient had pneumonia, as confirmed by CT, the chest radiograph was normal. Chest radiography has not been recommended as a first-line imaging modality for the diagnosis of COVID-19 due to its limited sensitivity in the detection of ground-glass opacities and other incipient pulmonary findings of the infection, which are evident on CT. However, nonspecific chest radiography findings have been reported occasionally, particularly for patients with severe disease.[4,5] The role of CT in COVID-19 evaluation is the subject of much discussion. Some authors suggest that CT has a pivotal role, whereas other investigators are less optimistic. The predominant CT findings are multifocal, bilateral, peripheral, and basal-predominant ground-glass opacities, often with round and/or oval morphology and/or consolidation. The crazy-paving pattern may be observed.

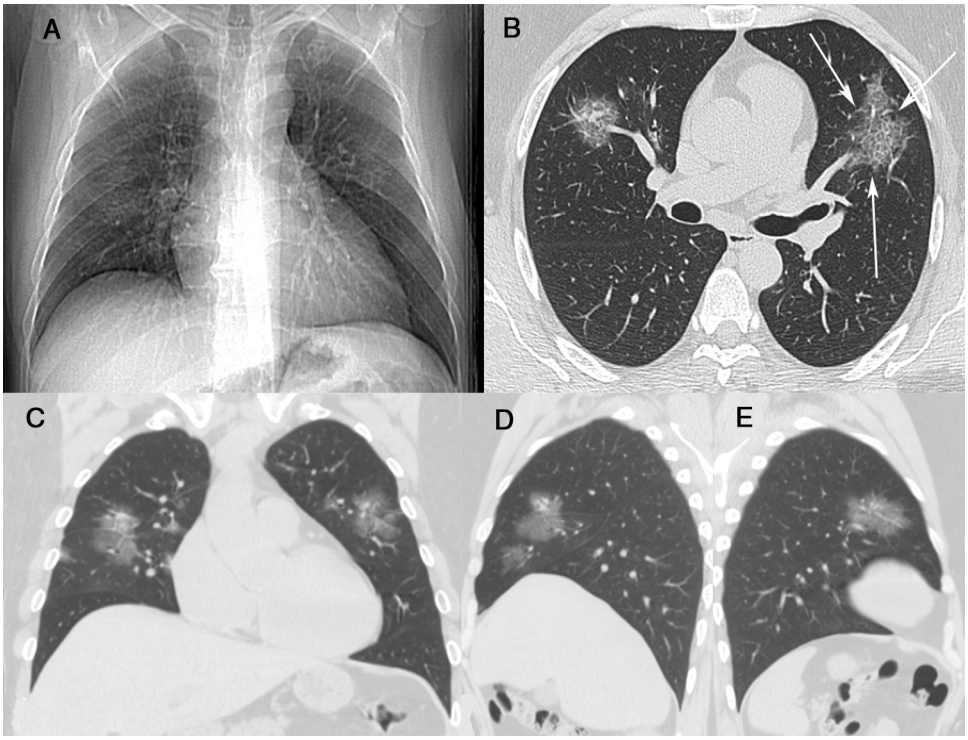

Figure 1 (A) A posteroanterior chest radiograph was considered normal. Unenhanced chest computed tomography with axial (B), coronal (C) and sagittal (D and E) maximum-intensity projection imaging demonstrated areas of ground glass opacity, many with round and oval morphologies, in both lungs. Not also in B inter- and intralobular septal thickening with a crazy-paving pattern (arrows).

This pattern is defined as thickened interlobular septa and intralobular lines superimposed on a background of ground-glass opacities. Pleural effusion, small lung nodules, cavitation, and lymphadenopathy are very uncommon findings.[2,5,6] These CT findings are not specific to COVID-19; similar results can be obtained for other infectious and non-infectious diseases.[6]

However, two characteristics of the ground-glass opacities may suggest the diagnosis of COVID-19 in the context of the current pandemic. The presence of multifocal nodular (round or oval) ground-glass opacities[7,8] and/or the association of these opacities with reticulation (the crazy-paving pattern)[8–10] should alert the radiologist to the possibility of COVID-19 infection. The latter finding appears particularly when the disease progresses. Our patient presented both findings. We believe that these two findings are important for the diagnosis of COVID-19, although the crazy-paving pattern is less specific; Amorim et al.[11] observed it in 15% of 70 patients with confirmed H1N1 infection.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Severe rifampicin-induced thrombocytopenia in a patient with miliary tuberculosis

Tuberculosis is a potentially treatable infectious disease caused by *Mycobacterium tuberculosis* Complex. Pulmonary presentation is the most frequent, with non-pulmonary forms being more commonly observed in children and immunocompromised patients. Tuberculosis remains a major public health problem in Portugal, although its incidence has been decreasing (15,6 cases/100,000 inhabitants, according to the Portuguese National Statistical Institute, 2017). Newly diagnosed tuberculosis patients are empirically treated with a combination of four drugs: isoniazid, rifampicin, pyrazinamide and ethambutol.[1] No antituberculous drug is free of risk, and the World Health Organization (WHO) recommends monitoring and reporting suspected or confirmed adverse drug reactions (ADR) caused by antituberculous drugs.[2] Most ADR are benign, result from inherent toxicity to the drug and can be minimized by dosage adjustment, exposure duration reduction or by vitamin supplementation.[3] Less frequently, ADRs are immune-mediated and can present as cutaneous, hematological or systemic manifestations. These are rarer and more unpredictable, imposing both diagnostic and therapeutic challenges.[4] Rifampicin, one of the most important antituberculous agents, is a well-tolerated and effective drug. Most frequent adverse reactions to rifampicin (Table 1) include gastrointestinal effects, cutaneous reac-

Table 1 Frequency of the adverse events to rifampicin (Adapted).[7]

System organ class	Frequency	Adverse events
Infections	Unknown	Pseudomembranous colitis; Influenza
Blood system disorders	≥1% and <10%	Thrombocytopenia
	≥0,1% and <1%	Leukopenia
	Unknown	Disseminated intravascular coagulation; Eosinophilia; Agranulocytosis; Hemolytic anemia
Immune system disorders	Unknown	Anaphylactic reaction
Nervous system disorders	≥1% and <10%	Headache; Dizziness
Eye disorders	Unknown	Tear discoloration
Vascular disorders	Unknown	Shock; Flushing; Vasculitis; Bleeding
Respiratory disorders	Unknown	Dyspnea; Wheezing; Sputum discolored
Gastrointestinal disorders	≥1% and <10%	Nausea, vomiting
	≥0,1% and <1%	Diarrhea
Hepatobiliary disorders	Unknown	Hepatitis; Hyperbilirubinemia
Skin and subcutaneous tissue disorders	Unknown	Erythema multiforme; Stevens-Johnson syndrome; Toxic epidermal necrolysis; Drug reaction with eosinophilia and systemic symptoms; Pruritus
Musculoskeletal disorders	Unknown	Myopathy; Bone pain
Renal and urinary disorders	Unknown	Acute kidney injury

tions, hepatotoxicity and flu-like syndrome. Immunological reactions, such as hemolytic anemia, agranulocytosis and thrombocytopenia, are less frequent.[3] Immune-mediated thrombocytopenia induced by rifampicin, first described in 1970, is a potentially fatal ADR. It is characterized by rapid platelet destruction following drug administration in susceptible individuals and occurs more frequently in situations of intermittent administration or reintroduction after a period of discontinuation.[5]

The authors report a clinical case of a 60-year-old male patient with ulcerative colitis who maintained active disease, even after corticosteroid and azathioprine therapy. Biological therapy with an anti-TNF-α was started, after exclusion of latent tuberculosis. Approximately 4 months later he presented anorexia, night sweats and weight loss. Laboratory results showed hemoglobin 10,4 g/dL, lymphocytes 300/μL, sodium 132 mEq/L, lactate dehydrogenase 426 U/L, C-reactive protein 153 mg/L, negative IGRA test and HIV serology. CT-scan showed scattered micronodules in the pulmonary parenchyma, a necrotic mediastinal adenopathic conglomerate, a necrotic hilar adenopathy and homogenous hepatosplenomegaly. As the patient presented no cough, a bronchoalveolar lavage was collected, which was positive for acid-fast bacilli. The nucleic acid amplification test detected the presence of *Mycobacterium tuberculosis* Complex and a definitive diagnosis of miliary tuberculosis was established. First-line antituberculous drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) were initiated, with good tolerance. On the 15th day of therapy, laboratorial findings showed increased transaminases (AST 329 U/L, ALT 270 U/L) and hyperbilirubinemia (total bilirubin 2,15 mg/dL), which determined the temporary suspension of the antituberculous agents. After normalization, antituberculous drugs were sequentially reintroduced according to the following scheme: amikacin, levofloxacin and pyrazinamide; subsequently introduced ethambutol, with suspension of amikacin; subsequently added rifampicin. About 6 days after rifampicin reintroduction, an abrupt drop of platelet count from $241 \times 10^3/\mu$L to $2 \times 10^3/\mu$L occurred, with associated epistaxis. The antiplatelet antibody test was negative and other possible causes of thrombocytopenia were excluded. Severe thrombocytopenia induced by rifampicin was assumed and the drug was discontinued. After platelet transfusion and methylprednisolone pulses, the platelet count returned to normal values. The patient was discharged to the Center for Pneumological Diagnosis, medicated with levofloxacin, ethambutol, pyrazinamide and isoniazid. After that, *Mycobacterium tuberculosis* Complex isolated from the sputum cultural exam showed resistance to isoniazid and pyrazinamide, and the therapeutic regimen was changed to levofloxacin, ethambutol, cycloserine and clofazimine, for 12 months.

Immunocompromised patients and intermittent treatment, as was the case of this patient, are predisposing factors for hypersensitivity reactions to antituberculous agents.[4] The mechanisms responsible for it are not yet fully identified, but it is known that they are based on an immunological mechanism: rifampicin is thought to bind non-covalently to the platelet membrane glycoproteins, causing conformational changes in the glycoprotein Ib/IX complex, and increasing the affinity of pre-existing natural antibodies (present in low concentrations and with low affinity in the absence of this drug), with consequent platelet destruction.[6] The mechanism of hypersensitivity is type II (cytotoxic hypersensitivity, antibody-dependent) according to the classification of Gell and Coombs.[4] There is no definitive diagnostic method to confirm the responsibility of rifampicin in this type of hypersensitivity. In the absence of laboratory confirmation, the diagnosis can be corroborated by the normalization of the platelet count after suspension of the drug in question. Although it is a diagnosis of exclusion, a high degree of suspicion is necessary for a rapid diagnosis.

This case is highlighted by its rarity and severity, with the occurrence of multiple adverse reactions to the antituberculous drugs in an immunocompromised patient with miliary tuberculosis. The WHO recently published the initial results of a pilot study about the surveillance of antituberculous agents' adverse events, named aDSM (active tuberculosis Drug Safety Monitoring and management), which demonstrates monitoring is feasible.[2] The authors also wish to emphasize that, although uncommon, the occurrence of rifampicin-induced thrombocytopenia is a potentially serious and fatal ADR, which imposes its suspension and contraindicates its reintroduction.

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Ethical disclosures

Protection of human and animal subjects: The authors declare that no experiments were performed on humans or animals for this study.
Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received enough information and gave their written informed consent to participate in the study.
Right to privacy and informed consent: The authors declare that no patient data appear in this article.

Conflict of interest

None.

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The effect of alcohol consumption in the treatment of nontuberculous mycobacteria

To the editor:

Nontuberculous mycobacteria (NTM) are considered opportunistic pathogens. They are widely distributed in the environment, and several species are associated with a wide range of infections, most commonly affecting the lung.[1–3] The increasing number of immunocompromised patients and predisposing diseases – such as chronic obstructive pulmonary disease (COPD), silicosis and bronchiectasis—as well as the increasing life expectancy of patients with cystic fibrosis, are factors contributing to a rising incidence of NTM disease.[2–4] However, patients can develop NTM disease without any apparent underlying cause. This suggests that NTM disease is a multifaceted disease, and the genetic background or environmental exposures could, also, increase susceptibility to infection.[1–3] Population-based studies across Europe report a steady increase in NTM isolation and related lung disease over time. In Portugal, epidemiological studies are scarce but are in line with

Table 1 Baseline characteristics of the study population - data are presented as n (%) or median (min-max); HIV: human immunodeficiency virus; COPD: chronic obstructive pulmonary disease.

Baseline characteristics	Total
Male	369 (60.5)
Age (years)	58 (19-97)
Alcohol consumption	65 (11.5)
Underlying diseases	
HIV infection	133 (21.8)
COPD	63 (10.3)
Diabetes mellitus	27 (4.4)
Lung cancer	10 (1.6)
Other neoplasms	19 (3.1)
Drug abuse	51 (8.9)
Imprisonment/Homelessness/Community shelter	21 (3.6)
NTM lung disease	540 (89)
Sputum	355 (64.8)
Bronchoalveolar lavage	157 (28.6)
Pleural fluid	9 (1.6)
Lung biopsy	1 (0.2)
Missing data	18
NTM extra-pulmonary disease	70 (11.5)
Blood culture	13 (2.4)
Urine	5 (0.9)
Lymph node aspirate	5 (0.9)
Missing data	47
Species of nontuberculous mycobacteria	
Mycobacterium avium/intracellulare	340 (55.7%)
M. kansasii	78 (12.8%)
M. gordonae	39 (6.4%)
M. xenopi	34 (5.6%)
M. chelonae	23 (3.8%)
M. fortuitum	23 (3.8%)
M. abscessus	10 (1.6%)
Other	63 (10.3%)

these reports. Two studies, conducted in Lisbon Area, found NTM to account for approximately 12% of all mycobacterial isolates,[5,6] and hospital-based research[7] showed a definite rise in the number of NTM isolates each year of the study, and 89% of those were found to be clinically significant, fulfilling the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) criteria.[2]

NTM disease is complex to manage and a significant cause of morbidity and mortality.[4] Treatment is long and requires multiple drugs, which can be challenging due to side effects and different resistance profiles.[2] Therefore, the treatment success rate remains unsatisfactory.[4] Host factors and comorbidities can influence the outcome, and this is rarely covered by studies reported to date or in the current guidelines.

The present study aimed to identify the effect of alcohol consumption on the treatment outcome of NTM disease.

This study collected information from the structured questionnaire filled in by clinicians who initiate treatment for NTM disease and which is stored in the Portuguese National Epidemiological Surveillance Commission for Tuberculosis. We retrospectively reviewed the data from patients with NTM disease from January 2003 to December 2016. All patients met the diagnostic criteria for NTM disease from the ATS/IDSA guidelines. Clinical and socio-demographic data were collected. Alcohol consumption was self-reported in the questionnaire at time of diagnosis and was defined as the presence or absence of consumption. Excluded from the main outcome analysis were patients still in treatment, those who had discontinued the therapy, those lost to follow-up or transferred out.

Treatment outcome of NTM disease was binarily evaluated as a good or bad outcome. Good outcome was defined as culture conversion after initiation of treatment and maintenance of a negative culture for $\geqslant$12 months on treatment. Bad outcome was defined as no culture conversion or as death while being treated for NTM disease. Simple logistic regression models evaluated univariate effects, and multiple logistic regression models identified the simultaneous effects of potential risk factors for a bad outcome. Selection of the final model was based on the backwards algorithm combined with the results from the univariate analysis. The statistical analysis was performed with the R language and software environment for statistical computation [The R Project for Statistical Computing, https://www.r-project.org/, version 3.4.3]. The significance level was set to $\leq$0.05.

During the study period, 610 patients were eligible. The median age was 58 years (min-max, 19–97 years), and 369 (60%) of the patients were male. The vast majority of patients had NTM lung disease (n = 540, 89%). Alcohol consumption was reported at diagnosis in 65 (11.5%) patients. Table 1 shows the population demographic and clinical characteristics.

A favourable outcome was achieved in 517 (84.8%) patients, and 93 (15.2%) had an unfavourable outcome. The median total antibiotic treatment duration was longer in patients with a good outcome than in those with a bad outcome (376 vs. 167 days; $p < 0.001$). The (crude) odds ratio (OR) for a bad outcome among the individuals who declared alcohol consumption was almost 3.5 times the same odds for those that declared they did not drink (95% CI:1.91–6.21, $p < 0.001$).

The final multiple logistic regression model revealed that alcohol consumption was associated with bad outcome (OR 2.01, 95% CI:1.05–3.87, $p < 0.001$). This effect was adjusted for history of COPD (OR 2.38, 95%CI: 1.22–4.63 $p = 0.011$) and other co-morbidities (OR 3.29, 95%CI: 1.26–8.61 $p = 0.015$), cancer (OR 4.47, 95%CI: 1.86–10.72, $p = 0.001$), having at least one previous treatment (OR 1.86, 95%CI: 1.01–3.43 $p = 0.023$) and HIV-infection (OR 2.09, 95%CI: 1.2–3.97 $p = 0.001$). Female gender was identified as a statistically significant protective factor (OR 0.45, 95%CI: 0.24–0.84 $p = 0.001$). Fig. 1 represents the Crude OR and Adjusted OR for a bad outcome of NTM disease.

Our results showed that alcohol consumption doubled the odds for a bad outcome, after adjustment for COPD and other comorbidities, cancer, at least one previous treatment, HIV-infection and gender. Among all these confounders, only the female gender was significantly identified as a protective factor.

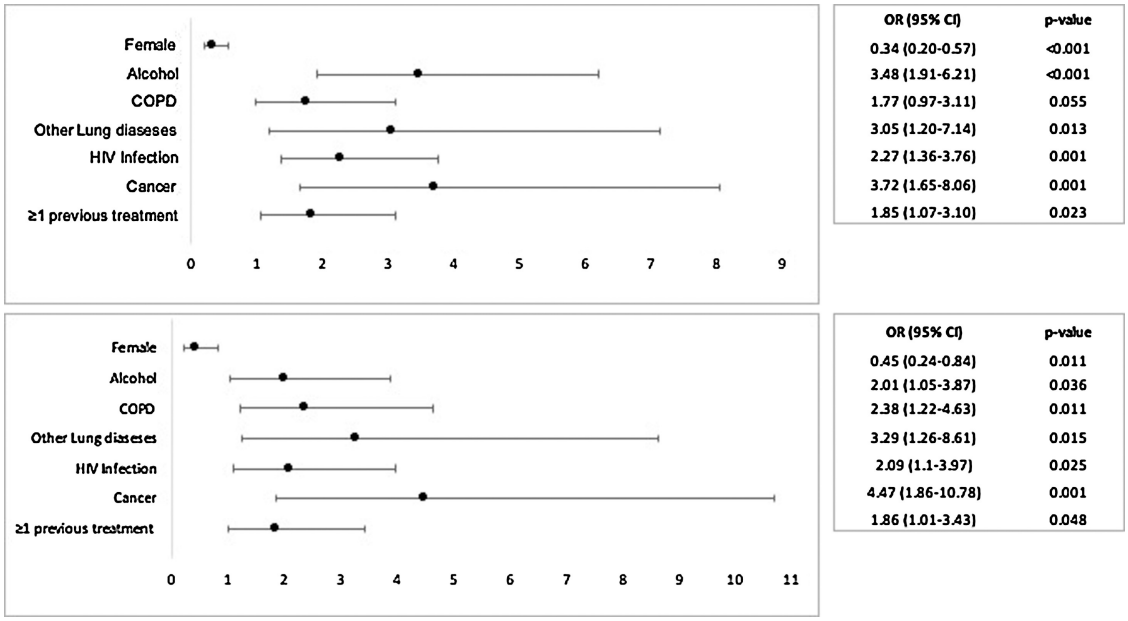

Fig. 1 Forest Plot representation of the crude odds ratios (above) and adjusted odds ratios (below) for a bad outcome of NTM disease.

The ATS/IDSA provides guidelines for the prevention, diagnosis and treatment of NTM infections.[2] In the case of NTM disease—in which immediate symptomatic benefits are not always obvious, and treatments can be long and toxic—compliance with therapy is often low. In every patient, the decision to treat NTM disease involves balancing the benefits and the risks of drug toxicity,[4] and it is essential to manage the patient's underlying diseases, such as alcohol dependence, COPD or cancer.

For this study, we relied on self-reported alcohol consumption at diagnosis, which might be the main limitation, as it may not reflect the drinking pattern over the time of the treatment. Other limitations include its retrospective nature, possible incomplete data from the nationwide forms and overestimation of unfavourable outcomes (older patients, more likely to be male, to have alcohol consumption or several comorbidities).

In conclusion, this study supports the hypothesis that alcoholism influences the prognosis of NTM disease. After adjustment for potential risk factors, alcohol consumption was estimated to double the odds of an unsuccessful outcome, underlining the need for close monitoring among patients with alcohol dependencies to improve treatment outcomes.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Immunotherapy rechallenge in patients with non-small-cell lung cancer

Immunotherapy is an effective treatment option for patients with non-small-cell lung cancer (NSCLC) with advanced disease. Several immune checkpoint inhibitors (ICI) have significantly improved survival of patients with NSCLC.[1] The safety profile of immunotherapy differs from the known safety profile of chemotherapy and includes immune-related adverse events (irAEs) such as fatigue, rash, pruritus, diarrhea and arthralgia, occurring in >20% of patients.[2] A recent meta-analysis reported all-grade immune-related lung toxicity (pneumonitis) in 4.1% of patients with NSCLC treated with ICIs, which was reported as grade $\geq$3 in 1.8% of patients.[3] In daily practice, it is important to know whether it is possible to rechallenge a patient with NSCLC with the same PD-1 inhibitor after resolution of an irAE to be able to continue providing clinical benefit.

Case presentation

We report the case of a 63-year-old female patient diagnosed in December 2014 with NSCLC (cT2N2M0), localized at the right upper lobe. She received neoadjuvant chemoradiotherapy with intravenous cisplatin 75 mg/m^2 plus vinorelbine 25 mg/m^2 on days 1 and 8 in 3-week cycles and 60 Gy (in 2 Gy per fraction) from January 2015 until April 2015. After completing 2 cycles she was not a candidate for surgery due to the persistence of N2 (evaluated by Endobronchial Ultrasonography [EBUS]), so she continued with 2 more cycles of chemoradiotherapy until May 2015. In January 2016, the patient showed disease progression in the lung (Fig. 1A), so she started a second-line of treatment with nivolumab (3 mg/kg intravenously every 14 days) attaining a partial response in March 2016 after 4 treatment cycles. In April 2016, the patient was admitted with grade 3 fever and increased dyspnea that occurred even on minimal exertion. These symptoms had been ongoing for 2 weeks before being admitted to the hospital. An X-ray was performed, showing bilateral dispersed alveolar opacities (Fig. 1B). The main differential diagnoses were infection, immune-related toxicity, radiation-induced pneumonitis, and disease progression. Thoracic computed tomography (CT) (Fig. 2A), bronchoscopy with bronchoalveolar lavage (BAL) and bronchoalveolar aspirate (BAS) were performed to ensure the correct diagnosis. Negative bacterial cultures ruled out the possibility of infection and cytology did not show malignant cells. Although late radiation pneumonitis was difficult to exclude, the time elapsed between the end of the radiotherapy treatment and the beginning of the symptoms suggested an immunerelated pneumonitis. Moreover, irradiated lungs are more susceptible to develop pneumonitis when treated with ICI. The patient was diagnosed with a grade 3 immune-related pneumonitis and the PD-1 inhibitor had to be permanently stopped, despite having attained a partial response. Pneumonitis was treated with high doses of corticosteroids (methylprednisolone 1 mg/kg/day) followed by tapering. Patient symptoms improved after 1 week of corticosteroid treatment, with complete clinical and radiological recovery after 11 weeks of treatment (Fig. 2B). On May 2017, during a follow-up visit, a thoracic CT scan showed disease progression. Considering the patient's previous response to immunotherapy, including 14 months of stable disease after stopping treatment, nivolumab rechallenge was proposed as a treatment option despite the toxicity reported. To avoid new irAEs, nivolumab (3 mg/kg intravenously every 14 days) was reinitiated along with low dose corticosteroids (methylprednisolone 8 mg/day). After four cycles, the patient achieved a partial response in the lung tumor with no further lung toxicity.

Discussion

Immunotherapy-related lung toxicity is rare but can be life-threatening.[2] The clinical presentation of pneumonitis usually consists of non-specific symptoms. However, it is essential to consider pneumonitis among the differential diagnoses in patients receiving treatment with PD-1 or PD-L1 inhibitors, before the respiratory function worsens.[3] To correctly diagnose pneumonitis, a bronchoscopy must be performed to rule out other etiologies, such as infection. The main treatment for the irAE of pneumonia is the administration of high doses of corticosteroids (1–1.5 mg/kg) with subsequent tapering when symptoms and radiological imaging show improvement.[4] Moreover, according to the evidence described in the literature,[4,5] permanent cessation of immunotherapy is the standard procedure in a patient experiencing a grade 3–4 irAE. However, clinicians should always consider the potential loss of clinical benefit for patients

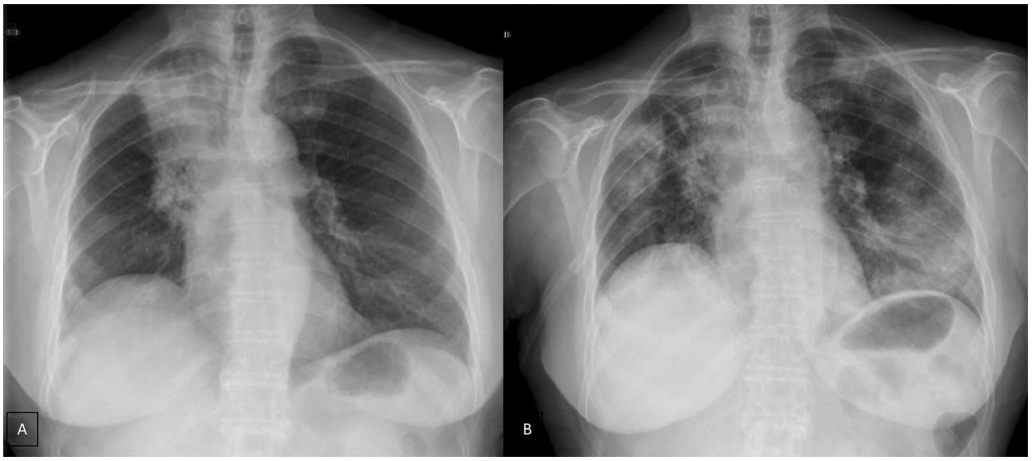

Figure 1 A. Postero anterior chest radiograph shows air space consolidation of rigth upper lobule with lung volume decrease (radiotherapy fibrosis). B. Postero anterior chest radiograph shows new heterogeneous bilateral air space opacities.

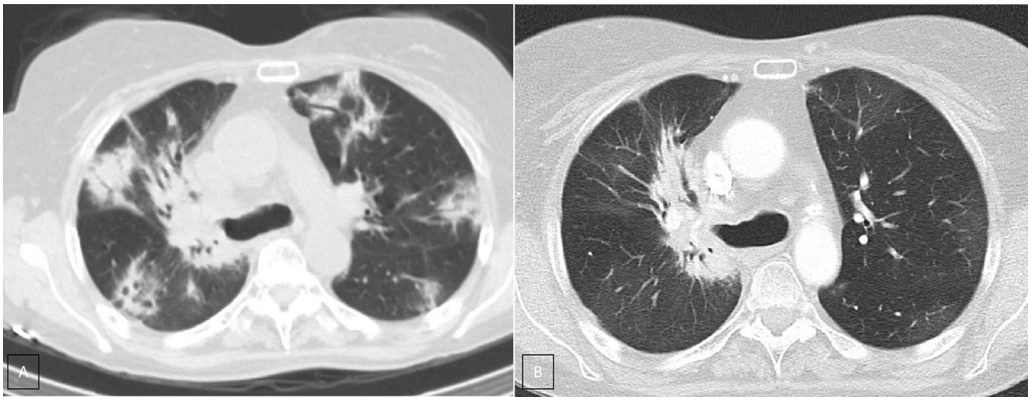

Figure 2 A. CT scan (lung window) shows multiple peripheral poorly defined areas of focal consolidation, very suggestive or organizing penumonia. B. CT scan (lung window), three month later shows resolution of peripheral areas of focal consolidation, but persistence of parahilar consolidation because of radiation fibrosis. Note the bronchiectasis and volume loss and the sharp demarcation between normal lung tissue and areas of fibrosis.

in these situations. Although the experience described in our patient reflects a single case, other case series have shown that rechallenging with a PD-1 inhibitor could be an option for patients with NSCLC, even after discontinuation due to toxicity.[6] Currently, a few trials, such as the REPLAY study (NCT03526887) carried out by the Spanish Lung Cancer Group, are evaluating pembrolizumab in NSCLC that had failed after obtaining benefit from a checkpoint inhibitor. Furthermore, other studies are assessing the risk of recall toxicities when restarting immunotherapy. A study of patients who have been diagnosed with immune-related pneumonitis showed that 25% of these patients experienced a recurrence when rechallenged with PD-1/PD-L1 inhibitor.[7] In summary, ICI rechallenge in patients with NSCLC who experienced a grade 3–4 irAE could be an option, although more evidence is needed.

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An uncommon cause of dyspnea in a 64-year-old woman

Dear editor,

Pulmonary hypoplasia is a rare congenital abnormality in which normal pulmonary tissues are present but underdeveloped.[1] It is usually diagnosed during childhood, and there are very few patients who survive beyond 18 years,[2] because they generally die due to intercurrent infections and other congenital abnormalities. Because of this, there are few patients who reach adult age.[3] A review of the literature shows that the first case of an adult patient was reported in the year 1964.[4]

We present a case of a 64-year-old woman, previously hypertensive, obese (BMI 35) and ex-smoker (30 pack-years). She had been reporting recurrent respiratory infections since childhood, which were treated with antibiotics by her family doctor. She was admitted to hospital with chronic non-productive cough and dyspnea of two years of evolution which increased until it became dyspnea on minimal exertion in the previous month. The clinical picture was not accompanied by chest pain, orthopnea, hemoptysis or weight loss.

In the physical examination, the patient's vital signs were normal, with an oxygen saturation of 89%. Cardiac auscultation revealed normal heart sounds. Pulmonary examination findings revealed decreased breath sounds in the right lung, without wheezing.

Laboratory tests did not show alterations with negative D-dimer. With regard to gasometry, the patient presented global respiratory failure (pH 7.44, pO_2 50 mmHg, pCO_2 52 mmHg, HCO_3 35.3 mmol/L).

The thoracic X-ray revealed volume loss in right hemithorax, atelectasis of right upper lobe and tracheal deviation to that side, without pleural effusion or other hyperdense areas (Fig. 1).

A computerized tomography (CT) was carried out to characterize the radiological findings described and to rule out a pulmonary neoplasm as a first possibility. This test revealed a lack of right pulmonary artery and right pulmonary veins, with hypoplasia of the right lung and displacement of mediastinal structures toward that side. Abundant collateral bronchial and intercostal circulation could be seen on the right side. The hypoplastic lung revealed arterial supply dependent on the abdominal aorta and venous drainage toward the inferior vena cava. On the other hand, there was compensatory hyperinflation of the left lung and hypertrophy of left pulmonary arteries (Fig. 2).

Afterwards, pulmonary function test results were obtained, which were compatible with very severe obstructive ventilatory defect, increased pulmonary resistance and air trapping. The bronchodilator test was negative.

In addition, the echocardiography suggested pulmonary arterial hypertension with mean pulmonary artery pressure of 60–65 mmHg without any other alteration.

The patient is currently receiving pulmonary rehabilitation and domiciliary oxygen. Due to persistent daytime hypoventilation ($pCO_2 \geq 45$ mmHg) caused by multifactorial origin, she is being treated with non-invasive mechanical ventilation, which has improved her basal status and gasometry.

Discussion

Sometimes, dyspnea may present as a diagnostic challenge. It is a very unspecific symptom which is present in many conditions, mainly cardiovascular and respiratory diseases.

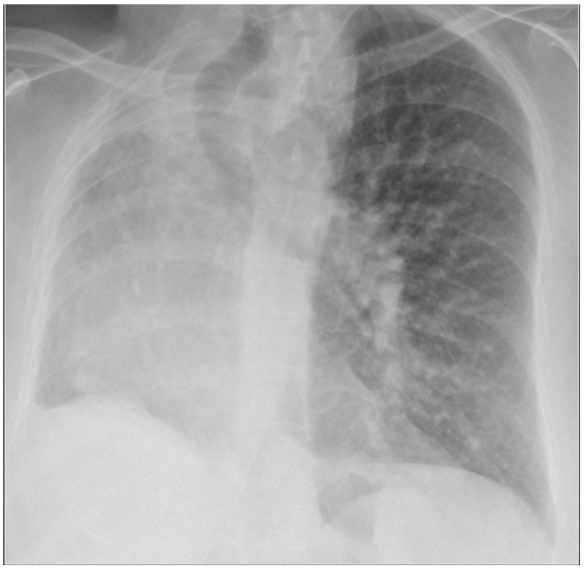

Figure 1 Thoracic X-ray: contracted hyperlucent hemithorax.

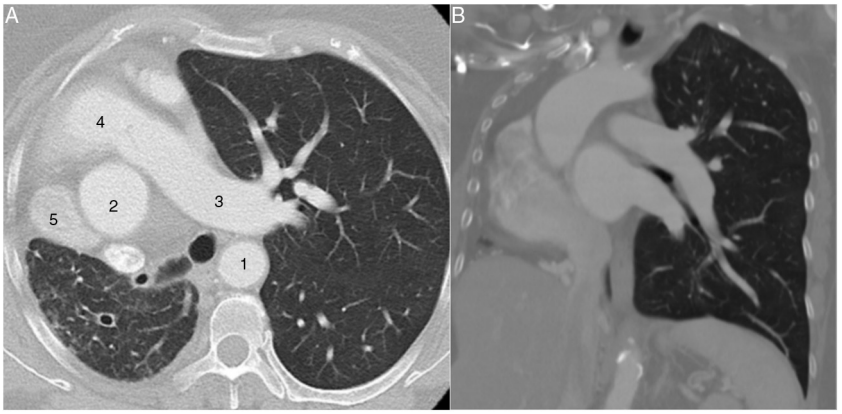

Figure 2 (A and B) CT scan. (1) Descendent aorta; (2) ascendent aorta; (3) left pulmonar artery; (4) pulmonary trunk; (5) superior vena cava.

Generally, the patient diagnosed with pulmonary hypoplasia is asymptomatic,[5,6] which means that most of the times the diagnosis is incidental, following a thoracic X-ray in the context of an acute process, as happened with the present patient.

The left lung is more commonly affected,[7] and in up to 50% of the cases there is an association with cardiovascular, gastrointestinal, genitourinary, neurological or musculoskeletal malformations.[8] In all cases, it is important to rule out any potential association with other diseases such as cystic fibrosis, immunological deficiencies or inborn errors of metabolism.[8] In our case, no other malformation or associated disease were found.

Currently, the diagnostic technique of choice is thoracic CT scan,[9] because it makes it possible to visualize the rudimentary lung as we described in the clinical picture.

A simple thorax X-ray generally shows opacity and a decrease in the intercostal spaces of the affected hemithorax, herniation of the healthy lung and a mediastinum displaced toward the affected hemithorax. It is not uncommon to find skeletal abnormalities such as kyphoscoliosis. The differential diagnosis must be carried out using entities that reduce the volume and increase the density of the hemithorax: atelectasis, mainly due to pulmonary neoplasm; post-pneumonectomy changes; fibrothorax; and tuberculosis.[10]

There are other tests that can assist in diagnosis, such as bronchoscopy, pulmonary angiography, bronchography, ventilation–perfusion scintigraphy and magnetic resonance.[8]

Pulmonary function tests generally show a restrictive ventilatory disorder. In some cases, such as the one in our study, they may also present an obstructive component caused by age, hyperinflation or the presence of recurring infections, stimulated by the production and retention of secretions in the rudimentary pulmonary tissue.[7]

Pulmonary artery agenesis and hypoplasia is a rare cause of pulmonary hypertension caused by the situation of hyperflow in the remaining pulmonary artery.[11]

The most favorable survival rates have been observed in cases of left lung hypoplasia because of the satisfactory compensatory hypertrophy of the larger right lung.[12,13]

The global treatment of pulmonary hyperplasia is medical care in most cases, with respiratory physiotherapy and intensive treatment of bronchopulmonary infections.[7]

To sum up, isolated pulmonary hypoplasia in adults is extraordinarily uncommon, as we highlighted in our case. That is the reason why this entity should be included in the differential of a chest radiograph with a contracted hyperlucent hemithorax.

Authors' contribution

Virginia Guevara drafted the manuscript, Soraya Jodra and Marco Lopez managed drafting, Miguel Ángel Hernández collected and retouched the pictures, José María González and Miguel Barrueco supported data collection and all authors revised the manuscript and approved its final version.

Conflicts of interest

All authors declare that there is no conflict of interest regarding the publication of this article.

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