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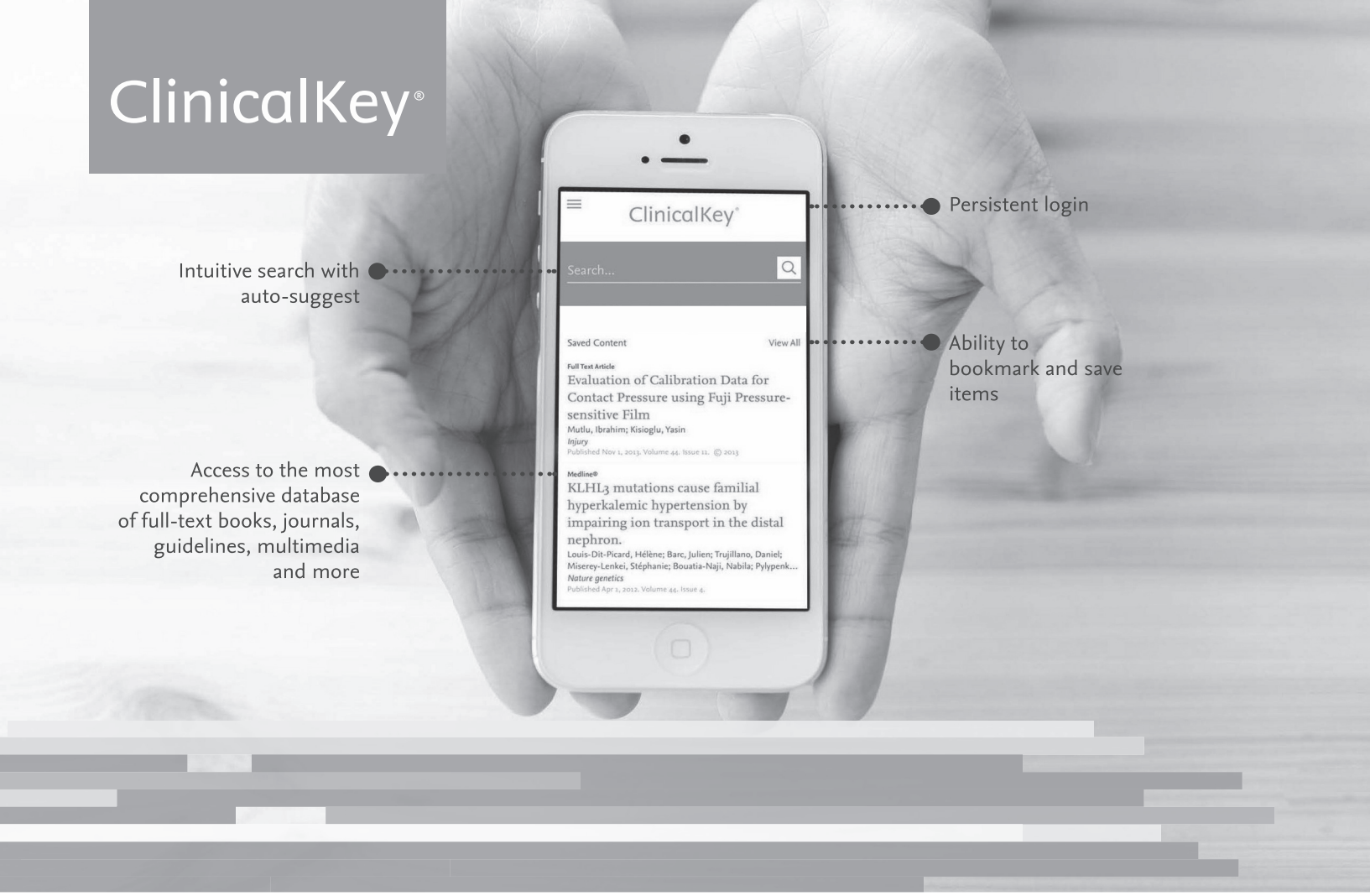

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COMMENT

High-flow oxygen therapy in palliative care: A reality in a near future?

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Commentary

Chronic respiratory diseases are prevalent among hundreds of millions of people in the world[1] and their prevalence in Portugal is increasing, with asthma and Chronic Obstructive Pulmonary Disease (COPD) being the most prevalent.[2] Indeed, according to the World Health Organization COPD is already considered the third leading cause of death worldwide.[3]

In the course of time chronic respiratory diseases lead to severe symptomatic burden for patients which reflects on their family members and society and with high health costs associated.[2] This highlights the importance of providing palliative care (PC) with a holistic approach, focusing on the quality of life of patients and their families, preventing and relieving suffering in respiratory patients as presented by Martins et al.[4]

Its recognised that PC in the last 4 decades has pioneered symptomatic control and has addressed end-of-life issues / decisions in patients with neoplastic pathology, but little attention has been given to patients with progressive and irreversible chronic respiratory pathologies with limited / reserved prognosis.[5]

The proactive involvement of PC in respiratory patients like those with severe COPD has already been shown to have a positive impact and among them dyspnea is the most prevalent symptom, which can be quite disabling at all levels and enhanced by several factors reflected in PC in the concept of "total dyspnea".[6]

Its known that there are a range of treatment strategies for dyspnea both pharmacological and non-pharmacological to ensure symptomatic relief,[7] oxygen therapy being one of them but according to PC research and recommendations the routine use of oxygen treatment for shortness of breath is not recommended[8] and it is imperative to determine whether the use of the so-called "Palliative oxygen" is appropriate.[9]

At the end-of-life the delivery of oxygen can be made by conventional oxygen therapy (COT) or by non-invasive ventilation (NIV). As there is no clear evidence of symptomatic benefit of palliative oxygen in the literature its use should be on an individualized basis and the role of NIV as palliative treatment is still very uncertain. The rationale for end-of-life NIV should be to provide comfort and relief of dyspnea, but the use of NIV in patients with an order for non-resuscitation remains controversial, largely due to the lack of clarity in the defined end-of-life objectives.

Related to COT and NIV a new oxygen therapy has emerged, high-flow nasal cannula oxygen (HFNC) designed to provide oxygen at high flows with an optimal degree of heat and humidification, which is well tolerated and easy to use specially in the intensive care unit but in PC setting it is still very limited.[10]

HFCN therapy has specific indications and has some advantages in relation to COT or NIV because it can be less claustrophobic, produces less skin breakdown, and does not impede respiratory patients from eating or talking.[10]

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Physiologically, HFNC maintains the integrity of mucociliary function by delivering heated and humidified gas at natural body conditions, it reduces the anatomical dead space, improves carbon dioxide wash-out, reduces the work of breathing, generates a positive end-expiratory pressure and a constant fraction of inspired oxygen.[7,11]

Clinically, HFNC effectively reduces dyspnea and improves oxygenation in respiratory failure from a variety of aetiologies, thus avoiding escalation to more invasive supports.[10] In fact, in exacerbated COPD patients studies have already shown that HFNC is able to keep PaCO2 unmodified, while oxygenation slightly deteriorates as opposed to NIV and also the work of breathing is reduced with HFNC by a similar extent to NIV, while it increases by 40-50% during COT.[11]

These physiological and clinical effects, specifically the comfort of the technique which is also reported to be more comfortable than COT and NIV,[11] indicate its potential outside the intensive care unit, namely in the PC context.

In end-of-life situations, there are few studies that attempt to compare HFNC with other treatment strategies and the majority of them compared with NIV. Peters et al[12] examined 50 subjects with a do-not-intubate directive and with hypoxemic respiratory failure who received HFNC and many subjects did not need to escalate to NIV. The use of HFNC was also compared with NIV in patients with end-stage interstitial lung disease, a condition associated with particularly severe hypoxaemia and devastating dyspnea and HFNC was better tolerated as the patients could eat and converse until just before death.[13]

In PC the ability to communicate with family and friends to allow them to resolve and discuss end-of-life issues and the possibility of oral food intake is commonly desired by patients at the end-of-life[10] suggesting that HFNC in these patients is a reasonable palliative treatment.

Another advantage of HFNC is that severe patients in the last phases of their disease who require a high FiO2 and wish to die at home can be more easily treated in their own houses reducing hospital stay. A recent study retrospectively examined a cohort of severe patients with end-stage respiratory failure, including interstitial lung diseases, cancer and COPD, who were discharged home on long-term HFNC.[14] The survival of these patients was poor, but HFNC allowed the patients to return home and to be treated at reasonable cost. The role of this device, therefore, should be considered in PC.[10]

HFNC has remained a novelty in the world of non-invasive respiratory support in the last decade, which is why it is essential to carry out more robust studies to better define its real potential, specifically in addressing dyspnea in PC setting.[15]

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COMMENT

Functional status in the COVID-19 era: ALERT, ALERT, ALERT!

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The mapping review by Simonelli and coworkers[1] in this issue of Pulmonology raises awareness of a highly meaningful domain for patients with COVID-19, i.e., functional status, which seems to need urgent attention from daily routine respiratory assessments, independently of disease severity and care setting.

COVID-19 has suddenly affected millions of people worldwide [2] with resource constraints in healthcare systems. Research and clinical focus have been placed on the pathophysiology and screening of the disease, to prioritise those in need of hospitalisation. However, a patient centred assessment, beyond the pathophysiological aspects of the disease, is needed to reveal the unique needs of people with COVID-19 and informal caregivers, guide decision-making with multidisciplinary teams on the most appropriate interventions and optimise outcomes. This falls into the International Classification of Functioning, Disability, and Health (ICF) developed by the World Health Organization.[3-5]

Several impairments in body functions and structure, such as dyspnoea, fatigue, cough, muscle weakness and myalgias have been reported in the acute phase, across levels of COVID-19 severity.[6] Such impairments lead to limitations in activities (e.g., walking, moving around, lifting and carrying objects) and restrictions in participation (e.g., engaging in recreation and leisure activities, carrying out the daily routine and in employment) of daily life. This means functional status in patients with COVID-19 is decreased. The health condition itself and contextual factors, i.e., personal (e.g., age and emotional status) and/or environmental (e.g., indoor and outdoor air quality and climate), may act as barriers or facilitators.

Functional status is an individual's ability to perform normal daily activities required to meet basic needs, fulfill usual roles, and maintain health and well-being.[7] Measures of functional capacity (maximum capacity of a person to perform a daily life activity, e.g., the six minute walking distance test (6MWT) or 1-minute sit to stand test (STS) and/or of functional performance (activities people actually do during the course of their daily lives, e.g., Barthel Index or Functional Independence Measure) are used in the literature to assess functional status as they assess different but complementary aspects.[7,8] Decreased functional status includes struggling to perform basic activities (e.g., showering, getting dressed, housework and climbing stairs), and/or work and/or leisure activities.[9]

Preliminary evidence shows that more than 70% of individuals with COVID-19 present functional status impairment at hospital admission and approximately 30% are still impaired at discharge.[10,11] Functional status impairment has been corroborated in two recent systematic literature reviews.[1,8] The exact prevalence of this impairment in patients with COVID-19 and its evolution over time is still unknown. Three main reasons contribute to this lack of

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knowledge. Assessment of these patients continues to be focused on pulmonary/physiological measures and level of functional status is often not established. The largest proportion of individuals had "mild-to-moderate" disease,[12] recovered isolated at home or in institutions and functional status was rarely part of their assessment. When functional status is assessed, various measurement tools are used across different levels of disease severity and timings, which limits comparisons across studies.[1,8] Nevertheless, the persistent impairments over time, across disease severity, already reported in the literature [13-17] also impact on functional status,[18] forming a downward spiral of activity avoidance, and affecting a large proportion of the population with COVID-19. Moreover, decreased functional status has been associated with worse prognosis in patients with COVID-19 [19] hence, it does not just affect individuals, but also increases reliance on informal caregivers [20] and healthcare systems.

Therefore, functional status impairment leads to huge individual and societal burden and should not be considered as a marginal consequence of the pandemic. In fact, it should be classified as a treatable trait as it is highly meaningful/clinically relevant, easily identified and measured, and can be treated/modified.[21] Its integration into the pandemic patient-centered assessment and management should be seen as a priority and not omitted from treatment options, especially non-pharmacological ones (e.g., physical activity, physiotherapy, pulmonary rehabilitation); so the most suitable person-centred intervention is offered to the most appropriate patient in the most appropriate setting. This means that the unmet needs for rehabilitation are currently aggravated and a one-size-fits all approach to address functional status will be of very limited use given the wide range of impairments, limitations and restrictions across COVID-19 severities and even within the same severity. Therefore, the need to improve access to different rehabilitation interventions across healthcare sectors has never been so evident.

Simonelli and coworkers[1] reviewed the measures used to assess physical performance in patients with COVID-19. They included 33 studies and found 28 different measures being used although, the Barthel index (42.4% of studies), the 6MWT (36.4%), the short physical performance battery (21.2%) and the 1-minute STS (12.1%) were the most frequently reported. They corroborated the short- and long-term functional status impairment in this population.[11,14] The low/fair quality of the research in this field and the different aspects of functional status assessed by the measures found were also highlighted.

The authors are to be commended for calling attention to a highly meaningful and yet neglected domain for individuals, informal caregivers and overall society in the COVID-19 era. Results of their systematic review provide some guidance on assessing functional status in this population and may contribute to design and implement rehabilitation interventions to specifically address this domain in those in need.

High quality research and clinical attention to the assessment and rehabilitation of functional status and improved communication and navigability across healthcare sectors (primary, secondary, tertiary) are urgently needed, independently of the disease severity or healthcare setting, if we want to promote autonomy and maximum functioning of this population.

Declaration of competing interest

The authors have no conflict of interest to declare.

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COMMENT

In memoriam Claudio F. Donner

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Claudio F.Donner (1948-2021) unexpectedly passed away. The news reached most friends and colleagues while still on their annual leave but rapidly spread all around the community astonishing everyone. Too early he left in grief his wife Franca and the daughter Valentina, his family living in Borgomanero a city close to Novara placed in the western-north part of Italy.

Claudio Donner was an excellent medical doctor from the moment he graduated from the University of Pavia and subsequently got diplomas in medical specialties. Respiratory medicine was his primary interest in clinical practice and he dedicated himself in particular to the chronic respiratory patients with conditions leading to inability in the daily life. For this reason, he started his career in 1973 at the "Salvatore Maugeri Foundation Research Institute, Center of Veruno" where he served until 2006 as chief of the Division of Pulmonary Disease, and then as director of the Department of Pulmonary Rehabilitative Medicine of that institution. In recent years he worked as the medical director of "Mondo Medico Multidisciplinary and Rehabilitation Clinic" in Borgomanero.

Together with patient care Claudio Donner rapidly developed his stance as a clinical scientist and researcher on a wide range of topics including pathophysiological mechanisms of exercise, acute and chronic respiratory failure, pulmonary rehabilitation and COPD, sleep respiratory disorders and quality of life in patients with chronic and acute on chronic respiratory failure. He contributd to the widening of the concept of rehabilitation as the fundamental care option in respiratory patients by co-authoring international statements[1,2] fostered by prestigious scientific societies representing the Respiratory Medicine in the world. He was one of the first to understand the great value of intensive exercise training as a determinant part of the rehabilitation process for disabled and symptomatic patients, introducing scientific collaboration through his fellows together with the major world experts in the field.[3] Finally, he is the author of several textbooks (the last one on Pulmonary Rehabilitation just released this year by Francis&Taylor editorial Group) and numerous original scientific papers: the PubMed online library reports 207 peer-reviewed articles published in international scientific journals worldwide.[4] Not least, Claudio Donner was founder and past editor-in-chief of scientific journal Monaldi Archives for Chest Disease (1993-2002), as well as associate editor of Respiratory Medicine since 2005, past co-editor (1990-2004) of the Italian Review of Respiratory Disease (1990-2004) and of Multidisciplinary Respiratory Medicine (2006-2016). Moreover, he was very active in the field of respiratory medicine through teaching initiatives while he was also on the faculty of medical schools in Ferrara, Turin, and Novara. In 2001, was appointed as the contact person of the National Committee for Continuous Education by the Italian Ministry of Health.

"*For these reasons, Claudio Donner made a substantial contribution to upgrade and modernize pulmonology* — says Dr.Bruno Balbi present director of the Clinic in Veruno — *thus making our clinic recognized all over the world*".

Claudio Donner served professional associations in a number of capacities including as president of the Italian

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Association of Hospital Pulmonologists (AIPO) (1995-1997) and of the Italian Interdisciplinary Association for Research in Lung Disease (AIMAR) (2003-2012). He was also president of the non-profit Italian Foundation 'World of Breath' since 2013.

At an international level, he served as head of the Clinical Assembly (1996-1998) and secretary general within the European Respiratory Society (ERS), president (2002-2006) of the Pneumology Section and Board of the European Union of Medical Specialists (UEMS) (2002-2006), and member of the UEMS Management Council (2004-2006). He was also international governor of the Italian Chapter of the American College of Chest Physicians (ACCP) (2009-2012). Commended for his professional involvements, he was honored with numerous awards, most recently receiving a fellowship of the European Respiratory Society (FERS) and special recognition by AIPO.

The community of European pulmologists certainly mourns the loss of a great professional and also recognizes his humanity. He had a life-long commitment to people and promoted services through the local Rotary Club which he joined and served as president in recent years.

It is very difficult to do him justice in this short obituary but we are firmly convinced that everyone who met and knew him during his life is now able to testify on his spectacular early vision for our medical specialty, so we all miss him in our community.

On the very last day of his life a journal published a commentary, co-authored by himself with international friends and experts, dealing with telemedicine as a new frontier to "*enhance and extend the management of care*" in respiratory patients.[5] This illustrates his professional will for doctors to always look beyond the horizon and to never give up.

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Consent to publish data

No consent to disclose.

Conflicts of interest

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ORIGINAL ARTICLE

Plasmapheresis reduces cytokine and immune cell levels in COVID-19 patients with acute respiratory distress syndrome (ARDS)

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Abstract
Background: In December 2019, pneumonia associated with a novel coronavirus (COVID-19) was reported in Wuhan, China. Acute respiratory distress syndrome (ARDS) is the most frequently observed complication in COVID-19 patients with high mortality rates.
Objective of study: To observe the clinical effect of plasmapheresis on excessive inflammatory reaction and immune features in patients with severe COVID-19 at risk of ARDS.
Materials and methods: In this single-center study, we included 15 confirmed cases of COVID-19 at Masih Daneshvari Hospital, in March 2020 in Tehran, Iran. COVID-19 cases were confirmed by

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RT-PCR and CT imaging according to WHO guidelines. Plasmapheresis was performed to alleviate cytokine-induced ARDS. The improvement in oxygen delivery (PaO_2/FiO_2), total number of T cells, liver enzymes, acute reaction proteins, TNF-α and IL-6 levels were evaluated.
Results: Inflammatory cytokine levels (TNF-α, IL-6), and acute phase reaction proteins including ferritin and CRP were high before plasmapheresis. After plasmapheresis, the levels of PaO_2/FiO_2, acute phase reactants, inflammatory mediators, liver enzymes and bilirubin were significantly reduced within a week ($p < 0.05$). In contrast, although the number of T helper cells decreased immediately after plasmapheresis, they rose to above baseline levels after 1 week. Nine out of fifteen patients on non-invasive positive-pressure ventilation (NIPPV) survived whilst the six patients undergoing invasive mechanical ventilation (IMV) died.
Conclusion: Our data suggests that plasmapheresis improves systemic cytokine and immune responses in patients with severe COVID-19 who do not undergo IMV. Further controlled studies are required to explore the efficacy of plasmapheresis treatment in patients with COVID-19.

Introduction

In December 2019 coronavirus disease (COVID-19) was first diagnosed in the city of Wuhan in China; this pandemic disease has since spread rapidly around the world.[1] The lung as the main target organ of COVID-19 can cause wide spectrum of pulmonary involvement, ranging from mild, upper respiratory tract infections to life threatening lower respiratory tract infections, including the development of acute respiratory distress syndrome (ARDS).[2] The pathology of COVID-19-related ARDS and its severity depends upon the patient's immune status and target organ involvement.[3] Flow cytometry analysis of blood in critically ill patients with COVID-19 revealed that the $CD3^+$, $CD4^+$ and $CD8^+$ cell counts were greatly reduced.[4] This lymphopenia is likely to result from high plasma inflammatory mediators negatively regulating T cell survival/proliferation leading to T cell exhaustion in these patients.[5] This dysregulation of T cells may lead to enhanced disease severity and a poor prognosis with a high mortality rate.[6]

Effective treatment of the systemic response in severe and critically ill COVID-19 patients is key to reducing the associated mortality. Various therapeutic techniques have been used to control the inflammatory storm in these patients with COVID-19-related ARDS.[7] Plasmapheresis and other blood purification techniques are recommended for the treatment of critically ill patients with a high degree of systemic inflammation. Thus, in the current study we assessed the effectiveness of plasmapheresis on systemic cytokine and immune cell levels in COVID-19 patients irrespective of whether they were undergoing invasive mechanical ventilation (IMV) or non-invasive positive-pressure ventilation (NIPPV). All patients were admitted to the Masih Daneshvari Hospital, Tehran, Iran between March and April 2020. The duration of treatment and survival were also analyzed.

Patients and methods

Study design

The study was conducted at the Masih Daneshvari Hospital which was the referral center for COVID-19 patients at the Shahid Beheshti University of Medical Sciences (Tehran, Iran) between March-April 2020. The study protocol was approved by the ethics committee of University and was registered on the Iranian Registry of Clinical Trials (www.irct.ir, IRCT20150107020592N23). Written informed consent was obtained from all study participant, fifteen critically ill adult patients with confirmed COVID-19 as determined by clinical criteria and positive RT-PCR assays. Critically ill patients were defined as those with clinical deterioration requiring admission to the intensive care unit (ICU) and who required either invasive or non-invasive ventilation, the initial blood sample was measured immediately upon the patient's admission to the ICU and prior to receiving any treatment.

Inclusion and exclusion criteria in patient selection

All patients were older than 18 years of age and met the criteria of the Berlin definition for the diagnosis of ARDS.[8] All patients with COVID-19-induced ARDS who fulfilled these criteria were included in this study. Exclusion criteria included a record of ongoing albumin allergy, neoplastic diseases, inflammatory disease, active bleeding, chronic renal and hepatic impairment, recent myocardial infraction or coronary artery bypass graft, HIV infection or severe chronic respiratory disease.

Therapeutic approach

Conventional treatments such as NIPPV or IMV were initially applied. Patients received either intravenous or enteral

administration of high protein, low carbohydrate nutritional supplements. Furthermore, water-electrolyte imbalances, intravascular fluid replacement, body temperature control, diuresis and other symptoms were treated as required. Patients received antiviral drugs such as Favipiravir orally (1600 mg) twice on the first day and 600 mg from the second day onwards, intravenous injection (IV) of Remdesivir 200 mg as a single dose on day 1 followed by 100 mg once daily for a total duration of 5 days. Moreover, all patients who developed respiratory tract infections were treated with intravenous infusion of *Vancomycin* and Meropenem at standard doses.

The therapeutic effect on severe COVID-19 patients was assessed by measuring blood parameters including the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2); plasma inflammatory mediator and acute phase protein levels ;Interleukine-6 (IL-6), Tumor necrosis-alpha (TNF-α), ferritin, C reactive protein (CRP), polycalcitonine (PCT); CD3+, CD4+ and CD8 + T cell numbers and liver function tests aspartate transaminase (AST), alanine aminotransferase (ALT) and bilirubin) as well mortality. The survival time was calculated from the time of patient ICU admission to the time the patient was discharged from the hospital.

Plasma purification technique

Removal of inflammatory mediators from the plasma using blood purification techniques such as plasmapheresis plays a key role in the management of various diseases and may attenuate the response particularly in the early phase of ARDS.[8–10] Plasmapheresis was performed whether the patient remained under IMV or NIPPV to improve O_2 saturation and reduce pro-inflammatory mediator levels. Plasmapheresis was performed via femoral venous catheters at a blood flow rate of 50—120 ml/min based on the patient's blood pressure using a JMS fully automated Sds-20 Hemodialysis Machine.[11] It was implemented over six hours per day, three times weekly for all patients whose clinical condition did not improve. Blood samples were collected before and after each plasmapheresis to enable measurement of blood parameters.

During each session a volume of 40 mL/kg bodyweight of patient's plasma was exchanged with an equal volume of 5% human albumin solution and 0.9% saline. In four patients, based on their ABO blood group matching, received fresh plasma from donors with positive detection of anti-SARS-CoV-2 IgG and IgM in their whole blood in addition to albumin and saline. After the first plasmapheresis session the effectiveness was evaluated and confirmed by the presence, or progression, of hemodynamic instability and the development of organ dysfunction. Patients were followed until discharged from ICU or death.

Data collection

All patients were assessed for sequential (sepsis-related) organ failure assessment (SOFA) and acute physiology and chronic health evaluation II (APACHE II) scores on the day of ICU admission. Whole blood samples were collected from patients before and after plasmapheresis in EDTA tubes.

Table 1 Demographics and baseline characteristics of patients infected with COVID-19 (n = 15).

Characteristic	Mean ± SD /No. (%)
Age, year	57.6 ± 12.1
Male sex	9(60.0)
SOFA score	9.6 ± 1.5
APACHE II score	23.7 ± 2.7
Underlying disease	
Hypertension	4(26.7)
Diabetes	3(20.0)
Hypertension + Diabetes	1(6.7)
Cardiovascular disease	1(6.7)
Cardiovascular disease+ Hypertension + Diabetes	1(6.7)
None	5(33.3)
Ventilation support at baseline	
Invasive mechanical ventilation	4(26.7)
Non-invasive mechanical ventilation	11(73.3)
Length of ICU stay, day	9.6 ± 2.3
Survival	9(60.0)

SOFA = Sequential Organ Failure Assessment; APACHE = Acute Physiology and Chronic Health Evaluation.

Plasma was isolated and then stored at -70 °C until analysis. Cytokine (TNF-α and IL-6) detection was performed by ELISA (Immolate, DPC Biermann Bad Nauheim, Germany), lymphocyte subset analysis was determined by flow cytometry analysis (FACS, Beckman Coulter, IN, USA) by using FITC-, PE- and APC-labeled antibodies for CD3, CD4 and CD8 T cells respectively (all from BD Pharmangin, CA, USA). The other biochemical parameters were determined using an automatic biochemical analyzer.

Statistical analysis

The data were analyzed using the statistical package IBM SPSS version 24.0 and descriptive statistics (Statistical Package for the Social Sciences, Chicago, IL). The categorical variables are expressed as proportions and frequencies. The Kolmogorov–Smirnov test (KS test) was used to test normality of continuous variables. Normally distributed continuous variables are summarized as means and standard deviations. The paired *t*-test and Mann-Whitney *U* test were used to compare the mean/median between two groups. P values <0.05 were considered significant.

Results

Patient characteristics

Table 1 shows the demographic information of participating COVID-19 infected patients. The mean age of the patients was 57.6 ± 12.1 years. Nine (60%) patients were male and six (40%) were female. At baseline the mean of APACHE II and SOFA scores were 23.7 ± 2.7 and 9.6 ± 1.5, respectively. Ten patients had comorbidities including hypertension (HTN, 26.7%), diabetes mellitus (DM, 20.0%), HTN + DM (6.7%), cardiovascular (6.7%) and cardiovascular + DM + HTN (6.7%). All

Table 2 Laboratory findings of patients infected with COVID-19 on admission to ICU (n = 15).

Variable	Before (Mean ± SD)	After (Mean ± SD)	After one week (Mean ± SD)	P-value
Arterial blood gas analysis				
PaO2/FIO2, mm Hg	184.3 ± 56.1	224.0 ± 57.2		<0.001
Infection and immunity				
Procalcitonin, ng/mL	0.2 ± 0.2	0.1 ± 0.1		0.012
C-reactive protein, mg/dL	47.3 ± 17.7	28.5 ± 20.5		<0.001
Ferritin, ng/mL	1027.3 ± 396.9	654.0 ± 320.0		<0.001
$CD3^+$ T lymphocyte (/μL)	247.7 ± 112.9	172.7 ± 60.9	273.6 ± 98.0	0.014
$CD4^+$ T lymphocyte (/μL)	176.9 ± 60.5	128.6 ± 34.9	238.4 ± 63.4	0.046
$CD8^+$ T lymphocyte (/μL)	132.2 ± 60.0	88.0 ± 36.1	207.0 ± 81.7	0.003
Biochemical test				
AST, U/L	37.1 ± 17.5	26.0 ± 17.1		<0.001
ALT, U/L	43.9 ± 19.0	34.5 ± 20.2		<0.001
Total bilirubin, mmol/L	56.2 ± 11.8	33.9 ± 10.4		<0.001
Inflammatory mediators				
IL-6, pg/mL	8.3 ± 1.8	5.7 ± 1.3		<0.001
TNF-A-α, pg/mL	9.2 ± 3.6	4.0 ± 0.8		<0.001

PaO2/FIO2= arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen; AST = aspartate transaminase; ALT = alanine aminotransferase; IL-6= interleukin -6; TNF-A- α= tumor necrosis factor-α.

patients had respiratory involvement at admission, four patients with PaO_2 /FiO_2 lower than 100 urgently required IMV whilst NIPPV was used for the other subjects. During the study, two patients on NIPPV developed severe hypoxemia requiring intubation and mechanical ventilation.

Before & after comparisons

Table 2 and Fig. 1 show the oxygen status (PaO_2/FiO_2), blood mediator and T cell numbers before and after plasmapheresis. Plasmapheresis was associated with significant and rapid improvements in oxygenation status ($p < 0.001$, Fig. 1A), hepatic function ($p < 0.001$, Fig. 1B-D), reduced inflammatory mediators ($p < 0.001$, Fig. 1E-F) and acute phase reactant levels ($p < 0.05$, Fig. 1G-I). However, T cell subset numbers were significantly decreased ($p < 0.05$, Fig. 1J-L).

One week after plasmapheresis, the levels of all lymphocyte subsets increased to above the levels seen at baseline in patients who improved ($p < 0.05$, Table 2). The timing of the improvement in lymphocyte count was consistent with the time point of the improvement in clinical course. Overall, plasma levels of inflammatory mediators and acute phase reactants were negatively correlated with blood T cell counts in severe patients with COVID-19 pneumonia.

Case-crossover design

A conditional logistic regression model based on adjusting the time trend was used to investigate the effect of using plasmapheresis on patient survival to eliminate confounding patient characteristics.[12] Plasmapheresis was used every 48 h according to the patient's condition and the level of IL-6. The results of our case-crossover design are summarized in Table 3. Plasmapheresis has a significant effect on patient survival ($P = 0.002$) with an Odds Ratio (1.171) indicating that plasmapheresis increased survival by 17%. The likelihood ratio test was 59.54 with 2 degrees of freedom.

Prognosis analysis

The survival rate of patients is shown in Table 1. The primary outcome was improved clinical outcome in severe COVID-19 patients after plasmapheresis. Nine (60%) out of twelve critically ill patients with SARS-CoV-2 infection who underwent NIPPV survived. Unfortunately, the other 6 more severe COVID-19 patients on IMV died. The median length of ICU stay in patients who survived was 9.6 ± 2.3 days.

Discussion

The current study was designed to evaluate the effect of plasmapheresis on systemic cytokine and immune cell levels in severe COVID-19 patients with ARDS. Therapeutic plasmapheresis in critically ill patients with COVID-19 reduced excess pro-inflammatory cytokine, liver function and acute phase protein levels which could help to support vital organ function. In addition, plasmapheresis improved oxygenation status and lymphocyte subset counts. Moreover, all subjects on NIPPV who underwent plasmapheresis survived. These data emphasize the need for controlled studies of plasmapheresis in patients with severe COVID-19 with ARDS.

COVID-19 pneumonia induces a progressive hypoxemia and inflammatory response which can develop into acute lung injury and multi-organ failure as a serious consequence.[13] Patients with severe COVID-19 ARDS have a higher mortality rate as compared with the mortality rate commonly seen in severe ARDS resulting from other diseases.[14] To date, the management of ARDS in COVID-19 remains supportive and most therapeutic interventions use re-purposed drugs and no COVID-19-specific treatments are available.[15] As such severe COVID-19 patients have

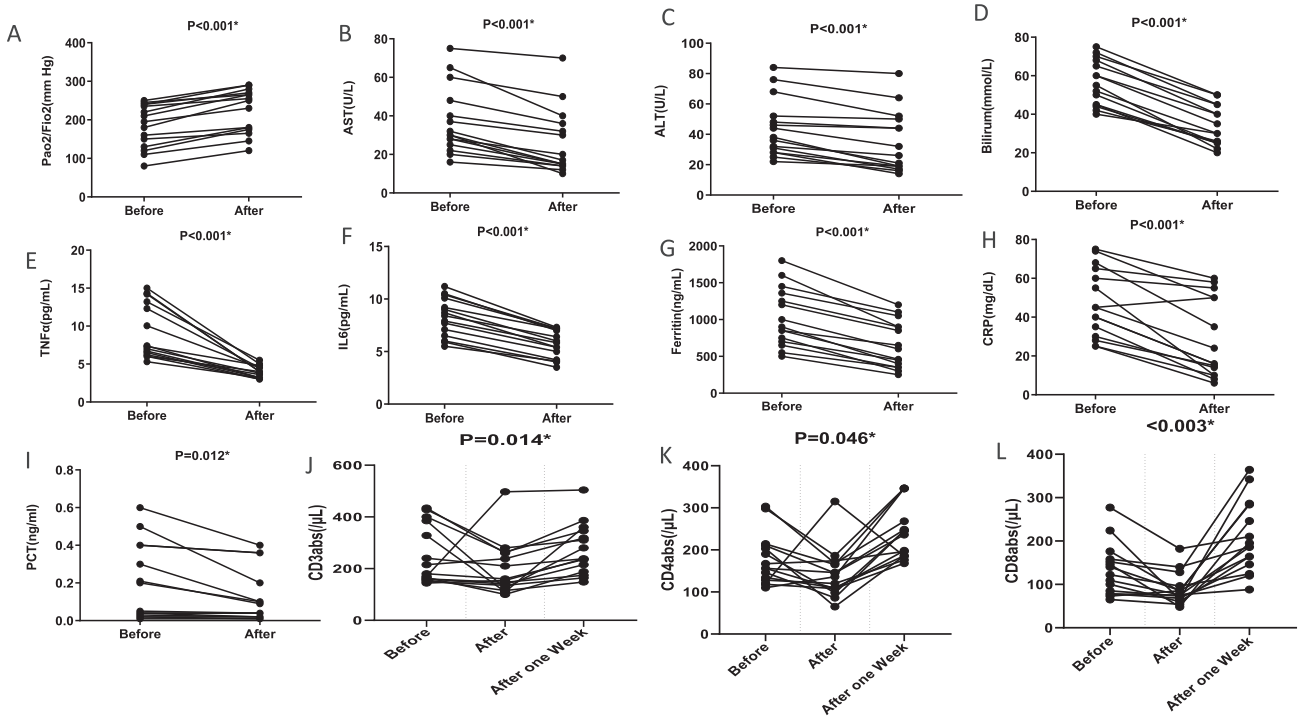

Figure 1 Effects of Plasmapheresis on cytokine and immune cell levels in COVID-19 patients with acute respiratory distress syndrome (ARDS). Oxygenation status [ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2)] was evaluated in arterial blood (A). Serum was isolated from whole blood without anticoagulant and liver function was evaluated by measuring AST (B), ALT (C) and Bilirubin (D). The serum levels of interleukin (IL)-6 (E) and TNF-α (F) were evaluated by ELISA. Acute phase proteins including Feritin (G), CRP (H) and PCT (I) were evaluated by biochemical methods. The percentage of CD3 (J), CD4 (K) and CD8 (L) T cell subsets was also recorded. Data are presented as values for each individual. P values for each comparison are indicated on the individual panels.

Table 3 Summary output of case-crossover design.

Items	Coefficient	OR	SE	Lower 0.95	Upper 0.95	P-value
Exposure (Plasmapheresis)	0.157	1.171	0.059	1.059	1.294	0.002*
Time	0.066	1.059	0.041	0.987	1.155	0.110

been treated with antimicrobial agents, antiviral, antimalarial and corticosteroid therapies with variable degrees of effectiveness.[16,17]

The efficacy of blood replacement therapy in removing inflammatory mediators, immune complexes and in the management of the cytokine storm has shown in multiple disorders[18,19] including in critically ill COVID-19 patients.[9,20,21] In addition, plasmapheresis depletes elevated levels of serum TNF-α and IL-6 following transplantation.[22] IL-1 is important in the early stage of ARDS and is associated with subsequent chemokine production and edema and targeted reduction IL-1β has been used therapeutically.[23] However, high plasma levels of IL-6 and high IL-8 levels in bronchoalveolar lavage fluid are associated with a higher mortality in ARDS patients.[24] Severe COVID-19 patients with ARDS have high levels of TNF-α and of IL6 particularly those requiring ICU admission suggesting that the cytokine storm might be important in severe disease.[25] In addition to these pro-inflammatory cytokines, a role for anti-inflammatory cytokines such as IL-4 and IL-10 has also been postulated in COVID-19.[26]

Previous studies of plasmapheresis in COVID-19 patients have not been associated with detailed analysis of the molecular and biochemical mechanisms underlying the successful intervention. We show here that plasmapheresis results in a rapid reduction in TNF-α and IL-6 blood levels and that this is associated with improvement in clinical outcomes in severe COVID-19 patients on NIPPV.

Enhanced systemic levels of key liver enzymes and of slightly elevated bilirubin levels is seen in severe COVID-19 subjects rather than mild patients and is linked to levels of liver damage increasing from 14.8% to 53%.[27,28] Furthermore, in fatal cases of COVID-19 the incidence of liver injury might reach as high as 58.06%[29] to 78%.[30] Studies in acute liver failure shows that plasma replacement reduces the amount of blood accumulated toxins and improves liver function tests.[31] Plasma replacement also effectively removed systemic TNF-α and IL-6 in patients with severe acute hepatic

failure.[32] Our data on severe COVID-19 patients clearly demonstrated that plasmapheresis also improves liver function in these patients as evidenced by a reduction in the elevated baseline serum hepatic enzyme levels.

CD3 is an important marker of mature T lymphocytes and helps to activate the $CD4^+$ T cell and $CD8^+$ T cells which play an important role in antiviral immunity.[33] Excessive activation of T cells during COVID-19 infection results in a dramatic T cell exhaustion evidenced by the reduced number of total blood T cells, which is, in turn, correlated with disease progression[5,34] and severity of COVID-19 patients.[6,35]

Previous studies have reported that plasmapheresis could be a useful adjunct to mechanical ventilation in acute respiratory failure.[36,37] In addition, clinical studies show that blood purification techniques, play a key role in effectively reducing the mortality of patients with severe COVID-19.[7] However, the evidence to date is insufficient to recommend the routine use of plasmapheresis to correct the hypoxemia, which can lead to multiorgan dysfunction due to advanced modes of treatment.[38] However, plasmapheresis may be used based on disease severity and the availability of resources. Importantly, we demonstrate that plasmapheresis improves some clinical variables in our patients such as the PaO_2/FiO_2 ratio although we cannot confirm a significant survival benefit due to a lack of control subjects.

Our study has several limitations. First, only 15 patients with confirmed COVID-19 were studied. Second, it was an uncontrolled single-center study; it would be useful to conduct a controlled multicenter study either in Iran or ideally across several countries to evaluate the efficacy of plasmapheresis in COVID-19 infection. In our study, plasmapheresis improves oxygenation, lymphocyte counts and demonstrated benefits in managing the cytokine storm in severe COVID-19 patients with ARDS.

Multiple testing could be an issue in the current study and even more so in transcriptomic and other unbiased omic analysis. It is possible that the results shown may reflect false positives due to multiple testing and that multiple corrections of the raw p values may provide a better reflection of the true significance of the differences reported here. However, using an FDR value may hide possible important factors and we feel that reporting the raw p values provides an opportunity to draw conclusions about the data and the need for subsequent validation. Since this disease is new and has many unknown dimensions, in this study and other ongoing studies, all possible factors and indicators that may change due to this disease were examined.

We were unable to demonstrate an effect on mortality as only our less severe COVID-19 patients using NIPPV survived and survival may reflect the severity of disease and/or the effect of NIPPV. All subjects who required IMV and had plasmapheresis died which again may reflect the severity of the disease. It is important to perform controlled studies to delineate the effect of the intervention per se.

To conclude, our study demonstrated that the therapeutic plasmapheresis as a blood purification technique offers safety and efficacy in removal of inflammatory cytokines, acute phase proteins and improves tissue oxygenation.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Comparing the cost-effectiveness of two screening strategies for latent tuberculosis infection in Portugal

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Screening

Abstract
Introduction and objectives: Screening for latent tuberculosis infection (LTBI) in close contacts of infectious TB cases might include Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRA), in combination or as single-tests. In Portugal, the screening strategy changed from TST followed by IGRA to IGRA-only testing in 2016. Our objective was to compare the cost-effectiveness of two-step TST/IGRA with the current IGRA-only screening strategy in immunocompetent individuals exposed to individuals with respiratory TB.
Materials and Methods: We reviewed clinical records of individuals exposed to infectious TB cases diagnosed in 2015 and 2016, in two TB outpatient centers in the district of Porto. We estimated medical, non-medical and indirect costs for each screening strategy, taking into account costs of tests and health care personnel, travel distance from place of residence to screening site and employment status. We calculated the incremental cost-effectiveness ratio (ICER) as

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the cost difference between the two screening strategies with the difference number of LTBI diagnosis as a measure of cost-effectiveness, assuming that treating LTBI is a cost-effective intervention. We also calculated adjusted odds-ratios to test the association between diagnosis of LTBI and screening strategy and estimated the total cost for averting a potential TB case.
Results: We compared 499 contacts TST/IGRA screened with 547 IGRA-only. IGRA-only strategy yielded a higher screening effectiveness for diagnosing latent tuberculosis infection (aOR 2.12, 95%CI: 1.53 - 2.94). ICER was €106 per LTBI diagnosis, representing increased effectiveness with a slightly increased cost of IGRA-only screening strategy.
Conclusions: Our data suggests that in Portugal LTBI screening with IGRA-only is more cost-effective than the two-step TST/IGRA testing strategy, preventing a higher number of cases of TB cases.

Introduction

Systematic diagnosis and treatment of latent tuberculosis infection (LTBI) is a key part of the TB elimination strategy in low-incidence countries.[1] Screening strategies in individuals with close contact with infectious cases of TB include the tuberculin skin test (TST) followed by the interferon-gamma-release assay (IGRA) in individuals with positive TST results (two-step strategy); single-step IGRA testing; and single-step TST testing.[2]

IGRA tests have specificity greater than 95% in the diagnosis of LTBI.[3] The TST specificity is similar (97%) in populations not vaccinated with Bacillus Calmette-Guérin (BCG), but is considerably lower (60%) in those vaccinated.[3] Sensitivity of the two tests is roughly the same: 80-90% for IGRA; 80% for TST.[3,4] Some studies have shown that the progression rate (likelihood that a person with a positive test will develop active TB) is higher in IGRA-positive individuals.[5,6,7]

A cost-effectiveness study in the United Kingdom estimated that two-step TST/IGRA screening strategy is less costly than single-step IGRA testing (£162,387 *vs.* £ 203,983 per 1000 contacts).[2] However, this study only considered medical costs. In France, a decision analysis model, considering only direct medical costs, showed that in almost all scenarios QuantiFERON (QFT) was more effective and cost-effective than TST in detecting LTBI.[8]

One study in Brazil, though, showed that the most cost-effective strategy was TST (US$ 16,021/averted case) and that the incremental cost-effectiveness ratio was US$ 227,977/averted TB case for QFT-GIT.[9] Another study of individuals entering the Dallas County Jail (Texas, United States) reported a substantially higher positivity rate of IGRA than TST: these authors suggested that sensitivity of TST screening was lower, and that IGRA was more time-efficient and associated with four-fold lower indirect costs. The overall cost per LTBI case detected was nearly three-times higher for the TST than the IGRA.[10]

A recent report of the European Centre for Disease Prevention and Control used a deterministic TB transmission model to predict the impact of different LTBI screening and treatment strategies for several risk-groups, including contacts of TB cases. They concluded that from the healthcare perspective, LTBI screening is most cost-effective when done using the two-step approach (TST first and, if positive, followed by IGRA).[11,12]

Given the heterogeneous results of different studies, the World Health Organization advised more research in this field.[13]

The Portuguese National Health Service maintains TB outpatient centers that are responsible for TB and ITBL diagnosis, treatment, and screening across the country, under technical guidance from the National Tuberculosis Programme. In the Northern Region, TB outpatient centers switched from the two-step TST/IGRA to the single-step IGRA-only screening strategy, after shortages in tuberculin supply. Before this switch, TST was performed to exposed contacts immediately after diagnosis of TB in index case and repeated 8-10 weeks after the last exposure of risk, followed by IGRA testing (QuantiFERON Gold Plus ®) whenever TST was positive. After 2016, IGRA-only (QuantiFERON Gold Plus ®) was performed only once, 8-10 weeks after the last exposure to index case of TB. The IGRA assay available during the study period in the Northern Region was the QFT-Plus assay.[14,15]

The objective of this study was to compare the cost-effectiveness of the two strategies described above, in terms of medical costs (for the healthcare system) and direct and indirect non-medical costs related to LTBI screening (excluding treatment costs), for LTBI screening in close contacts of confirmed cases of respiratory TB.

Material and Methods

Patient Selection

We examined clinical records of all individuals screened for TB and LTBI in two TB outpatient centres from the Northern Health Region: Penafiel (180,000 inhabitants, annual TB incidence rate of $47.7/10^5$ in 2012-16) and Vila Nova de Gaia (330,000 inhabitants, annual TB incidence rate of $26.0/10^5$ in 2012-16).[16] Only individuals exposed to an infectious TB patient, diagnosed from 1 January 2015 to 31 December 2016, were included. Exclusion criteria were those described in Figure 1.

We extracted socio-demographic information (sex, age, parish of residence, employment status), clinical information (history of TB/LTBI, immunosuppression, diagnosis of TB during screening), LTBI screening test information (screening strategy, date[s], result[s], diagnosis, initiation of

Figure 1 Eligible and included records, with reference to exclusion criteria.

treatment), and information on the index TB cases (diagnosis date, sputum smear results).

Cost Effectiveness

Cost-effectiveness was expressed as an incremental cost-effectiveness ratio (ICER), which was calculated by dividing the cost difference between the two screening strategies with the difference number of LTBI diagnosis.[11,17] We assumed that treating LTBI is a cost-effective intervention and focused only in the differences between strategies until the moment of LTBI diagnosis.

The median costs in the TST/IGRA and TST-only groups were compared using Mann-Whitney test. The proportion of individuals diagnosed with LTBI, number of visits to the TB outpatient center, and adherence to screening were also compared for these two groups using the Chi-squared test or Fisher's exact test, as appropriate. Adjusted odds-ratios (aORs) and 95% confidence intervals (95% CIs) for each screening strategy and diagnosis of LTBI were calculated using logistic regression. Screening strategy, sex, age, place of residence, professional status (employed/unemployed), TB outpatient center, index case sputum smear positivity, infectious period, and site of disease in the index case were included in the initial regression models. In this procedure, a backward stepwise approach was used, and at each step, the least significant variable that was not a substantial confounder (whose removal would lead to a change of more than 20% in the OR of one or more parameters remaining in the model) was removed. Sex and index case sputum smear positivity were retained regardless of *p*-value.

Direct individual medical costs were calculated as the sum of estimated costs from the screening test(s), specimen transportation to the testing laboratory, and the work of healthcare professionals (collection and testing of specimens) — data provided by the Northern Regional Health Administration for 2014-2016. IGRA (QuantiFERON-TB Gold Plus) cost was €37.66 (including ELISA kit, antigen, and mitogen) and the TST cost was €1.00 (including tuberculin). Disposable material costs were estimated using online prices (including laboratory materials, blood collection materials, tuberculin needles and syringes, gloves, compresses), and were calculated as €0.31 for one TST and €0.57 for one IGRA.

Direct non-medical costs were estimated per screened individual by multiplying the number of visits to the health center by the distance traveled (calculated taking into account patient's address), with an estimated cost of €0.10 per km. To assess the impact of this estimate on final results, a sensitivity analysis was also performed using an estimated cost of €0.35 per km, the reference value used by the Portuguese Government. This cost was adjusted considering that contacts of the same index case could share their mean of transport if they went to the TB outpatient center on the same day.

Indirect costs per screened individual were calculated by multiplying the number of visits to the health center by the half-daily average income (from *Instituto Nacional de Estatística*, Statistics Portugal) for working individuals. Half-daily income was used in order to not overestimate indirect costs, considering that TB is associated with socio-economic deprivation.[18,19] A sensitivity analysis was also performed using daily average income. The number of potentially averted TB cases was estimated based on the number of individuals who started LTBI treatment, a 10% lifetime risk of developing TB, and a 70% efficacy of treatment (assuming that all patients who began LTBI treatment finished their treatment).[20]

Definitions

The following definitions were used in this study:

- Adherence to screening: proportion of individuals who showed up for screening that completed all recommended screening steps;[21]
- Confirmed respiratory TB patient: person with a positive respiratory TB diagnosis (tracheal, laryngeal, bronchial, pulmonary, and/or pleural), confirmed by a positive culture for *Mycobacterium tuberculosis complex* (MTC) or a positive smear plus MTC nucleic acid detection in sputum or bronchoalveolar lavage;[22]
- Close contact: person who had close contact with a patient who had respiratory TB for a cumulative time of at least 8 h if sputum smear-positive, or 40 h if sputum smear-negative (National Tuberculosis Programme recommendation);[23]
- Immunosuppressed individual: individual receiving chemotherapy, radiotherapy, an immunosuppressive drug, or infected with HIV;[21]
- Period of infectiousness: time interval during which MTC may be transferred between individuals, estimated as the number of days between onset of symptoms and TB diagnosis;[24]
- Latent tuberculosis infection: positive IGRA test in an individual who does not have active TB;[24]
- Medical direct costs: healthcare-related costs (screening tests, specimen transportation to the testing laboratory, and work of healthcare professional);[21]
- Non-medical direct costs: costs related to the transportation of an individual to a TB outpatient center for screening;[21]
- Indirect costs: productivity loss from an individual's absence from work because of travel to the TB outpatient center for screening.[21]

Stata® IC 15.0 (Student version) was used for statistical analysis. Ethical approval for this study was obtained from the Ethics Boards of the Institute of Public Health of the University of Porto (CE17061) and the Northern Regional Health Administration (39/2017).

Results

From 1428 eligible close contacts of infectious cases of TB, 303 (21%) met the exclusion criteria and were rejected from the analysis (Figure 1). From the remaining 1125 individuals, 578 (51%) had been screened in 2015 using the TST/IGRA strategy and 574 (49%) were screened in 2016 using the IGRA-only strategy. In order to assure that we were comparing the costs of screening contacts of the same number of TB cases, we included all 2016 TB cases and the same number of cases diagnosed in 2015 starting from the end of the year

(79 contacts screened with TST/IGRA in January/February 2015 were excluded).

Baseline Comparison of Groups

The median age of screened individuals was 38 years-old (interquartile range [IQR]: 25.0-51.0), 54% were women, and 58% (n = 641) were employed. Their places of residencies were a median of 11 km (IQR 6.5-15.5) and 14 min (IQR 8.5-19.4) away from the visited TB outpatient center. The two groups had no significant differences in terms of age, sex, employment status, and distance to the visited TB center (Table 1). However, the IGRA-only group had a significantly higher proportion of individuals who were exposed to highly infectious TB patients (positive sputum smears) (Table 1). The proportion of contacts diagnosed with LTBI and the adherence to screening were also greater in the IGRA-only group.

Multivariable Analysis

After adjusting for sex, age, TB outpatient center, index case sputum smear results, and period of infectiousness, the IGRA-only group had an increased risk for diagnosis of LTBI (aOR = 2.12, 95% CI: 1.48—2.93) (Table 2).

Total average costs were €42.71 per screened individual in the TST/IGRA group and €55.21 in the IGRA-only group; the corresponding median values were €43.71 and €60.23, respectively (Table 3). Medical direct costs were higher in the IGRA group, but non-medical direct costs and indirect costs were higher in the TST/IGRA group (Table 3). The cost per LTBI diagnosis was €280.42 in the TST/IGRA group (76 per 499 screened individuals) and €205.44 in the IGRA group (147 per 547 screened individuals). The estimated number of potentially averted cases of TB was 5 in the TST/IGRA group and 8 in the IGRA-only group. Thus, the cost per potentially averted TB case was €4412.48 in the TST/IGRA group (€21,312.29/4.83) and €3719.20 in the IGRA group (€30,199.87/8.12).

Sensitivity Analysis

After changing the previous assumptions regarding travel (cost/km of €0.35 instead of €0.10, and average daily income instead of average half-daily income), total costs were €64.48 per screened individual in the TST/IGRA group and €65.63 per individual in the IGRA-only group (median €72.20 and €71.12, respectively) (Table 3). The cost per LTBI diagnosis was €423.36 in the TST/IGRA group (76 in 499 individuals) and €244.22 in the IGRA group (147 in 547 individuals). The cost per potentially averted TB case was €6661.60 in the TST/IGRA group (€32,175.52/4.83) and €4421.13 in the IGRA group (€35,899.61/8.12). Medical direct costs were greater in the IGRA group, but non-medical direct costs and indirect costs were greater in the TST/IGRA group.

Incremental cost-effectiveness ratio (ICER)

The calculated ICER was €106 per LTBI diagnosis, representing increased effectiveness with a slightly increased cost of IGRA-only screening strategy.

Discussion

Our comparison of two groups of close contacts of TB cases who followed different LTBI screening strategies showed that, when compared to the TST/IGRA group, the IGRA-only group had increased odds of having LTBI diagnosed (aOR = 2.12, 95% CI = 1.53—2.94) . Adherence to screening was also higher in the IGRA-only group, probably because this strategy requires fewer visits to the TB outpatient centers. From a societal perspective, the IGRA-only strategy appears to be more cost-effective than TST/IGRA strategy, because it has a lower cost per diagnosed LTBI case (€205.44 *vs.* €280.42) and a lower cost per potentially averted case of TB (€3,719.20 *vs.* €4,412.48).

Table 1 Characteristics of screened contacts by strategy used.

	TST/IGRA strategy n=499	IGRA strategy n=547	p-value
Median age	37	39	0.108
Proportion of male individuals	49%	44%	0.118
Proportion of working individuals	59%	57%	0.689
Median distance from place of residence to TB outpatient center in kilometers	11	10	0.148
Median time needed to travel from place of residence to TB outpatient center in minutes	15	13	0.014
Average number of contacts per index case	5	6	
Proportion of contacts of a TB case with positive sputum-smear	66%	80%	<0.001
Median infectious time of TB cases	56 days	67 days	0.370
Proportion of contacts who were exposed to a pulmonary TB case (not pleural)	97%	99%	0.118
Proportion of diagnosed LTBI	15%	27%	<0.001
Median number of visits to the TB outpatient center	4	2	<0.001
Adherence to screening	81%	86%	0.038
First step screening concluded	98%		

LTBI: latent tuberculosis infection.

Table 2 Logistic regression model for diagnosis of LTBI (final model).

Variables	Reference group	Other categories	Odds Ratio	95% confidence interval
Screening strategy	TST/IGRA strategy	IGRA strategy	2.12	1.53 - 2.94
Sex	Female	Male	1.11	0.81 - 1.51
Age group	5-10 years	11-17 years	2.89	0.76 - 10.89
		18-29 years	2.88	0.83 - 10.01
		30-39 years	2.43	0.69 - 8.55
		40-49 years	2.11	0.60 - 7.42
		50-59 years	3.25	0.92 - 11.51
		≥60 years	3.92	1.10 - 13.94
TB Outpatient Center	Gaia TB outpatient center	Penafiel TB outpatient center	1.09	0.79 - 1.49
Infectious characteristics of index case	Negative sputum smear	Positive sputum smear	0.97	0.67 - 1.41
Index case infectious period	≤30 days	30-59 days	0.93	0.57 - 1.54
		60-89 days	1.40	0.90 – 2.21
		90-119 days	1.58	0.92 – 2.68
		>120 days	1.83	1.17 – 2.86
Constant	0.05			0.01- 0.17

LTBI: latent tuberculosis infection.

The odds ratio for LTBI diagnosis was greater in the IGRA-only group than in the TST/IGRA group in Penafiel (high TB-incidence) than in Vila Nova de Gaia (medium TB-incidence). There is evidence that the TST and IGRA have similar sensitivity[3,4] but the increased specificity of two-step strategies comes with a lower sensitivity. Previous studies showed that increasing age and immunosuppression are associated with false negative results, especially with TST.[25] Other preconditions, like inflammatory diseases, might be associated with IGRA false negative results.[26] Nevertheless, we used data from healthy individuals, >5 years old, without HIV infection, diabetes or pharmacological immunosuppression (table 1). We expect very few false positive results with the IGRA-only screening strategy, because of its high specificity, but no gold-standard test is available for confirmation.

Previous cost-effectiveness studies suggested that two-step screening was less effective averting active TB cases, but more cost-effective than IGRA-only screening.[2] The present study also considered the effect of societal costs, and included not only medical costs but also non-medical direct and indirect costs. Our results suggests that the IGRA-only strategy is more cost-effective, mainly because of its higher effectiveness in diagnosing LTBI (and potentially averting TB cases) and decreased indirect costs (less productivity lost by individuals and society). As expected, the IGRA-only strategy represents increased costs for health services, because of the unit cost of the IGRA test itself and associated laboratory work. The incremental cost-effectiveness ratio of € 103 per LTBI diagnosis represents the amount of money spent for the outcome of interest. We considered effectiveness only for LTBI diagnosis, and not for treating LTBI (this was studied elsewhere[11]).

This may have led to an overestimation of the number of potentially averted cases of TB in both groups. A selection bias in the IGRA-only group may have occurred, because individuals in this group were exposed to more infectious TB cases (80% of index cases were sputum-smear positive in the IGRA-only group, but only 68% were sputum-smear positive in the TST/IGRA group). This might have occurred because the criteria used to identify eligible contacts were stricter for the more expensive screening strategy. However, including infectiousness in our regression model should have eliminated this bias.

Table 3 Screening costs by screening strategy (median [IQR], in EUR)

	Assumptions 1 (cost/km €0.10; half-average income)			Assumptions 2 (cost/km €0.35; average income)		
	TST/IGRA	IGRA-only	p-value	TST/IGRA	IGRA-only	p-value
Medical direct	€12.83 [12.83 – 12.83]	€49.74 [49.74 – 50.95]	<0.001	€12.83 [12.83 – 12.83]	€49.74 [49.74 – 50.95]	<0.001
Non medical direct	€3.23 [1.33 – 4.56]	€0.91 [0.36 – 1.51]	<0.001	€11.31 [4.64 – 15.98]	€1.80 [0.50 – 3.05]	<0.001
Indirect	€17.50 [0.00 – 28.49]	€8.75 [0.00 – 14.25]	<0.001	€34.99 [0.00 – 56.99]	€17.50 [0.00 – 28.50]	<0.001
Total	€43.71 [16.14 – 52.37]	€60.23 [50.64 – 66.64]	0.006	€72.20 [24.44 – 86.34]	€71.12 [50.64 – 84.65]	0.2116

LTBI: latent tuberculosis infection. IQR: interquartile range.

Conclusion

From a societal perspective, IGRA-only screening appears to be more cost-effective than TST/IGRA screening for LTBI, with a lower cost per LTBI diagnosis and a lower cost per potentially averted TB case. These results indicate an increased effectiveness of IGRA-only screening, at an only slightly increased cost.

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ORIGINAL ARTICLE

Classification of cardiorespiratory fitness using the six-minute walk test in adults: Comparison with cardiopulmonary exercise testing

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Abstract
Background: The six-minute walk test (6MWT) distance could facilitate the assessment of cardiorespiratory fitness (CRF) in clinical practice as recommended. We aimed to develop a CRF classification using the 6MWT distance in asymptomatic adults considering the treadmill maximum oxygen uptake ($\dot{V}O_{2max}$) as the gold standard method.
Methods: We evaluated $\dot{V}O_{2max}$ and 6MWT distance in 1295 asymptomatic participants aged 18–80 years (60% women). Age- and sex-related CRF was classified based on the percentiles as very low (<5th percentile), low (5th–25th percentile), regular (26th–50th percentile), good (51st–75th percentile), excellent (76th–95th percentile), and superior (>95th percentile) for both $\dot{V}O_{2max}$ and 6MWT distance. We investigated the 6MWT distance cut-off (%pred.) with the highest sensitivity and specificity for identifying each $\dot{V}O_{2max}$ classification.

Abbreviations: AHA, American Heart Association; CRF, cardiorespiratory fitness; $\dot{V}O_{2max}$, maximum oxygen uptake; CPET, cardiopulmonary exercise testing; 6MWT, six-minute walk test; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; $\dot{V}CO_{2max}$, carbon dioxide production.

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Results: $\dot{V}O_{2max}$ declined by 8.7% per decade in both men and women. The 6MWT distance declined by 9.3% per decade in women and 9.5% in men. We formulated age- and sex-related classification tables for CRF using the 6MWT distance. Moreover, the 6MWT distance (%pred.) showed excellent ability to identify very low CRF (6MWT distance $\leq$ 96%; AUC = 0.819) and good ability to differentiate CRF as low (6MWT distance = 97%–103%; AUC = 0.735), excellent (6MWT distance = 107%–109%; AUC = 0.715), or superior (6MWT distance > 109%; AUC = 0.790). It was not possible to differentiate between participants with regular and good CRF.
Conclusion: The CRF classification by the 6MWT distance is valid in comparison with $\dot{V}O_{2max}$, especially for identifying adults with low CRF. It could be useful in clinical practice for screening and monitoring the cardiorespiratory risk in adults.

Introduction

It has been recommended that cardiorespiratory fitness (CRF) should be considered as a vital sign in cardiovascular health assessment.[1,2] The gold standard for CRF expression is the maximum oxygen uptake ($\dot{V}O_{2max}$) obtained at the end of a cardiorespiratory exercise testing (CPET). In low-resource environments, submaximal and field exercise tests or even CRF estimates should be implemented.[1,2] Despite consistent evidence on its relevance, the CRF evaluation has not yet been incorporated as a routine test for cardiovascular risk assessment in clinical practice.[2]

Field tests are performed when neither sophisticated equipment for direct assessment of $\dot{V}O_{2max}$ nor human resources with a high level of training are available. Among the most appropriate field tests for individuals at higher cardiovascular risk and controlled chronic diseases is the six-minute walk test (6MWT). The 6MWT has been validated in several populations, including asymptomatic individuals,[3] and a 6MWT distance has been proven to adequately predict the $\dot{V}$ O_{2max} obtained in the laboratory.[4–6] This characteristic makes the 6MWT a simple and less costly CRF assessment tool. In addition, this test is more representative of activities of daily living than other walking tests.[3,4]

Tables of normalcy and specific $\dot{V}O_{2max}$ prediction equations could facilitate the use of CRF assessment as a routine test for screening cardiovascular risk in clinical practice. Accordingly, simple field tests that require minimal resources to be performed and equations for the prediction of $\dot{V}O_{2max}$ are essential for the inclusion of CRF evaluation in different clinical settings.[1]

We hypothesized that the 6MWT is valid for classifying CRF compared to the gold standard ($\dot{V}O_{2max}$), thereby appropriately identifying adults with low CRF. Accordingly, we aimed to develop a CRF classification table using the 6MWT distance in asymptomatic adults considering the treadmill $\dot{V}O_{2max}$ as the gold-standard criterion. We also evaluated age- and sex-related changes in CRF and the correlation between the 6MWT distance and $\dot{V}O_{2max}$.

Methods

Sample and recruitment

Eligible participants were adults over the age of 18 years with no evidence of a self-reported previous medical diagnosis of cardiopulmonary disease, locomotor disorders, electrocardiographic abnormalities at rest or on exertion, or other problems that prevented them from performing physical exercises safely. We recruited participants through social networks, posters at regional universities, and local print media. We excluded participants who presented with spirometry suggesting obstructive ventilatory disturbance (forced expiratory volume in 1 s [FEV1]/forced vital capacity [FVC] < 0.75), who had severe arrhythmias at rest that could potentially be lethal during CPET, and who presented signs and/or symptoms and stress electrocardiography suggestive of myocardial ischemia. The results suggesting poor effort or operational problems during the CPET were excluded from the study. The ethics committee of our university approved this study (#186.796). All participants signed an informed consent form prior to participation.

Clinical and sociodemographic evaluation

Baseline assessments included participants' age, sex, and the presence of self-reported main risk factors for cardiovascular diseases, including older age ($\geq$45 years for men and $\geq$55 years for women), systemic arterial hypertension, diabetes mellitus, dyslipidemia, current smoking habits, medication use, and a family history of premature coronary heart disease. We also assessed the participants' physical activity level in daily life using validated triaxial accelerometers (ActiGraph GT3X+, MTI, Pensacola, FL)[7–9] as previously described.[10] The participants completed seven consecutive days of assessment during waking hours. To be considered valid, it was necessary to have at least ten hours of continuous monitoring, starting from the moment of awakening. The participants used the accelerometer until bedtime, except

during the shower and aquatic activities. We considered physically inactive participants to be those with less than 150 min of moderate-to-vigorous physical activity or less than 75 min of vigorous physical activity per week.[11,12]

Anthropometric assessment

Body mass and height were measured on a calibrated digital scale with a stadiometer (Toledo Prix 2096PP, Brazil). We calculated the body mass index (BMI) in kg/m^2 and defined obesity as a BMI $\geq$ of 30 kg/m^2. We also measured waist and hip circumferences with a non-extensible tape using previously standardized methods.[13]

Spirometry

A forced vital capacity maneuver with a calibrated spirometer (Quark PFT, COSMED, Pavonadi Albano, Italy) was performed according to the criteria established by the American Thoracic Society.[14] We quantified the FEV1, FVC, and FEV1/FVC ratio. For those who had FEV1/FVC < 0.7 on prebronchodilator spirometry, we conducted forced spirometry 15 min after the patient inhaled 400 μg of salbutamol.[15,16]

Cardiopulmonary exercise testing

Following a ramp protocol, we performed CPET on a treadmill (ATL, Inbrasport, Curitiba, Brazil), with individualized speed and inclination increases based on the estimated $\dot{V}O_{2max}$.[9] Metabolic, cardiovascular, and ventilatory responses were measured breath-by-breath using a gas analyzer (Quark PFT, COSMED, Italy). We performed the same altitude, atmospheric pressure, and temperature tests, and a cardiologist supervised all the tests. Oxygen uptake ($\dot{V}O_2$) breath-by-breath was measured and the average $\dot{V}O_2$ was calculated every 15 s. The arithmetic average of $\dot{V}O_2$ in the last 15 s at the end of the test, just before the recovery phase, was considered representative of $\dot{V}$ O_{2max}. Maximum effort was defined as a maximum heart rate above 85% of the predicted value (220 − age_{years}) and gas exchange rate ($\dot{V}CO_2$ / $\dot{V}O_2$) > 1.0. CPET was conducted with continuous monitoring of the electrocardiogram.

Six-minute walk test

We performed the 6MWT according to the guidelines of the American Thoracic Society and European Respiratory Society.[3] Since the literature suggests no learning effect of the 6MWT in apparently healthy individuals, we conducted only one test in the present study.[17] We instructed individuals to walk the maximum distance possible for six minutes on a 30 m long, flat, and straight corridor indoors. Two traffic cones indicated the route, and the hallway was marked every 3 m. Standardized instructions and verbal encouragement were provided to the participants every minute. We registered the 6MWT distance in meters and the percentage of the predicted values.[17]

Statistical analysis

We performed a descriptive analysis of the data presented as mean $\pm$ standard deviation for continuous variables and frequencies and percentages for categorical variables. We compared the results of men and women using the Student's t-test for independent samples (continuous variables) and the x^2 test (categorical variables). We also evaluated the best-fit correlation between 6MWT distance and $\dot{V}O_{2max}$ (e.g., linear, exponential, and quadratic, using the statistical package curve estimation tool).

We determined age- and sex-related changes in $\dot{V}O_{2max}$ and 6MWT distance using box plot graphs, wherein we calculated the average decline per decade (18–29, 30–39, 40—49, 50–59, 60—80 years) and sex-related differences were calculated. We evaluated the interaction between sex and age using a two-way analysis of variance (ANOVA) considering the aforementioned age groups and sex as factors.

Descriptive statistics were used to elaborate tables of norms for $\dot{V}O_{2max}$ and 6MWT distance. We calculated the median of the values (50th percentile) and the 5th, 25th, 75th, and 95th percentiles, representing very low, low, regular, good, excellent, and superior CRF.

So that our results could be used in other countries, we developed a CRF classification based on the 6MWT distance, expressed as a percentage of the predicted value.[17] $\dot{V}O_{2max}$ was used as the gold standard criterion to develop ROC curves, in which we identified the 6MWT distance with the best combination of sensitivity and specificity to predict the classification of $\dot{V}O_{2max}$. We calculated the areas under the ROC curves and considered those with values > 0.80 as excellent and those with values between 0.70 and 0.80 as good.[18] The other values were deemed inadequate.

The probability of alpha error was set at 5% for all analyses. Statistical analyses were performed using STATA software, version 14, and MedCalc software, version 19.

Results

In total, 1525 participants were assessed for eligibility, and 1517 met the inclusion criteria. Of these, 1447 participants completed all of the assessments. After exclusion, the results of 1295 men and women aged from 18 to 80 years were analyzed (Fig. 1).

The participants were predominantly women (60%). On average, they were middle-aged and overweight. Women showed a higher cardiovascular risk than men (Table 1).

The proportion of accelerometer-based physical inactivity was lower (30%) than that described for the general population. The participants used the accelerometer for 884 $\pm$ 76 min/day. The percentages of total time spent in sedentary behavior, light physical activity, and moderate-to-vigorous physical activity were 73%, 22%, and 5%, respectively.

Considering the age groups of 18–29, 30–39, 40—49, 50–59, 60–69, and 70–80 years, $\dot{V}O_{2max}$ declined with advancing age per decade in men by 9.2%, 8.7%, 8.8%, 8.1%, and 8.8%, and women by 9.4%, 8.7%, 7.8%, 9.4%, 8.2%, both averaging 8.7% per decade. There was a significant interaction between age and sex, with $\dot{V}O_{2max}$ always

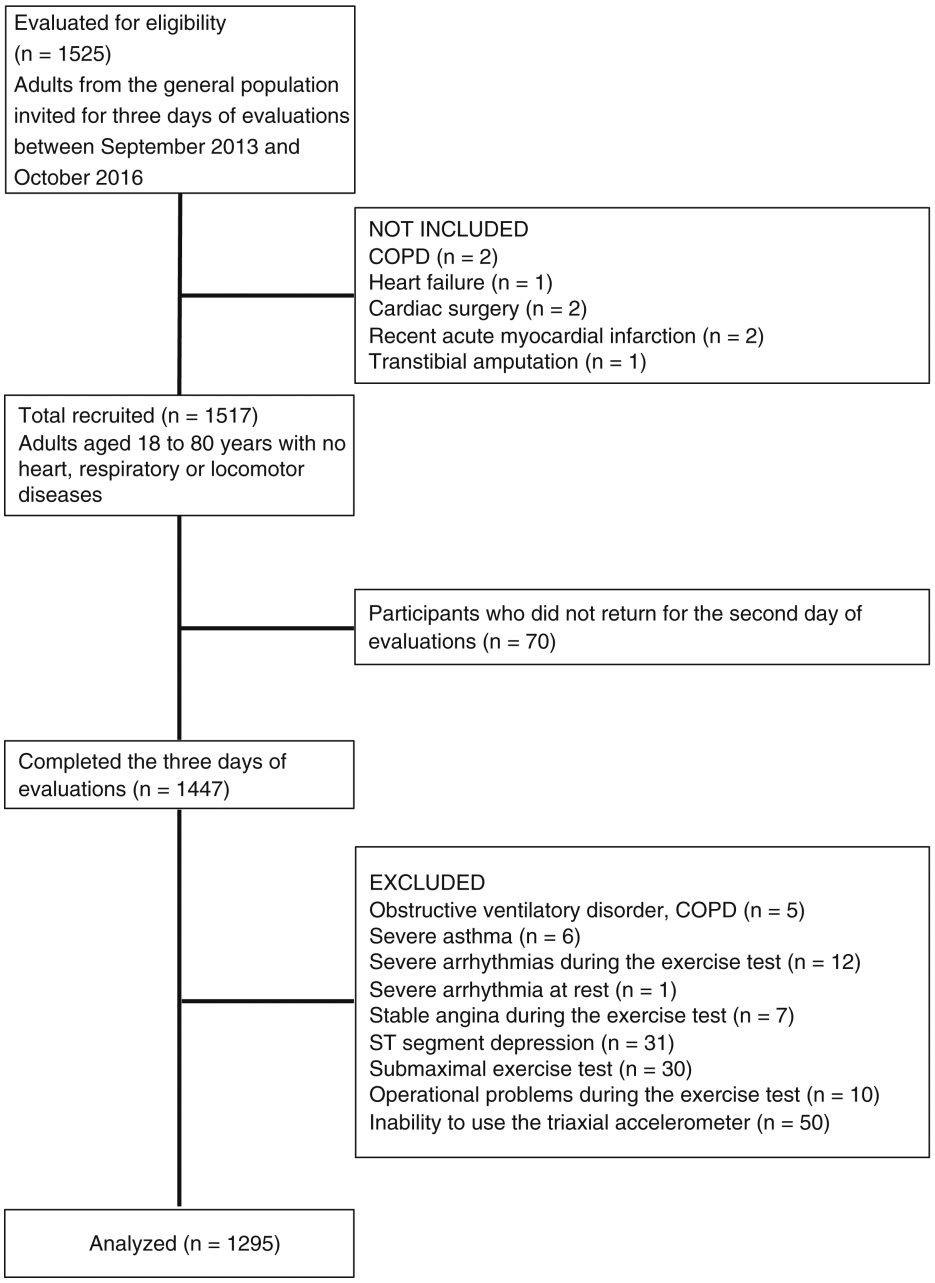

Figure 1 Flowchart of the study.

being significantly higher for men. However, such differences decreased progressively with advancing age (Fig. 2A).

Regarding the 6MWT distance in the age groups 18–29, 30–39, 40—49, 50–59, 60–69, and 70–80 years, the decline per decade was 9.8%, 9.5%, 9.1%, 9.5% and 8.8% for women and 9.9%, 9.4%, 9.5%, 9.9%, and 9.2% for men. On average, the 6MWT distance declined by 9.3% and 9.5% per decade for women and men, respectively. Unlike $\dot{V}O_{2max}$, we observed an interaction between sex and age with considerable differences between men and women with advancing age (Fig. 2B).

The 6MWT distance showed a significant correlation with $\dot{V}O_{2max}$, best explained by an exponential equation, with an evident ceiling effect for participants with a higher $\dot{V}O_{2max}$. The 6MWT distance alone explained approximately 55% of the total $\dot{V}O_{2max}$ variability (Fig. 3).

We stratified the CRF classification table as very low, low, regular, good, excellent, and superior considering a balanced proportion of participants in the age groups of 18—27, 28—34, 35—42, 43—51, 52—59, and 60—80 years, according to $\dot{V}O_{2max}$ (Table 2) and 6MWT distance (Table 3).

The percentage of the predicted 6MWT distance showed excellent ability to predict very low CRF, considering the CRF classification obtained using $\dot{V}$ O_{2max} as the gold standard. It was also able to predict low, excellent, and superior CRF well, although it could not differentiate between regular and good CRF (Fig. 4). Based on the cut-off values obtained through ROC curves, we classified the CRF based

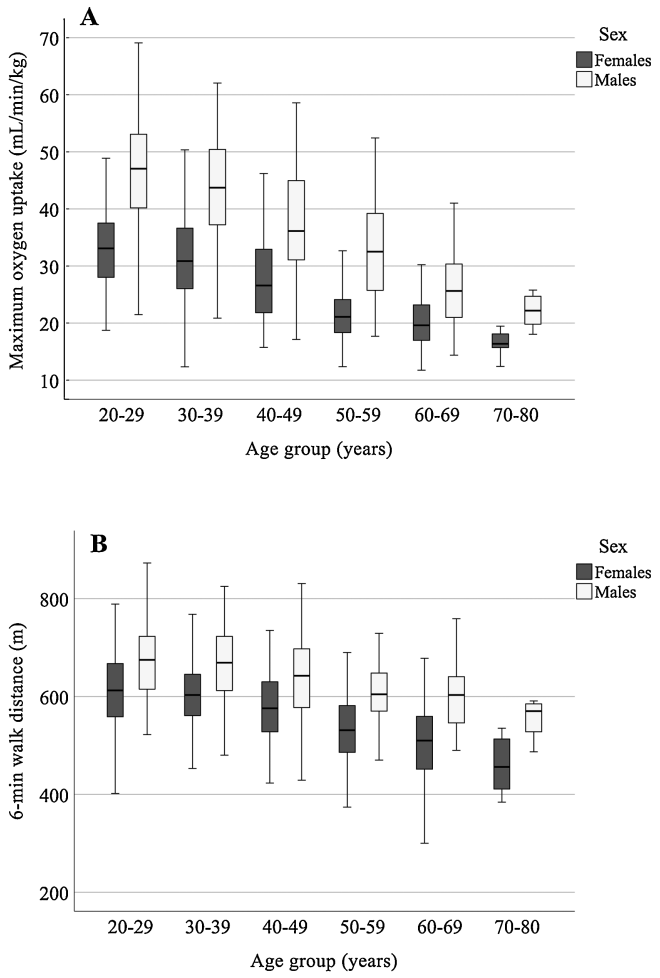

Figure 2 Age- and sex-related changes in cardiorespiratory fitness in the studied sample. Maximum oxygen uptake ($\dot{V}$ O_{2max}) declined with advancing age, per decade, in men (9.2; 8.7; 8.8; 8.1; and 8.8%) and women (9.4; 8.7; 7.8; 9.4; 8.2%) with a significant interaction between sex and age, indicating reduction of the difference with aging (A). The distance covered in the six-minute walk test declined by 9.8, 9.5, 9.1, 9.5 and 8.8% for women and 9.9, 9.4, 9.5, 9.9 and 9.2% for men with a significant interaction between sex and age, indicating increased difference with aging.

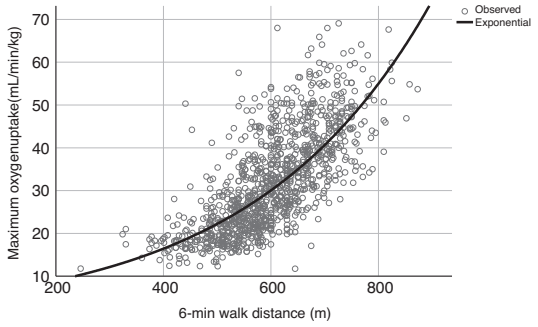

Figure 3 Correlation between the distance covered in the six-minute walk test and maximum oxygen uptake ($\dot{V}O_{2max}$) obtained in the cardiopulmonary exercise test ($R^2 = 0.548$).

Table 1 General characteristics of the studied sample.

	Females (n = 777)	Males (n = 518)
Age (years)	42 ± 14	40 ± 13
Weight (kg)*	72.4 ± 16.8	81.3 ± 15.6
Height (m)*	1.59 ± 0.06	1.73 ± 0.07
Body mass index (kg/m^2)*	28.6 ± 6.3	27.0 ± 4.6
Waist circunference (cm)*	88 ± 15	90 ± 13
Hip circunference (cm)*	105 ± 13	100 ± 9
Waist to hip ratio*	0.86 ± 0.08	0.89 ± 0.07
Lean body mass (kg)*	46.5 ± 7.6	62.7 ± 9.1
Lean body mass (% of total)*	65.0 ± 7.9	77.7 ± 7.2
Fat body mass (kg)*	26.1 ± 10.9	18.9 ± 9.4
Fat body mass (%)*	34.6 ± 7.4	22.1 ± 6.8
FVC (L)*	3.15 ± 0.64	4.77 ± 0.86
FVC (% pred.)*	95.7 ± 13.7	97.3 ± 12.9
FEV1 (L)*	2.60 ± 0.56	3.82 ± 0.74
FEV1 (% pred.)	95.5 ± 13.4	95.0 ± 13.7
FEV1/FVC (%)*	82.4 ± 5.9	80.7 ± 7.5
Cardiovascular risk, n (%)		
Family history*	265 (34.1)	126 (24.3)
Arterial hypertension*	162 (20.8)	54 (10.4)
Diabetes mellitus*	88 (11.3)	25 (4.8)
Dyslipidemia*	224 (28.8)	74 (14.3)
Current smoking	96 (12.4)	51 (9.8)
Physical inactivity#,*	192 (24.8)	103 (20.0)

FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s.
* $p < 0.05$: males vs. females.
\# Directly assessed by triaxial accelerometers.

on the 6MWT distance as a percentage of the predicted (Table 4).

Discussion

To the best of our knowledge, this is the first study to formulate CRF classification tables using the 6MWT distance rather than the gold standard ($\dot{V}O_{2max}$). We present CRF classification tables based on a simple, valid, reliable, reproducible, and responsive field test to express CRF. The 6MWT distance classification was valid for mainly identifying individuals with low CRF. Our results will allow a more straightforward screening of cardiovascular risk in the clinical setting.

The 6MWT can be performed in corridors as short as 20 m, and, in case of mild outdoor temperature, outdoors, which opens up varying prospects for using the 6MWT in clinical practice as a routine strategy. We observed that the relationship between the 6MWT distance and $\dot{V}$ O_{2max} was not linear. Our results indicate what has already been described as a ceiling effect, i.e., after a certain distance, minimal increases in the 6MWT distance are associated with substantial changes in $\dot{V}O_{2max}$.[19] Therefore, we believe that our research meets the current AHA recommendations regarding the importance of routinely assessing and improving CRF in the clinical setting.[1]

One of the most relevant results of the present study was the creation of a CRF classification table based on the 6MWT distance, facilitating the interpretation of CRF assessments

Table 2 Classification of cardiorespiratory fitness for men and women based on maximum oxygen uptake ($\dot{V}O_{2max}$) obtained directly in a cardiopulmonary exercise test on a treadmill following a ramp protocol.

Age (years)	Very low	Low	Regular	Good	Excellent	Superior
Males						
18—27	<31	31—40	41—47	48—53	54—62	>62
28—34	<27	27—37	38—43	44—49	50—61	>61
35—42	<25	25—34	35—42	43—49	50—56	>56
43—51	<19	19—30	31—35	36—42	43—53	>53
52—59	<18	18—25	26—32	33—39	40—49	>49
60—80	<17	17—21	22—25	26—31	32—47	>47
Females						
18—27	<21	21—28	29—33	34—38	39—48	>48
28—34	<19	19—26	27—30	31—36	37—45	>45
35—42	<17	17—24	25—30	31—35	36—44	>44
43—51	<16	16—20	21—24	25—32	33—43	>43
52—59	<14	14—18	19—21	22—24	25—30	>30
60—80	<13	13—16	17—19	20—22	23—27	>27

*According to the percentiles found: very low, <5th; low, 5th to 25th; regular, 26th to 50th; good, 51 st to 75th; excellent, 76th to 95th; higher >95th. $\dot{V}O_{2max}$ values presented in mL/min/kg.

Table 3 Classification of cardiorespiratory fitness for men and women based on the distance covered in a six-minute walk test.

Age (years)	Very low	Low	Regular	Good	Excellent	Superior
Males						
18—27	<564	564—614	615—677	678—724	725—817	>817
28—34	<544	544—611	612—663	664—713	714—776	>776
35—42	<522	522—607	608—668	669—720	721—780	>780
43—51	<490	490—567	568—627	628—692	693—742	>742
52—59	<475	475—576	578—606	607—656	657—758	>758
60—80	<447	447—546	547—591	592—630	631—756	>756
Females						
18—27	<489	489—570	571—621	622—669	670—754	>754
28—34	<504	504—552	553—603	604—642	643—738	>738
35—42	<489	489—562	563—600	601—640	641—690	>690
43—51	<441	441—519	520—567	568—627	628—688	>688
52—59	<418	418—486	487—525	526—579	580—652	>652
60—80	<370	370—445	446—510	511—558	559—645	>645

*According to the percentiles found: very low, <5th; low, 5th to 25th; regular, 26th to 50th; good, 51st to 75th; excellent, 76th to 95th; higher >95th. Six-minute walk distance values presented in meters.

Table 4 Classification of cardiorespiratory fitness based on the distance covered in the six-minute walk test compared to the maximum oxygen uptake obtained in the cardiorespiratory exercise test (gold standard criterion).

Classification	6-min walk distance (% pred.)
Very low	≤96
Low	97–103
Regular/Good	104–106
Excellent	107–109
Superior	109

% predicted by Iwama et al.[10]

via field tests in different clinical settings. Normal values were calculated and ROC curves were used to validate our data valid for identifying people with different CRF classifications. Therefore, if the 6MWT distance is expressed as a percentage of the predicted value, we may assume that our results will be valid internationally.

Considering the AHA's recommendations on the importance of identifying people with low CRF to prevent cardiovascular diseases,[1] our study makes it possible to estimate and interpret CRF in a straightforward, inexpensive, and effective way for clinical practice. We identified, with excellent sensitivity and specificity, very low CRF. In addition, we verified that a 6MWT distance <96% is a critical point for identifying individuals with CRF below the normal range. Sperandio et al.[20] obtained the same cut-off point to identify physically inactive individuals evaluated using accelerometers. These results indicate that a 6MWT distance below 96% is equally crucial for identifying low physical activity levels and fitness levels.

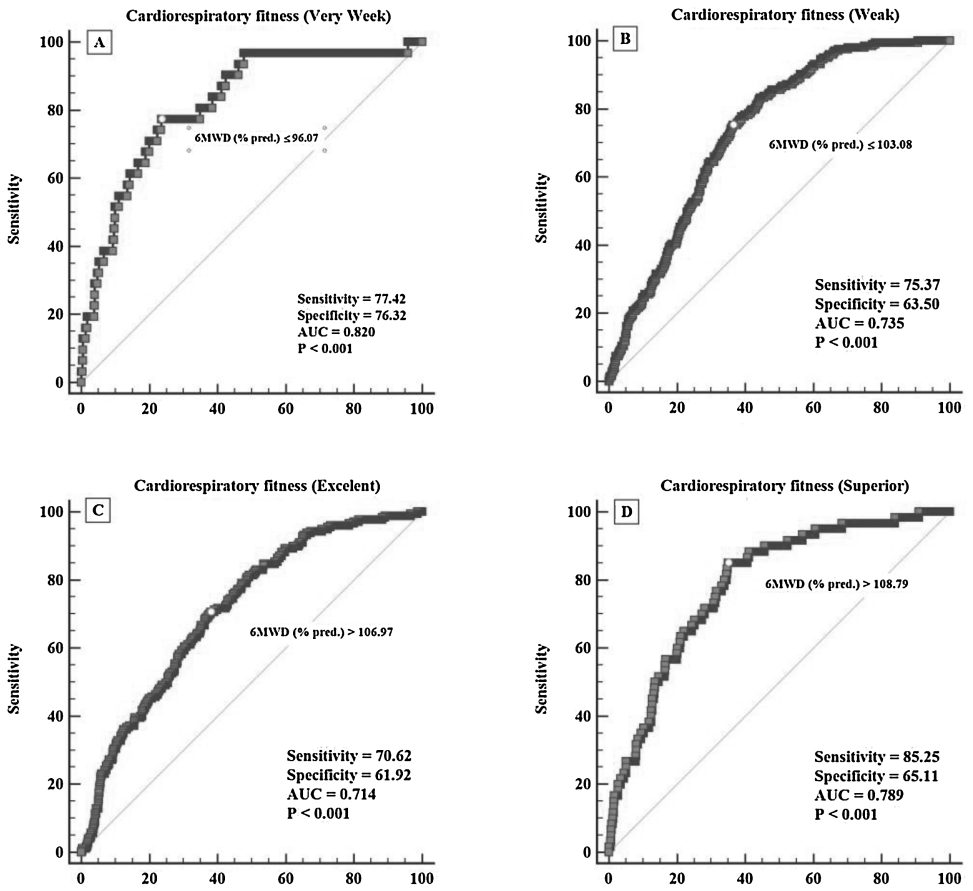

Figure 4 Receiver operational curves (ROC) for assessing the sensitivity and specificity of the distance covered in the six-minute walk test to identify individuals with the following percentiles of cardiorespiratory fitness classification: very low (A), < 5th; low (B), 5th to 25th; excellent (C), 76th to 95th; and superior (D) > 95th, according to the maximum oxygen uptake obtained in the treadmill cardiopulmonary exercise test.
AUC: area under the ROC curve.

There are several equations to predict the 6MWT distance in our population.[21–24] Britto et al.'s[24] equation has been suggested as the most suitable.[25] However, we have been using the equation proposed by Iwama et al.[17] for several years. In addition to not offering significantly different results, both for healthy individuals[23] and patients with chronic lung disease,[26] the equation proposed by Iwama et al.[17] has some advantages. First, due to its adequate cross-validation performed in another research center with different researchers.[27] Second, information on physical activity levels was evaluated using a validated instrument.[28] Third, the equation was developed for adults of a wide age range (18–84 years). Lastly, we calculated the 6MWT distance values obtained in the present study as the percentage of the predicted values using the equations of Brito et al.[23] and Iwama et al.,[17] resulting in a difference of only $1 \pm 6\%$ between the equations, which would hardly compromise the interpretation of the data described here.

We assessed the age- and sex-related changes in the 6MWT distance in adults over a wide age range sample size. The decline in $\dot{V}O_{2max}$ per decade found in the present study is very consistent with that previously described in Brazil and other countries.[29–32] Our results also reinforce previous data, indicating a decrease in CRF across the lifespan irrespective of sex.[33] Even so, the sex-related differences in CRF seem to be more pronounced earlier in life and begin to narrow in older adults.

Unlike $\dot{V}$ O_{2max}, for which sex-related differences decreased with advancing age, the 6MWT distance showed differences between men and women progressively increasing with advancing age.[29–32] Advanced age compromises the levels of anabolic hormones and the number of type II muscle fibers, more pronounced than in young men. Considering that the CPET is a maximal test, it requires the recruitment of fast-twitch motor units during a significant part of the test, justifying the lower advantage of men in the most advanced age groups. On the other hand, the 6MWT is a submaximal test that requires much less contribution from type II muscle fibers. The dynamic $\dot{V}O_2$ behavior during the 6MWT is monoexponential, with a tendency to stabilize after the third minute of the test.[19,24,34] Thus, the most considerable differences between men and women in older age occurred because 6MWT is performed mainly with oxidative metabolism in energy production.

Several studies have developed predictive models for $\dot{V}O_{2max}$ using non-exercise variables. In summary, these studies showed that regardless of the standard error of the estimate described, the models improved the prediction of

cardiovascular risk.[35] Therefore, considering the standard error of the exponential equation that we have proposed here to estimate V Ȯ2max based on the 6MWT distance, we believe that our results will be beneficial for routine CRF assessment in clinical practice.

This study has practical implications for health. First, the normality tables for the 6MWT can help assess and monitor CRF in the general population and patients with chronic diseases, improving overall cardiovascular risk screening. The strength of this study is that it provides a CRF classification table using a simple field walking test compared to a treadmill ramp protocol CPET in the Brazilian population. Further, despite its development in a specific population, we defined the CRF classification using 6MWT distance as % predicted, which opens up the opportunity to use our results internationally.

As limitations, we could cite the cross-sectional design as one of them, mainly considering the age- and sex-related changes in $\dot{V}O_{2max}$ and 6MWT distance. However, it should be recognized that the decline mentioned above obtained in longitudinal investigations may introduce bias from the loss of participants with lower levels of physical activity and fitness to follow-up. While the convenience sample could be a limitation, our main objective was to elaborate tables for CRF classifications; thus, the broad range of physical activity and fitness level becomes a potential instead. In addition, our sample's sociodemographic characteristics are quite similar to those of the general population in Brazil, apart from the level of education.

We conclude that the classification of CRF using the 6MWT distance is valid compared to the directly evaluated CRF ($\dot{V}O_{2max}$), especially for identifying adults with low CRF. Altogether, our results could be used in clinical practice to better screen and monitor cardiovascular risk in adults in the general population and in patients with chronic diseases.

Author contributions

VD is the guarantor of the study and takes responsibility for the accuracy of the data. VD and RN played the most crucial roles in this study and were responsible for study design and conception, statistical analysis, interpretation of the results, drafting, writing, and submission of the manuscript. MS, VL, AG, MR, and RA contributed to the study's conception and design, data collection, interpretation of the results contributed to drafting the article and critically revised it for relevant intellectual content. RA also contributed to exercise test supervision and was the main factor responsible for granting our participants' safety. ST and IG contributed to interpreting the results, article drafting, and critical revisions for prominent intellectual content.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Continuous noninvasive ventilatory support outcomes for patients with neuromuscular disease: a multicenter data collaboration

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Abstract
Background: Typically, patients with progressive neuromuscular disorders (NMDs) develop acute respiratory failure (ARF), are intubated, and when failing spontaneous breathing trials (SBTs) undergo a tracheotomy and receive tracheostomy mechanical ventilation (TMV). However, increasing numbers of patients use nasal noninvasive ventilation (NIV), initially for sleep and this is extended to continuous dependence (CNVS). This can be used as a strategy to assist in successful extubation . We retrospectively reviewed 19 centers offering CNVS and mechanical insufflation-exsufflation (MI-E) as an alternative to TMV.
Methods: Centers with publications or presentations concerning CNVS outcomes data were pooled for amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy (DMD), and spinal muscular atrophy type 1 (SMA1). Progression to CNVS dependence without hospitalization, duration of dependence, and extubations and decannulations to CNVS were recorded. Prolongation of life was defined by duration of CNVS dependence without ventilator free breathing ability (VFBA).
Results: There were 1623 part time (<23 h/day) NVS users with ALS, DMD, and SMA1 from 19 centers in 16 countries of whom 761 (47%) were CNVS dependent for 2218 patient-years. This included: 335 ALS patients for a mean 1.2 ± 1.0 (range to 8) years each; 385 DMD patients for 5.4 ± 1.6 (range to 29) years; and 41 SMA1 patients for 5.9 ± 1.8 (range to 20) years. Thirty-five DMD and ALS TMV users were decannulated to CNVS and MI-E. At data collection 494 (65%)

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patients were CNVS dependent but 110 (74 of whom with bulbar ALS), had undergone tracheotomies.
Conclusions: ALS, DMD, and SMA1 patients can become CNVS dependent without requiring hospitalization but CNVS cannot be used indefinitely for many patients with advanced upper motor neuron diseases.

Introduction and historical perspective

There have now been over 100 peer-reviewed articles, reviews and consensus papers on sleep and noninvasive ventilation (NIV). "NIV" has become synonymous with continuous positive airways pressure (CPAP) or bi-level positive airway pressure (BiPAP). All reported benefits but, there have not been any reports highlighting NIV for full ventilatory support. Nor, are there reports of the use of MIE with noninvasive ventilatory support (NVS) settings used in the 1950s as an alternative to TMV.[1] Survival is usually reported to be prolonged on the basis of randomizing sleep NIV with untreated cohorts. However, patients continue to weaken and develop ARF during respiratory tract infections irrespective of NIV use, when intubated, these patients often fail to wean and they undergo tracheotomy. However, in patients who lose all ventilator free breathing ability (VFBA), they typically have less than 100 ml of vital capacity (VC) and are apneic upon ventilator disconnection. Some centers have demonstrated that continuous noninvasive ventilatory support (CNVS) along with mechanical insufflation-exsufflation (MI-E) can be used indefinitely instead of tracheostomy mechanical ventilation (TMV) and ventilator "unweanable" patients can be extubated and decannulated to CNVS and MI-E.

Although in 1987 we first published CNVS via a nasal interface for a multiple sclerosis patient with no VFBA and 100 ml of VC,[2] with the release of a bi-level pressure cycled mode (BiPAP™, Respironics Inc., Murrysville, Pa) devices in 1990, NMD patients are being placed on BiPAP at less than NVS and full respiratory muscle rest settings. With advancing disease, some have had their sleep bi-level mode settings increased and were commenced on daytime mouthpiece NVS with a volume-cycled mode, however, once intubated for any reason they received a tracheotomy rather than continue CNVS.[3-7] Typically, most clinicians still do not offer diurnal mouthpiece (Fig. 1) and nasal NVS, when mask NIV use exceeds 15—20 h and tracheostomy is therefore recommended.

Indeed, even in 2015 diurnal mouthpiece NVS was described as a "novelty"[8] despite the fact that CNVS via mouthpiece was first described in 1953 and 257 such cases were reported in 1993.[4,9,10] In 1953, Dr. John Affeldt wrote that patients can have a simple mouth piece "...hang in the mouth, we even had one patient who has no breathing ability who has fallen asleep and been adequately ventilated by this procedure."[9]

In 1956 Hodes noted, "...tracheotomy may be a great disadvantage. It is very difficult to get rid of a tracheotomy tube when the VC is only 500 or 600 cc and there is no power of coughing, whereas, as we all know, a patient who has been treated in a respirator (body ventilator) from the first can survive and get out of all mechanical devices with a VC of that figure."[11] Thus, it was understood that tracheostomies could increase ventilator dependence because of inspiratory muscle deconditioning, tube induced secretions, hyperventilation by bypassing upper airway afferents, and possibly other factors.[12] As a result of TMV complications, a switch back to noninvasive approaches began in the 1980s.[13,14] However, CNVS and MI-E can only be a definitive alternative to TMV if patients can be extubated back to them during intercurrent intubations for ARF which several centers have reported doing.[15,16]

Airway secretion congestion, especially during intercurrent respiratory tract infections, causes 90% of episodes of ARF and intubations for Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA) type 1 patients,[6,17,18] and results in tracheotomies[19—21] when CNVS and MI-E are not used[17,22—24] to facilitate extubation.[15,16] Unlike invasive suctioning, MI-E does not favor right over left airways.[25—27] It can also be used via invasive airway tubes and has been reported to be critical for the successful extubation/decanulation of "unweanable" patients[13,16] as well as decreasing hospitalization rates.[17,22,28]

Thus, while the benefits of Bi-level NIV have been reported to be many but brief,[29—31] the purpose of this work is to demonstrate that CNVS can be used indefinitely as an alternative to TMV to prolong survival for years for patients with advanced NMD and patients can become dependent on CNVS with no VFBA without hospitalization.

Methods

The participating centers had a multidisciplinary team that included medical doctors and/or respiratory (physio)therapists with more than 10 years of experience in CNVS and MI-E in neuromuscular disorders with scientific presentations and peer-reviewed publications in these areas of research. Some centers also reported extubating ventilator unweanable patients to CNVS and MI-E. The participating clinicians obtained consent for the chart reviews from their Institutional Review Boards (IRBs) or ethics committees, however, three of the centers did not have them.

Nocturnal nasal NVS or Bi-level mode at NVS settings of greater than 15 cm H_2O pressure support were introduced to patients with symptomatic hypoventilation. When symptoms were unclear, SpO_2/end-tidal, transcutaneous carbon dioxide (CO_2) monitoring, or polysomnography was performed depending on the particular center. Typically, settings were prescribed over a volume range of 700—1500 ml or assist-control or pressure support pressures of 15—25 cm H_2O and therapists worked with patients to choose their desired

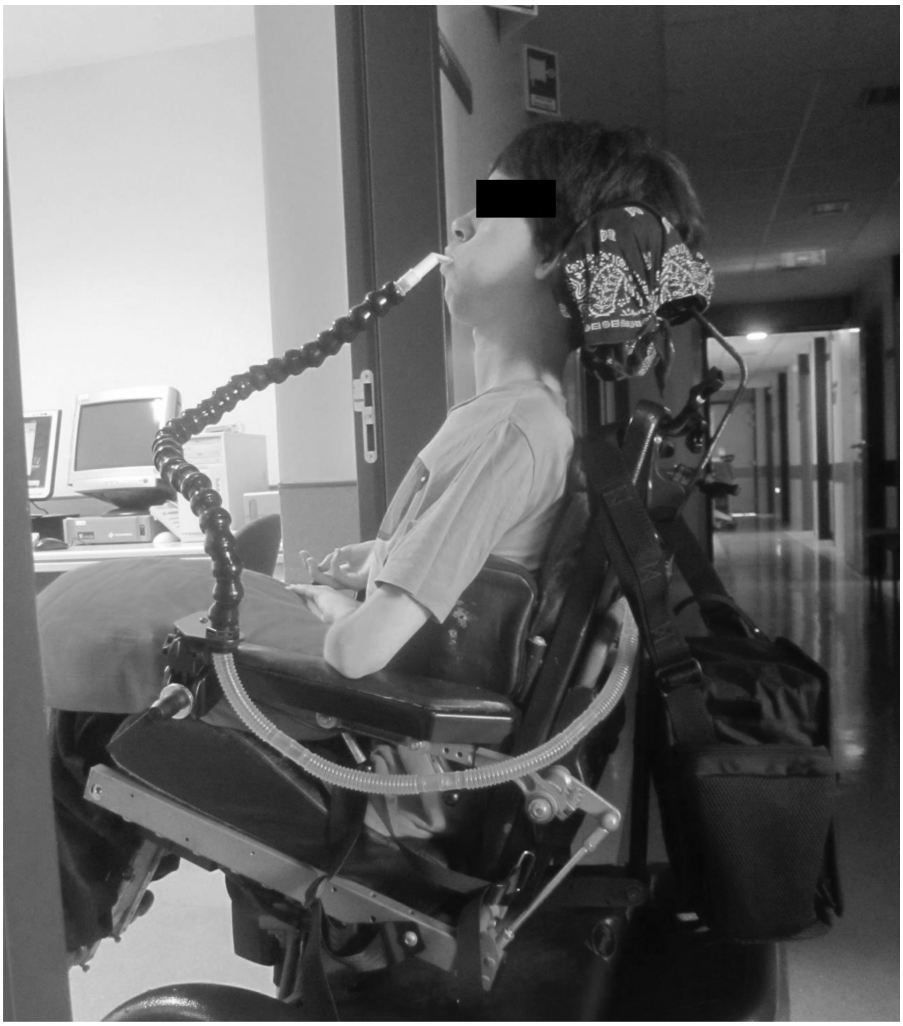

Figure 1 Patient with Duchenne Muscular Dystrophy using a 15 mm angled mouthpiece for daytime noninvasive ventilatory support. He has depended on continuous noninvasive ventilatory support for 10 years.

settings. Physiologic back-up rates for age were prescribed. No expiratory PAP or positive end-expiratory pressure (PEEP) was used in centers where portable ventilator circuits had an active valve circuit, otherwise bi-level devices were used at NVS settings. According to clinical indication, during nocturnal NVS, all patients used active external humidification devices.[32]

The extent of need for NVS was divided into Grades of 0—4. Patients with grades of 1—4 can become dependent on CNVS and MI-E temporarily or permanently when acutely ill. Grade 4 CNVS dependent patients become dyspneic with O_2 desaturation within seconds to minutes of disconnection and cannot survive without it (Fig. 1).

While European and North American centers typically used homecare life support ventilators (pressure and volume modes with internal batteries), these were often too expensive for South and Central American centers. These centers used homecare bi-level devices, with IPAP's typically to 20—25 cm H_20. including, at times, for daytime mouthpiece NVS. Bi-level devices were used at NVS settings with inspiratory pressures over 15 cm H_2O and minimum EPAP's. In all centers, patients performed LVR using manual resuscitators and volume cycling during the day. Nasal interfaces were used for sleep and often for daytime NVS. South American centers generally used MPV via a BiPAP device via angled mouthpieces with an HME in the circuit. More recently, the homecare life support ventilators have become more available but, are used with less expensive, disposable passive circuits for diurnal mouthpiece NVS with volumes of 700—1500 mls. Acutely ill intubated patients of the centers underwent tracheotomies elsewhere.

Likewise, the standard MI-E devices are generally unavailable in South America so inexpensive, locally produced MI-E devices and manually assisted coughing are used. As a result, MI-E-exsufflation flows (MI-E-EF) cannot usually be measured. A manual resuscitator and abdominal thrusts are used for manually assisted coughing. Patients are typically hospitalized to initiate NIV but some were also set up at regular out-patient visits, or in their homes depending on the center.

The data for DMD, ALS, and SMA1 were collated to determine duration of part-time (Grades 1—3) and for Grade 4 or CNVS dependence. Progression to CNVS without hospitalization, and numbers of extubations and decannulations of patients who could not pass SBTs before or after extubation or decanulation were also collate. Prolongation of life was

quantitated by duration of dependence on CNVS such that discontinuing it resulted in acute respiratory distress, blood gas deterioration, and certain death without quickly returning to it. Most had VCs of 0 to 250 ml but only a few centers monitored spirometry.

Descriptive data are reported as mean ± standard deviation (SD) with analysis performed by SPSS software (Release 24.0 SPSS, Chicago, I1, USA).

Results

Of the 23 centers contacted, 18 took part from 16 countries. Clinicians from five centers declined to participate either in order to publish independently (3 cases) or because of inadequate resources to gather data. Thirty-two clinicians from the 19 centers had 1623 NVS users.

The patients with Grades 1−3 dependence, their ages at onset and duration of part-time use, the number advanced to CNVS dependence and its duration, current age, the extubations and tracheostomy tube decannulations to CNVS, and the deaths while using CNVS or after undergoing tracheotomy are noted in Tables 1−3.

Of the 1623 part-time nasal NVS users, 761 progressed to CNVS dependence with no VFBA for 2218 patient-years of prolonged survival, 1148 patient-years for DMD, 577 for ALS, and 193 for SMA 1, without tracheostomies. At least 219 patients reported by 6 of the 19 centers progressed to CNVS without being hospitalized or developing ARF. This included 120 DMD patients from 6 centers, 85 ALS patients from 4 centers, and 14 SMA 1 patients from 3 centers. Since NVS was only begun for symptomatic hypoventilation, patients were told to use it only if benefits outweighed inconvenience. Since a variety of nasal, oro-nasal, and mouthpiece interfaces was offered, intolerance was limited to advanced bulbar ALS patients whose principal respiratory symptoms were due to stridor from upper airway collapse and airway secretion congestion rather than from hypoventilation. No DMD or SMA1 patients failed to tolerate NVS, and subsequently CNVS, and there were no skin or other complications that prevented use.

Only 8 of the 19 centers extubated/decannulated patients who failed all weaning parameters to CNVS and MIE.[16] Of 255 patients who were unweanable before and immediately after extubation, 252 were successfully extubated so only 3 ALS patients underwent tracheotomy due to multiple extubation failures in the 8 centers.

At the time of data collection 110 CNVS users had undergone tracheotomy, 108 of whom as a result of an episode of ARF not managed by the 8 centers that used the extubation protocol.[16] Thus, all of the DMD and most of the SMA1 patients who ultimately underwent tracheostomy did so at non-participating centers. Outcomes as a function of diagnosis are listed in Tables 1−3.

Discussion

Our results demonstrate that CNVS can prolong life for years for patients with little to no VFBA for patients without upper motor neuron signs and without resorting to tracheostomy. CNVS can even be used indefinitely for patients with little or

Table 1 Data on Amyotrophic lateral sclerosis.

Center	Number ptNIV	Age ptNIV (years)	Duration ptNIV (years)	Number CNVS	Age CNVS (years)	Duration CNVS (years)	Current Age (years)	Number CNVS noHosp	Extubations	Decannulations	Still Alive using CNVS	Deaths using CNVS	Total TMV
A	64	58.5 ± 12.0	0.9 ± 1.4	38	60.9 ± 10.4	2.3 ± 2.1	63±12.7	25	7	3	15	15	8
B	176	52.5 ± 5.6	0.9 ± 1.1	109	53.3 ± 5.3	0.8 ± 2.2	54.6 ± 5.7	34	15	6	67	42	22
D	62	58.0 ± 13.4	1.9 ± 1.9	20	57.1 ± 12.6	0.7 ± 0.6	61.4 ± 12.2	4	0	0	8	12	7
F	23	55±14	1.3 ± 1.6	11	55±15	1 ± 0.9	60±2	NK	4	1	2	9	5
G	83	56.1 ± 9.0	0.9 ± 0.9	19	55.5 ± 9.0	1.1 ± 2.1	NK	NK	0	0	6	13	6
I	4	67.8 ± 6.9	1.3 ± 0.8	4	69.3 ± 6.6	2.0 ± 1.9	70.5 ± 8.4	NK	0	0	1	3	1
J	78	59.5 ± 9.4	0.9 ± 1.1	27	60.3 ± 1.3	0.6 ± 0.5	62.2 ± 9.1	NK	0	0	14	13	6
L	120	64±24.2	NK	47	NK	1.8 ± 0.8	NK	NK	NK	NK	34	13	7
O	13	59.3 ± 10.4	1.3 ± 0.8	13	59.3 ± 10.4	2.1 ± 2.5	NK	NK	0	0	NK	NK	NK
Q	49	61.9 ± 13.4	0.9 ± 1.0	22	NK	0.3 ± 0.7	70.4 ± 7.6	22	0	0	12	10	6
R	150	58.6 ± 24.5	NK	33	NK	1.9 ± 0.2	NK	NK	0	0	29	4	6
TOTAL	**822**	**57.9 ± 12.6**	**1.0 ± 0.8**	**335**	**56.2 ± 4.9**	**1.2 ± 1.0**	**59.3 ± 7.6**	**85**	**26**	**10**	**188**	**134**	**74**

Legend − Number ptNIV − number of patients using part time (<23 hr/day) noninvasive ventilation (NIV); Age ptNIV- age when beginning part-time NIV; Duration ptNIV- time of use of part time noninvasive ventilation (NIV); Number CNVS - number of patients progressing to full time dependence on continuous noninvasive ventilator support; Duration CNVS- duration of dependence on full time CNVS; Current Age - age currently or at time of death; Still Alive- number of CNVS users still alive; Extubations/Decanulations - Number of extubations/decanulations of "unweanable" patients to full-setting CNVS; Deaths − deaths when using CNVS or after undergoing tracheotomy for ventilatory support; TMV − number of CNVS patients undergoing tracheotomy; NK − not known.

Table 2 Data on Duchenne muscular dystrophy.

Center	Number ptNIV	Age ptNIV (years)	Duration ptNIV (years)	Number CNVS	Age CNVS (years)	Duration CNVS (years)	Current Age (years)	Number CNVS noHosp	Extubations	Decanulations	Still Alive using CNVS	Deaths using CNVS	Total TMV
A	18	16.3 ± 4.6	3.4 ± 1.8	14	20.4 ± 6.3	5.4 ± 4.4	20.1 ± 9.2	12	7	2	11	3	0
B	120	20.3 ± 2.8	2 ± 2.1	101	22.3 ± 5.9	7 ± 5.9	30.3 ± 6.1	23	29	9	87	14	0
C	88	18.9 ± 3.3	5.4 ± 3.3	56	24.7 ± 4.6	5.8 ± 3.4	31±5.2	NK	8	2	46	10	0
D	28	20.5 ± 4.1	4.7 ± 3.4	4	27.2 ± 6.2	2 ± 0.8	25.3 ± 4.5	0	0	1	1	3	0
E	38	12.8 ± 2.9	2.1 ± 1.2	2	12±0.3	1.4 ± 1.9	14.9 ± 3	1	1	0	2	0	1
F	16	21±4	2 ± 1.6	9	25±2	1.8 ± 1.3	25±1	NK	1	2	5	4	0
G	25	18.3 ± 4	3.5 ± 2.4	11	21.9 ± 2.4	5 ± 4.4	26.9 ± 4.3	9	2	1	8	3	0
H	24	18±1.6	9.9 ± 4.5	24	28.1 ± 4.6	4.2 ± 2.8	32.3 ± 2.8	24	0	0	24	0	0
I	10	22.7 ± 3.2	1.7 ± 1.9	10	24.3 ± 4.1	4.6 ± 1.6	28.4 ± 4.6	10	0	4	10	0	0
J	9	18.7 ± 5.2	4.6 ± 2.2	4	23.3 ± 6.5	4 ± 2.8	27±5	NK	0	0	3	1	1
K	100	18.9 ± 3.2	8.3 ± 4.3	56	23.6 ± 3.5	5.7 ± 3	28.7 ± 4.2	38	1	0	23	33	12
L	162	17±12.9	NK	51	NK	NK	27.5	NK	12	4	30	21	5
M	4	21.3 ± 3	5 ± 3	4	25±4	3.8 ± 1.4	28	NK	0	0	2	2	0
N	6	22±2.8	3 ± 1.1	6	25±2.4	4.9 ± 3.2	29.9 ± 3.6	NK	0	0	4	2	0
O	3	20±3.9	10±5.6	3	30±4	2.4 ± 1.4	32.4 ± 3.9	3	0	0	3	0	0
P	36	20.8 ± 4.6	3.3 ± 1.8	17	24.5 ± 4.5	4.0 ± 2.6	28.2 ± 4.9	NK	0	0	8	9	7
S	13	19.8 ± 2.8	5.7 ± 2.2	13	25.5 ± 4.2	4.8 ± 3.6	30.8 ± 4.2	NK	0	0	11	2	2
TOTAL	**700**	**18.2 ± 4.9**	**4.5 ± 2.7**	**385**	**22.6 ± 6.6**	**5.4 ± 1.6**	**27.2 ± 4.2**	**120**	**61**	**25**	**278**	**107**	**28**

Legend – Number ptNIV – number of patients using part time (<23 hr/day) noninvasive ventilation (NIV); Age ptNIV- age when beginning part-time NIV; Duration ptNIV- time of use of part time noninvasive ventilation (NIV); Number CNVS - number of patients progressing to full time dependence on continuous noninvasive ventilator support; Duration CNVS- duration of dependence on full time CNVS; Current Age - age currently or at time of death; Still Alive- number of CNVS users still alive; Extubations/Decanulations - Number of extubations/decanulations of "unweanable" patients to full-setting CNVS; Deaths – deaths when using CNVS or after undergoing tracheotomy for ventilatory support; TMV – number of CNVS patients undergoing tracheotomy; NK – not knowned; S – Data from Metro-Health Medical center, Case Western Reserve University, USA gathered by Dr. David Birnkrant with great appreciation.

Table 3 Data on Spinal muscular atrophy type 1.

Center	Number ptNIV	Age ptNIV (years)	Duration ptNIV (years)	Number CNVS	Age CNVS (years)	Duration CNVS (years)	Current Age (years)	Number CNVS noHosp	Extubations	Decannulations	Still Alive using CNVS	Deaths using CNVS	Total TMV
A	11	0.3 ± 0.3	0.2 ± 0.4	10	0.4 ± 0.2	2.4 ± 1.7	5.3 ± 3.1	7	8	0	6	4	3
B	76	0.4 ± 0.3	0.6 ± 0.1	22	0.9 ± 2.7	9.4 ± 3.5	10.3 ± 3.4	5	121	0	19	3	3
E	3	0.5 ± 0.45	0.3 ± 0.3	4	0.6 ± 0.65	0.2 ± 0	1.2 ± 0.4	2	0	0	0	4	1
F	3	0.7 ± 0.8	1.4 ± 2.2	3	0.3 ± 0.1	0.1 ± 0	5 ± 5	NK	0	0	2	1	1
L	7	0.9	NK	1	0.1	0.3	4.8	NK	13	0	0	1	0
O	1	0.5	0.4	1	0.5	4.5	5	NK	0	0	1	0	0
TOTAL	**101**	**0.44±0.2**	**0.57±0.5**	**41**	**0.7 ± 0.3**	**5.9 ± 1.8**	**7.6 ± 3.4**	**14**	**142**	**0**	**28**	**13**	**8**

Legend — Number ptNIV — number of patients using part time (<23 hr/day) noninvasive ventilation (NIV); Age ptNIV- age when beginning part-time NIV; Duration ptNIV- time of use of part time noninvasive ventilation (NIV); Number CNVS - number of patients progressing to full time dependence on continuous noninvasive ventilator support; Duration CNVS- duration of dependence on full time CNVS; Current Age - age currently or at time of death; Still Alive- number of CNVS users still alive; Extubations/Decanulations - Number of extubations/decanulations of "unweanable" patients to full-setting CNVS; Deaths — deaths when using CNVS or after undergoing tracheotomy for ventilatory support; TMV — number of CNVS patients undergoing tracheotomy; NK — not known.

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no bulbar-innervated muscle function or vital capacity (VC) as for the SMA type 1 patients, none of whom had upper motor neuron signs. Indeed, while DMD and SMA1 patients used CNVS to prolong survival for over 5 years, significantly longer than for ALS ($p < 0.001$), and many with SMA1 did so despite absence of all bulbar-innervated muscle function and VC, most ALS patients could not become CNVS dependent despite retaining some bulbar-innervated muscle function. Unlike the DMD and SMA1 patients, the ALS patients had stridor.

CNVS and MI-E can only replace inspiratory and expiratory muscle function. With severe bulbar involvement, the SMA type 1 patients have to be positioned to drool rather than aspirate and, indeed, since the initial data collection, these centers now have more than 15 CNVS dependent SMA1 patients over 20 years of age without tracheostomy tubes, despite CNVS dependence from as young as 4 months of age and no measurable VC. On the other hand, when ALS patients develop stridor, decreased MI-E-EF, and a decrease in baseline O2 saturation, tracheostomy becomes necessary for survival.[33−36] Thus, although the majority of DMD patients' and SMA1 patients' lives could be prolonged by CNVS, this was not the case for the majority of ALS patients.[23,30,37−39] This is the first multicenter report on prolonging life by CNVS that includes patients with little to no VFBA, indeed, some with no measurable VC.[23,31,37−40] Besides DMD, ALS, and SMA1 CNVS users, all of the centers had CNVS users with other NMD diagnoses as well.[42−46]

Thus far, life has been extended to over age 50 for DMD by CNVS,[7] and by a mean of 5.4 years for 385 DMD patients in this study,[6,41,42] to age 27 for SMA1 by dependence on CNVS from as young as 4 months of age,[43,44] and by a mean of over 1 year for 25 to 42%, and to a maximum of 8 years, for ALS patients.[45] Such outcomes suggest that commonly reported "NIV failure"[46−48] can result from inadequate NIV settings, failure to use MI-E at adequate settings, and failure to use diurnal NVS[5] and air stacking.[49] This explains the "preference" for tracheostomy for patients not offered CNVS and MIE.[50,51]

Whereas special expertise is required for noninvasive management, since 19% of 157 successfully extubated unweanable patients in one study had critical care neuromyopathies and not NMD, the expertise should not be limited to isolated centers. There should also be no "inability of local medical infrastructure to support NIV"[52] except in countries where ventilators are not funded at all.

The impact of disease and ventilatory dependence on patients' health, daily life and well-being should also be measured directly from the patients themselves, by means of validated health status questionnaires. It is important to apply short, valid and easy to use tools to monitor NVS in clinical practice to promote a more efficient organization of home mechanical ventilation services.[53]

Virtual reality may also be a promising technology for implementing personalized, motivating and controlled strategies for home mechanical ventilation in severe respiratory patients. These include, for example, mobile applications for the self-management and tele-monitoring systems, allowing personalized treatments and monitoring.[54]

In conclusion, ventilator dependent patients with no VFBA cannot survive without continuous ventilatory support. This is now being provided noninvasively by using CNVS supplemented by MI-E in some centers. Patients unable to pass SBTs can also be successfully extubated to CNVS and MI-E. MI-E needs to be used in critical care; staff needs to be instructed in CNVS and MI-E; and respiratory therapists need to be specifically trained and given the time needed to train patients. Since TMV is associated with poorer survival in DMD,[6,55] and poorer quality of life[40,56] than is CNVS, these outcomes beg for wider application.

Piepers et al. pointed out that "Analysis of subgroups of patients with disease (ALS) that benefit more from NIV, and the timing of introduction of this treatment in patients with severe bulbar impairment, should be the subject of future study.[57] "We can now suggest that most ventilator dependent ALS patients cannot utilize CNVS because of the upper motor neuron signs that cause stridor and that this does not occur in DMD or SMA.

Key practical points of major strength of this study include:

1) Few if any patients with myopathic conditions or lower motor neuron disease who have access to CNVS and MIE should ever require tracheotomies.
2) Upper motor neuron bulbar ALS patients require tracheotomies when they develop stridor with low MIE-EF and O2 saturation baseline below 95% with CNVS.
3) Other than for ALS patients, ventilator unweanable patients with NMD can be extubated to CNVS and MIE with an over 99% success rate and thereby avoid tracheotomies.
4) Only 25−45% of ALS patient can become CNVS dependent, but they, and the DMD and SMA 1 patients can do so without being hospitalized, developing ARF, or being intubated.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Competing interests

MRG, JRB, YI, LS, JCW declare that they have no competing interests that have an interest in the subject of this manuscript.

Authors' Contributions

MRG and JRB wrote all drafts of the paper, gathered and analyzed all the data from the centers and actively participated in all the procedures of the study. YI and LS gathered information from the centers and added material to the text of the manuscript. JCW contributed to the methodological design of the study, revised and added material to the text of the manuscript. All authors red and approved the final manuscript.

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REVIEW

Measures of physical performance in COVID-19 patients: a mapping review

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KEYWORDS
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Abstract
Background and objective: There is evidence of short- and long-term impairment of physical performance in patients with COVID-19 infection, but a verification of measures of physical impairment in this condition is lacking. We reviewed the measures used to assess physical performance in these patients. Secondary targets were measures of exercise or daily life activities induced symptoms.
Methods: Medline, CINAHL, and Pedro databases were searched from January 2020 to February 2021 for articles in the English language. Two investigators independently conducted the search, screened all titles and/or abstracts based on the inclusion criteria and independently scored the studies. The quality of the studies was evaluated by two reviewers according to the NIH quality assessment tool for observational cohort and cross-sectional studies. Discrepancies were resolved through consensus.
Results: Out of 156 potentially relevant articles, 31 observational studies (8 cross-sectional), 1 randomized controlled trial, and 1 protocol were included. The quality of most of the 31 evaluable studies was judged as low (11 studies) or fair (14 studies). Sample sizes of the studies ranged from 14 to 20,889 patients. among the 28 reported measures, Barthel Index (42.4% of studies), Six-Minute Walking Distance Test (36.4%), Short Physical Performance Battery (21.2%) and 1-Minute Sit-to-Stand (12.1%) were the most used. Fifteen% and 36% of studies reported exercise induced desaturation and dyspnoea when performing the assessments, respectively. Other exercise induced symptoms were fatigue and pain. Studies reported wide ranges of impairment in physical performance as compared to "reference" values (range of mean or median reported values vs "reference values": 11—77 vs 100 points for Barthel Index; 11—22 vs 22—37 repetitions/min for 1m-STS; 0.5—7.9 vs 11.4 ± 1.3 points for SPPB; and 45—223 vs 380—782 m for 6MWT respectively).
Conclusion: This review found that a wide variety of functional status tests have been used, making comparisons difficult between studies. These measures show impairment in physical

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performance in COVID-19 patients. However, the quality of most of the studies was judged as low or fair.

Introduction

Clinical presentation of COVID-19 varies widely, ranging from no symptoms or light flu to pneumonia with acute respiratory failure requiring admission to the Intensive Care Unit (ICU) and possible death.[1—3] In addition to the physiological consequences, a high prevalence of impairment in physical performance is reported in patients recovering from COVID-19.[4—7] In patients without previous disabilities, maximal voluntary contraction for quadriceps and biceps was found to be 54% and 69% of predicted values, respectively.[4] In another study, 76% of patients reported at least one symptom, and 23% reported anxiety or depression up to 6 months after acute infection. The most common symptoms were fatigue, muscle weakness, or sleep difficulties.[5]

Thus the need for validated measures is of utmost importance, using safe equipment and procedures,[8] to evaluate the short- and long-term consequences of COVID-19. To the best of our knowledge, a review of the measures of physical performance used during the pandemic in COVID-19 patients is lacking. Standardisation of batteries of measures would allow us to make comparisons to be made among studies and the different follow-up time-points.

Therefore, we reviewed the measures used to assess physical performance in these patients. Secondary targets of our research were the measures of exercise or activities of daily life (ADL) induced symptoms.

Methods

We performed a mapping review, defined as a systematic search of data in a broad research field of the knowledge, and their presentation as a visual synthesis (map).[9] This study followed all Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and reported the required information accordingly.[10]

Search strategy

Medline, CINAHL, and Pedro databases were searched from January 2020 to February 2021 for articles in the English language. We also searched the references of retrieved articles to identify possible additional studies. Keywords used were COVID AND “physical performance” OR “functional status” OR “disability” OR “impairment” OR "physical function" OR “activities of daily life” OR "muscle function" OR “exercise tolerance” OR “exercise capacity” OR “exercise-induced desaturation” OR “dyspnoea” OR “rehabilitation”.

Inclusion criteria: The search was limited to randomised controlled trials (RCTs), observational (including cross-sectional) studies, and protocols, which used at least one measure of physical performance, either patientreported by means of questionnaires, or objectively measured by means of standardised test such as exercise, functional performance or functional capacity. For the purposes of this review, a measure was defined as quantitative data described in the study. As secondary targets we searched also the measures of exercise- or ADL-induced symptoms.

We included all studies on COVID-19 patients, diagnosed either by positive test using a swab from upper or lower respiratory airways or by clinical or radiological findings. No restrictions were placed on the procedures used to diagnose COVID-19 or on the setting (hospitalization, rehabilitation, follow-up). No restriction was applied regarding age, ethnicity or sex.

Exclusion criteria: Studies not reporting any measure of physical performance (e.g. studies measuring only lung function, blood chemistry, etc.), were excluded. Systematic reviews, case report and case series were also excluded. In terms of the quantitative description of measures, we excluded studies with data reported as other than mean (standard deviation: SD) or median [Interquartile range: IQR].

Quality assessment

The methodological quality of the studies was evaluated using the National Institute of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies.[11,12] For each study 14 items were assessed independently by two authors (CS, MP) to establish if risk of bias was absent or present or undeterminable. In addition, reviewers assigned each study an overall subjective rating of quality (low, fair, good).[11,12] Discrepancies were resolved through consensus or with the final judgment of a third author (MV): the percentage of inter-rater agreement was recorded.

Data collection and analysis

Two investigators (CS, MP) independently conducted the search of the databases, screening all titles and/or abstracts based on the inclusion criteria. Abstracts and/or full-text papers of all potentially eligible studies were retrieved and a record was kept of all studies not meeting the inclusion criteria together with the reasons for their exclusion. The same investigators independently inserted the data of potentially eligible articles in a Microsoft Excel (2013 version, Microsoft, Redmond, WA) institutional database. At the end of this process a dedicated meeting was held in order to define the final list of articles to be evaluated. Disagreement between investigators about eligibility was resolved by discussion and consensus: if consensus could not be reached, a third investigator (MV) adjudicated the findings.

For each study, we recorded type, country, number of centres involved, setting, sample size, patients’ age,

measures used, and whether or not exercise-induced desaturation (EID), or exercise or ADL induced symptoms were assessed. The performance of rehabilitation/physiotherapy programs was also recorded, if any. Among symptoms, we included all those symptoms measured during or at the end of exercise tests or during physical activity (e.g. ADL). Symptoms measured at rest or not related to physical activity (e.g. ageusia, headache, etc.) were not considered in this review. The effects of an intervention (if any) on these measures were beyond the scope of the study.

For each measurement, we recorded results (mean and SD or median and IQR). When available, the time between the disease onset (index event: positive swab, hospitalization or emergency department admission) and the first administration of the measure was recorded. For the four most used measures, we performed a quick literature search for predicted values and we compared them with the mean or median data reported in the included studies. No other quantitative analysis (e.g. of the scores obtained in the measurement scales) was carried out.

Results

We identified 156 potentially relevant articles. Thirty-one observational studies (8 cross-sectional), 1 RCT and 1 study protocol were eligible for the analysis (Fig. 1).

Quality of the studies

Table 1 shows the methodological quality of the studies. The inter-rater agreement of item definitions was very good: 94.2%. The overall quality was considered as low for 11 studies, fair for 14, and good for 6 studies. The most frequent motives for bias were the absence of assessor blinding and the missing justification of the sample size or power estimation.

Characteristics of the studies

Table 2 shows the characteristics of the included studies. Most studies were from Europe, six from Asia,[5,17,24,31,34,35] and one from the USA.[27] The sample size of each study

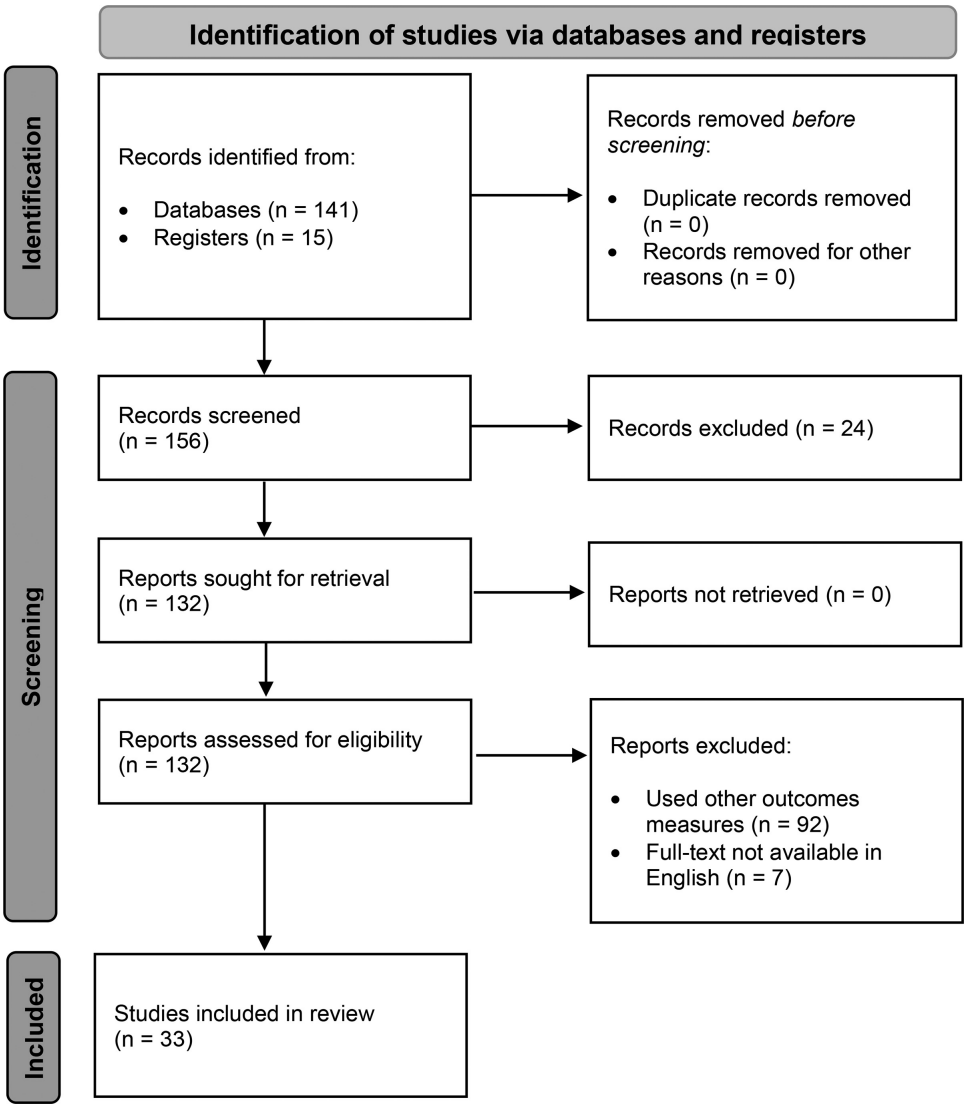

Fig. 1 Trial profile of literature search according to PRISMA Guidelines.

ranged from 14 to 20,889 participants, the mean or median age ranged from 49 to 72 years and in 13 out of 33 studies (39.4%) a rehabilitation program was performed. Twenty-eight measures were found, mostly administered in hospitalised subjects or during inpatient rehabilitation. Other settings were the emergency department (ED), ICU, and follow-up visits. Fig. 2 shows the proportion of studies using each measure of physical performance or of exercise or ADL induced symptoms, and the overall sample size of studies using each measure.

Measures of physical performance

The Barthel Index[44,45] (14 studies: 42.4%),[15,18,22,24,26,28–33,35,36,38] Six-Minute Walking Distance Test (6MWT) [46] (12 studies: 36.4%),[5,25,26,28,30,32–34,37,39–41] Short Physical Performance Battery (SPPB)[47,48] (7 studies: 21.2%)[4,21,22,26,30,42,43] and 1-Minute Sit-to-Stand (1m-STS)[49,50] (4 studies: 12.1%)[4,22,26,42] were the most used tests (Fig. 2). The Barthel Index was mainly used in the acute phase, whereas the 6MWT was assessed in interventional and

Table 1 Methodological quality assessment of the 33 studies included.

	Aim	Population	Participation rate > 50%	Recruitment	Sample size	Exposure definition	Timeframe	Adjustment for level of exposure	Exposure measures definition	Repeated exposure assessment	Outcome measure definition	Assessor blind	Loss to follow-up < 20%	Adjustment for confounding variables
Goodacre et al [13]														
McWilliams et al [14]														
Ceriana et al [15]														
Medrinal et al [16]														
Tay et al [17]														
Van Aerde et al [18]														
Ozyemisci Taskiran et al [19]														
Tuzum et al [20]														
Paneroni et al [21]														
Belli et al [22]														
Vilches-Moraga et al [23]														
Zhu et al [24]														
Fuglebjerg et al [25]														
Paneroni et al [4]														
Zampogna et al [26]														
Bowles et al [27]														
Curci et al [28]														
Wiertz et al [29]														
Zampogna et al [30]														
Sakai et al [31]														
Curci et al [32]														
Puchner et al [33]														
Liu et al [34]														
Zhangh et al [35]														
Piquet et al [36]														
Al Chickanie et al [37]														
Bertolucci et al [38]														
Sonnweber et al [39]														
Townsend et al [40]														
Daher et al [41]														
Baricich et al [42]														
Bellan et al [43]														
Huang et al [5]														

Colours show the risk of bias for each single item; green: absence of bias, red: presence of bias; yellow: at least one reviewer stated that the item could not be determined.

Table 2 Principal characteristics of the 33 included studies. Quantitative data are expressed as mean ± SD or median (IQR).

Reference	Country	Centres, n	Setting	PT/ Rehab	Patients, n	Age, years	Measures used	EID assessment
Goodacre [13]	UK	70	EM Dept	N	20,889	62.4 ± 19.7	Performance status of the PRIEST COVID-19 Clinical Severity Score	N
McWilliams [14]	UK	1	ICU	Y	110	53 ± 12	Manchester Mobility Score, Clinical Frailty Scale	N
Ceriana [15]	Italy	3	Step-down unit (ICU)	N	89	61.9 ± 11.3	Barthel Index, MRC muscle strength test: quadriceps and biceps	N
Medrinal [16]	France	2	ICU	N	23	66 ± 9	MRC muscle strength test, MIP, ICU mobility scale	N
Tay [17]	Singapore	1	ICU	N	51	56.3 ± 13.1	Functional Ambulation Category	N
Van Aerde [18]	Germany	1	ICU	N	486		MRC muscle strength test, Barthel Index	N
Ozyemisci Taskiran [19]	Turkey	1	ICU	Y	14		Handgrip strength, composite MRC muscle strength test, joints ROM	N
Tuzum [20]	Turkey	1	Ward	N	150	53.2 ± 15.5	Handgrip strength, Chalder Fatigue Scale, motion induced pain	N
Paneroni [21]	Italy	1	Ward	N	184	74 ± 12	SPPB	N
Belli [22]	Italy	1	Ward	Y	103	73.9 ± 12.9	1m-STS, SPPB, Barthel Index	N
Vilches-Moraga [23]	UK and Italy	13	Ward	N	831	71 (58–81)	Clinical Frailty Scale	N
Zhu [24]	China	28	Ward	N	432	49 (35–60)	Lawton's IADL scale, Barthel Index	N
Fuglebjerg [25]	Denmark	1	Ward	N	26	63 (29–85)	6MWT, Borg Dyspnoea after 6MWT	Y
Paneroni [4]	Italy	1	Ward	N	41	67.1 ± 11.9	1m-STS, SPPB, Muscle dynamometry, Single-Breath Counting test, Borg Dyspnoea and fatigue after 1-MSTS and ADL	Y
Zampogna [26]	Italy	1	Ward	N	56	69.4 ± 9.9	Barthel Dyspnoea Index, Barthel Index, SPPB, MRC muscle strength test of quadriceps and biceps, Single Breath Counting, 6MWT,	
1m-STS	N							
Bowles [27]	The USA	64	Home hospital acute care	N	1409	67 ± 15	ADL dependency, dyspnoea during ADL, motion induced pain	N
Curci [28]	Italy	1	Inpatient Rehab	Y	32	72.6 ± 10.9	Barthel Index, mMRC dyspnoea, 6MWT	N

Table 2 (*Continued*)

Reference	Country	Centres, n	Setting	PT/ Rehab	Patients, n	Age, years	Measures used	EID assessment
Wiertz [29]	Netherlands	1	Inpatient Rehab	N	60	59.9 ± 10.2	Barthel Index, MRC muscle strength test, dynamometry; joints ROM; fatigue and dyspnoea (numeric rating scale 0—10).	Y
Zampogna [30]	Italy	4	Inpatient Rehab	Y	140	71 (61—78)	SPPB, Barthel Index, 6MWT	N
Sakai [31]	Japan	1	Inpatient Rehab	Y	43	65 (21—95)	Barthel Index, ability to walk	N
Curci [32]	Italy	1	Inpatient Rehab	Y	41	72.1 ± 11.1	Barthel Index, mMRC dyspnoea, 6MWT, Borg RPE	N
Puchner [33]	Austria	2	Inpatient Rehab	Y	23	57 ± 10	6MWT, Barthel Index, MIP	N
Liu [34]	China	2	Inpatient Rehab	Y	72	69.1 ± 7.6	6MWT, FIM	N
Zhang [35]	China	1	Inpatient Rehab	Y			mMRC dyspnoea, Barthel Index, Patient Health Questionnaire-9 scale, Respiratory Symptoms scale	N
Piquet [36]	France	1	Inpatient Rehab	Y	100	66 ± 22	Barthel Index, 10-times sit-to-stand, Handgrip strength, Borg RPE	N
Al Chickanie [37]	France	1	Inpatient Rehab	Y	21	70.9 ± 10.6	MIP, MEP, Tinetti balance test, 6MWT, Handgrip strength, quadriceps dynamometry, Borg Dyspnoea	Y
Bertolucci [38]	Italy	1	Inpatient Rehab	Y	39	67.8 ± 10.8	Barthel Index, Functional Ambulation Category	N
Sonnweber et al. [39]	Austria	1	Home follow-up	N	109	58 ± 14	6MWT	N
Townsend et al. [40]	Ireland	1	Home follow-up	N	153	48 (35—59)	6MWT, Borg Dyspnoea scale, Chalder Fatigue Scale	Y
Daher et al. [41]	Germany	1	Home follow-up	N	33	64 ± 3	6MWT, Borg Dyspnoea and fatigue after 6MWT	N
Baricich et al. [42]	Italy	1	Home follow-up	N	204	57.9 ± 12.8	SPPB, 2MWT, 1m-STS	N
Bellan et al. [43]	Italy	1	Home follow-up	N	238	61 (50—71)	SPPB, 2MWT	N
Huang et al. [5]	China	1	Home follow-up	N	1733	57 (47—65)	mMRC dyspnoea, 6MWT	N

Abbreviations: EID, Exercise Induced desaturation; n, number; PT/Rehab, Physiotherapy/Rehabilitation; EM, emergency; ICU, Intensive Care Unit; MRC, Medical Research Council; MIP, maximal inspiratory pressure; ROM, range of motion; IADL, instrumental activities of daily living; mMRC, modified Medical Research Council scale; ADL, activities of daily living; ATS/ERS, American Thoracic Society/European Respiratory Society; RPE, rate of perceived exertion; MEP, maximal expiratory pressure; SPPB, Short Physical Performance Battery; 6MWT, 6-min walking test; 2MWT, 2-min walking test; 1m-STS, 1-min sit-to-stand; FIM, Functional Independence Measure; Borg RPE, Borg Rating Perception of Exertion scale; d, days; Y, yes; N, no.

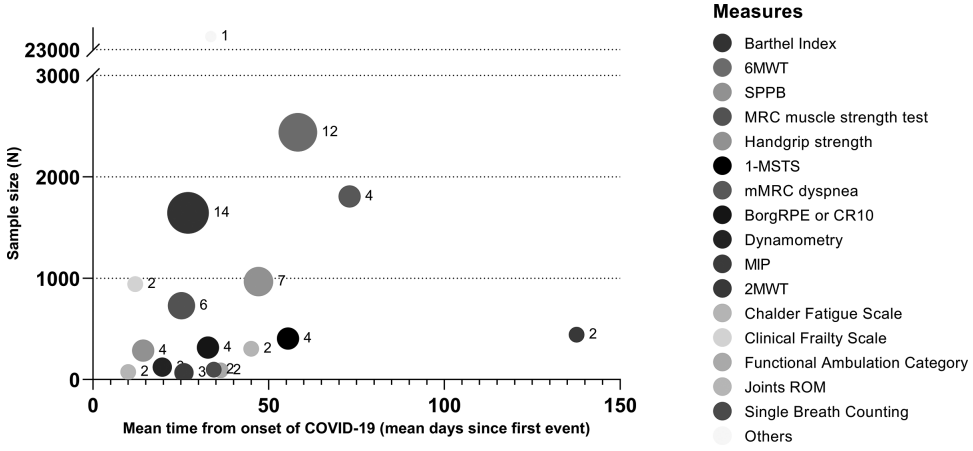

Fig. 2 Number of studies which used each measure of physical performance and exercise- or ADL-induced symptoms. The size of the circles describes the number of studies; *x* axis: time of measure performance from disease onset; *y* axis: overall sample size of studies using each measure.

follow-up studies. The SPPB was mainly used in the acute ward.

Table 3 shows sample sizes and results of the four most used measures of physical performance in the different settings. When comparing reported values with the reference values available in the literature, we found lower values for the Barthel Index (range of mean or median reported values vs "reference values": 11–77 vs 100 points[45]),

Table 3 Values of the most employed outcome measures in the 33 included studies (total population = 27,935 patients). Data are reported as mean ± SD or median (IQR).

	Reference	Setting	N	Mean ± SD Median (IQR)
Barthel index	Ceriana[15]	ICU	70	27.7 ± 31.0
	Zampogna [30]	R	140	55 (30–90)
	Sakai [31]	R	43	75 (0–90)
	Curci [28]	R	32	45.2 ± 27.6
	Curci [32]	R	41	43.4 ± 26
	Puchner [33]	R	23	83 ± 18
	Piquet [36]	R	100	77 ± 27
	Wiertz [29]	R	60	11 ± 6
	Bertolucci [38]	R	39	75 (0–100)
SPPB	Paneroni [21]	Ward	184	3.1 ± 3.9
	Paneroni [4]	Ward	41	7.9 ± 3.3
	Zampogna [26]	Ward	56	0.5 (0–6)
	Zampogna [30]	R	140	3.24 ± 3.69
	Baricich [42]	Home	204	11.2 ± 1.4
1STS	Belli [22]	Ward	43	14 ± 6
	Paneroni [4]	Ward	41	22.1 ± 7.3
	Zampogna [26]	Ward	19	14 (9.3–19.8)
	Baricich [42]	Home	204	19.7 ± 7.3
6MWT	Zampogna [26]	Ward	4	424 ± 35
	Curci [28]	R	6	45 ± 101
	Curci [32]	R	6	240 ± 81
	Puchner [33]	R	23	323 ± 196
	Liu [34]	R	72	159 ± 77
	Al Chickanie [35]	R	21	139 ± 144
	Zampogna [30]	R	42	229 ± 102
	Townsend[40]	Home	109	460 (225–640)
	Daher [41]	Home	33	380 (180–470)
	Huang [5]	Home	1733	495 (440–538)

Abbreviations: N, number of patients; R, rehabilitation centre; SPPB, Short Physical Performance Battery; 1STS; 1-Min Sit-to-Stand; 6MWT, 6-Min Walking Test; SD, Standard Deviation; IQR, Interquartile Range.

1m-STS (11−22 vs 22−37 repetitions/min in people aged 75−79 years [51]), SPPB (0.5−7.9 vs 11.4 ± 1.3 points [52]), and 6MWT (45−223 vs 380−782 m [53]) respectively.

Measures of dyspnoea and other exercise- or ADL-induced symptoms

Exercise-induced dyspnoea was assessed in twelve studies.[4,5,9,25−29,35−37,40,41] The most commonly used scale to assess dyspnoea in daily life was the modified Medical Research Council (mMRC) scale[54] used in four studies.[5,28,32,35] Two studies in a rehabilitative setting found the most severe score (level 5) in 87.5 and 90.2% of patients.[28,32] One study[5] reported that, at six months following disease onset, 26% of patients had mMRC levels greater than 1. Only one study[26] used the Barthel Dyspnoea Index[55] in a rehabilitative setting, and reported moderate levels of dyspnoea during ADL. Exercise-induced dyspnoea was evaluated at the end of the 6MWT by the Borg scale[56] in four out of twelve studies.[25,37,40,41] One study[4] assessed dyspnoea at the end of the 1m-STS. Two studies[27,29] used other numeric scales to measure exercise-induced dyspnoea.

Fatigue was assessed in seven studies.[4,20,29,32,36,40,41.] Two studies[20,41] used the Chalder Fatigue Scale, which is a dedicated tool to measure fatigue. Two other studies[4,41] measured fatigue with the Borg scale at the end of the 6MWT, and two more studies[23,36] measured the (Borg) Rate of Perceived Exertion. One study[29] assessed fatigue using a 0−10 numeric rating scale. Motion induced pain was assessed in two studies.[20,27]

Exercise induced desaturation

Exercise-Induced Desaturation was reported in five studies.[4,25,29,40,41] It was defined as oxygen saturation (SpO_2) $< 90\%$ in four studies;[25,29,40,41] in the other study,[4] it was defined as a reduction in SpO_2 by > 3 % points during the exercise tests. In the acute setting, 24−50% of patients demonstrated EID.[4,25] One study[29] in the rehabilitation setting reported EID in 38% of patients assessed.

Rehabilitation

Thirteen studies[14,19,22,28,30−38] included at least one rehabilitative intervention during the time-course of the study. Four studies[30,31,37,38] described structured multidisciplinary rehabilitation programs, while in five studies[14,19,23,31,36] the rehabilitation was a short intervention provided to respond to the needs of patients during the first phase of the pandemic. In two studies[28,32] the components were selected according to the patient's level of oxygen saturation.

Discussion

In this mapping review, we presented the measures of physical performance employed in studies on patients with COVID-19. In addition, we presented also the measures of dyspnoea and other exercise- or ADL-induced symptoms. In the studies evaluated, mostly of low or fair quality, we found twenty-eight measures used, the Barthel Index,[44,45] 6MWT,[46,53] SPPB[47,48,52] and 1m-STS[49-51] being the ones most frequently used. . The other tests were reported in a few studies or even in just one. A wide range of impairment in physical performance (e.g. from 11% to 77% of normal values for Barthel Index) was reported with the use of these tools.

Patients recovering from COVID-19 may show impairment in respiratory function,[57] and the majority of patients hospitalised with COVID-19 report persistent symptoms several months after infection onset.[5,58] However studies evaluating symptoms may suffer from recall bias and subjective rating of symptoms. Therefore, tools that objectively measure the functional consequences of COVID-19 disease in the short- and long-term are necessary.

In routine clinical practice, the Barthel Index is the most widely used scale to measure patients' motor and functional disabilities in ADL.[45] This index was developed for chronic and long-term hospital patients with neurological diseases to examine their performance before and after treatment and predict the time needed for motor rehabilitation and the degree of nursing aid required.[45]

The 6MWT is the gold standard field exercise test and it has been validated for most chronic lung diseases. It is sensitive, reproducible, easy to perform, and does not require any specialized equipment.[46]

The SPPB represents the sum of the scores in three component tests of functional relevance, namely standing balance, 4-meter gait speed, and the five-repetition sit-to-stand test.[47] The SPPB is the most commonly used performance-based measure for patients with chronic obstructive pulmonary disease (COPD). It is a standardized objective tool, rapid and simple to conduct, and less influenced by cultural and educational background than other self-reported measures. Because lower-limb strength is important for a satisfactory completion of the mobility activities, the SPPB has also been cited as a measure of lower-extremity function.[59] It has also been shown that the SPPB is significantly related to the capacity to perform ADL, such as changing and maintaining body position, carrying, moving, and handling objects, or walking and gait pattern.[47]

The 1m-STS requires only a chair and is easy to perform, making it feasible for use in the physician's office.[60] Studies to date have shown that the 1m-STS is well tolerated, sensitive, and reproducible in patients with COPD,[49] cystic fibrosis[61] and interstitial lung diseases.[50]

Dyspnoea is a symptom limiting exercise and ADL; therefore we searched the literature also for papers reporting this symptom. The severity of dyspnoea cannot be predicted from lung function; therefore, dyspnoea must be assessed specifically. Several instruments are commonly used to measure different domains of dyspnoea such as sensory-perceptual experience, affective distress, symptom impact or burden.[62] We found twelve studies investigating dyspnoea during physical activity with various scales.

Fatigue is an important debilitating symptom affecting all chronic respiratory diseases. It is a leading cause of consultations with major clinical implications. Despite its well-acknowledged negative impact on the patient's life, fatigue is still a misunderstood and underdiagnosed symptom in respiratory diseases such as COPD. Consequently, there is currently no specific intervention to treat all aspects of this symptom which is rather often considered as a secondary outcome in interventions aiming primarily to increase physical fitness and/or health related quality of life.[63] There is

low-grade evidence of a positive effect of exercise training on perceived fatigue, at least in patients with COPD.[64]

Pain during motion is a debilitating symptom responsible for reduced functional performance. No dedicated scales were used to investigate this symptom, but two studies reported the presence/absence of pain during motion.[20,27]

Exercise induced desaturation is associated with exercise limitation. When evaluating individuals with EID a crucial point is the definition, which varies widely across clinical trials, ranging from $SpO_2 \leq 88\%$ to a decrease in SpO_2 of $\geq 4\%$ with or without a nadir SpO_2 of $< 90\%$.[65–68]

The results of our review confirm that patients with COVID-19 infection of differing severity suffer from a decline in physical performance in the short-[4] and long-term.[5] The wide range of results as shown by the SD or IQR reported in the studies and the differences in findings across settings indicates differences in case mix and times of evaluation. However, it should be born in mind that, particularly in the first wave of the pandemic, the allocation of patients might have been influenced by organisational issues, such as bed shortage in ICU or acute wards, over and above the patient's clinical conditions. The different values of physical performance reported with the different measures used confirm that these tools assess somewhat different aspects of physical performance and highlight the need for a more homogeneous set of tools to measure the outcome of these patients.

The quality of most of the studies was judged as fair or low; this result was expected. The sudden outbreak of the pandemic and the rapid need of information from the scientific community have led to a high index of publications,[69] on the top of the overwhelming clinical pressure on researchers at the time which has resulted also in a higher level of retractions.[70]

This study has limitations. We conducted the search in a limited number of indexed databases, and keywords included dyspnoea but no other symptoms potentially relevant in physical performance tests. However, the most important limitation is the fact that the pandemic is still ongoing, which will result in increasing numbers of studies on the issue addressed. . However, we are confident that our search will contribute to those future studies (like in Heisenberg uncertainty principle).

Conclusion

This mapping review of measures used in COVID-19 patients shows studies mostly of low or fair quality, characterized by a large variability of measures, which overall indicate an impairment in physical performance. Our findings should be interpreted with caution. In fact, the studies were all, except one, observational with suboptimal methodological quality. Very different measures have been used which have different requirements (scale, availability of space...). Butthe choice of which measures to use according to the phase of the disease and setting of application is an issue that also need research on measurement properties in this population, which is still lacking. Better standardisation in the choice, timing and interpretation of measurement of physical performance is mandatory. Future RCTs or studies with higher methodological quality are required to clarify the validity of measures used in COVID-19 and in which setting, and verify the changes over time and/or in response to treatment.

Authors' contributions

CS and MP contributed to data acquisition and data analysis; all authors participated in drafting the article or critically revised it for important intellectual content. All authors contributed to the conception and design, data interpretation, final approval of the version to be published and agreed to be accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

Conflicts of interest

NA is the Chief Editor of Pulmonology. The other authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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REVIEW

Applicability of lung ultrasound in COVID-19 diagnosis and evaluation of the disease progression: A systematic review☆

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Abstract
Introduction: The COVID-19 pandemic originated in China and within about 4 months affected individuals all over the world. One of the limitations to the management of the COVID-19 is the diagnostic imaging to evaluate lung impairment and the patients' clinical evolution, mainly, in more severe cases that require admission into the intensive care unit. Among image examinations, lung ultrasound (LU) might be a useful tool to employ in the treatment of such patients.
Methods: A survey was carried out on PubMed to locate studies using the descriptors: ((Lung ultrasound OR ultrasound OR lung ultrasonography OR lung US) AND (coronavirus disease-19 OR coronavirus disease OR corona virus OR COVID-19 OR COVID19 OR SARS-CoV-2)). The period covered by the search was November 2019 to October 2020 and the papers selected reported LU in COVID-19.
Results: Forty-three studies were selected to produce this systematic review. The main LU findings referred to the presence of focal, multifocal and/or confluent B lines and the presence of pleural irregularities.

☆ Lung ultrasound in COVID-19: a systematic review.

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Conclusions: The use of LU in the evaluation of patients with COVID-19 should be encouraged due to its intrinsic characteristics; a low cost, radiation free, practical method, with easy to sanitize equipment, which facilitates structural evaluation of lung damage caused by SARS-CoV-2. With the increase in the number of studies and the use of ultrasound scans, LU has been shown as a useful tool to evaluate progression, therapeutic response and follow-up of pulmonary disease in the patients with COVID-19.

Introduction

COVID-19 (Coronavirus Disease 2019) is an illness caused by the SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) that mainly affects the breathing system.[1] Last year COVID-19 affected individuals all over the world. In total, over 98 million cases of the disease and 2 million deaths have been recorded.[2,3] The SARS-CoV-2 presents a 7% case fatality rate globally, however, it varies greatly in different countries of the world. The death rate of COVID-19 is not the best marker to estimate the severity of the illness, since its diagnosis is based on the Real Time Polymerase Chain Reaction (RT-PCR) and in many countries, like Brazil, the access to this resource is reduced due to lack of materials, equipment, transport logistics and laboratory staff to meet the demand for exams.[4,5] Thus, many SARS-CoV-2 colonization asymptomatic cases or those presenting mild severity are not recorded by the health system.

The COVID-19 became a global challenge in 2020 due to the SARS-CoV-2 high virulence and the fact that it has been able to cross borders and reach populations all over the world, causing high demand on health services and the need for the action of multidisciplinary teams throughout the pandemic.[5] Management of the disease requires the use of intensive care units; however, not all countries have been able to deal with the high number of individuals affected simultaneously and there has been a collapse in the health service of many countries that has resulted in the need for political interventions.[6] In the global context, social distancing has been described as the most efficient mechanism for reducing virus spread and controlling the COVID-19 pandemic.[7–9]

The COVID-19 clinical variability is mainly dependent on underlying diseases and age.[10] The literature reports alterations of the pulmonary function, and the use of lung high resolution computed tomography (HRCT) is advised to determine the extent of the damage.[11] However, this examination presents high cost, difficult accessibility for the patients affected, necessity of physical structure and patient transportation to the tomography equipment, exposure to radiation and lack of applicability during hospitalization. Thus, among the image exams, the lung ultrasound (LU) stands out and might become a useful tool for use in the treatment and follow up of patients with COVID-19, mainly in more severe cases when intensive care is required. In this context, we carried out this systematic review of the use of LU in COVID-19 in 2019 and 2020.

Methods

The systematic review was carried out using the data base PubMed/Medline and according to the preferred reporting items for systematic review and meta-analysis (PRISMA) covering the period from December 2019 to October 2020. The following descriptors guided the search: ((Lung ultrasound OR ultrasound OR lung ultrasonography OR lung US) AND (coronavirus disease-19 OR coronavirus disease OR corona virus OR COVID-19 OR COVID19 OR SARS-CoV-2)) with the following filters: clinical study; clinical trial; clinical trial protocol; clinical trial, phase I; clinical trial, phase II; clinical trial, phase III; clinical trial, phase IV; comparative study; controlled clinical trial; guideline; journal article; observational study; practice guideline; and randomized controlled trial. Also, the filter for Humans and English language were used.

From the 1,691 studies found, the papers excluded were: (i) 10 in other languages (8 published in Chinese and 2 in Spanish); (ii) 77 reviews and guidelines; (iii) 969 papers that addressed other image exams such as HRCT, positron emission tomography combined with computed tomography and thorax radiography without the use of LU; (iv) 483 due to the approach of different themes that were related to LU or those that had been developed using animals; (v) 77 guidelines and systematic reviews without association with LU (Fig. 1).

A total of 102 papers were evaluated, at least title and abstract, and some of these reports were selected to support this paper's introduction and discussion and provide some theoretical-scientific basis of LU, from those, 57 addressed the LU role in COVID-19 without evaluating patients with that disease. Consequently, 45 papers were selected for the literature review. The inclusion criterion was the search for references to the application of LU in the investigation of SARS-CoV-2 infection. Three authors (AOP, RMC and RU) selected the titles and abstracts of the papers individually and there was no disagreement regarding this choice of material to produce the systematic review. Out of the 45 papers, one was excluded for lack of access to the full text even after contacting the corresponding author and one was dismissed because it appeared twice in the search, that is, the same study was published in the same journal, once as a short communication and another time as a letter to the editor.

The data collected from each study were: author (year of publication), type of study, number of patients with COVID-19 or number of participants, COVID-19 diagnostic method,

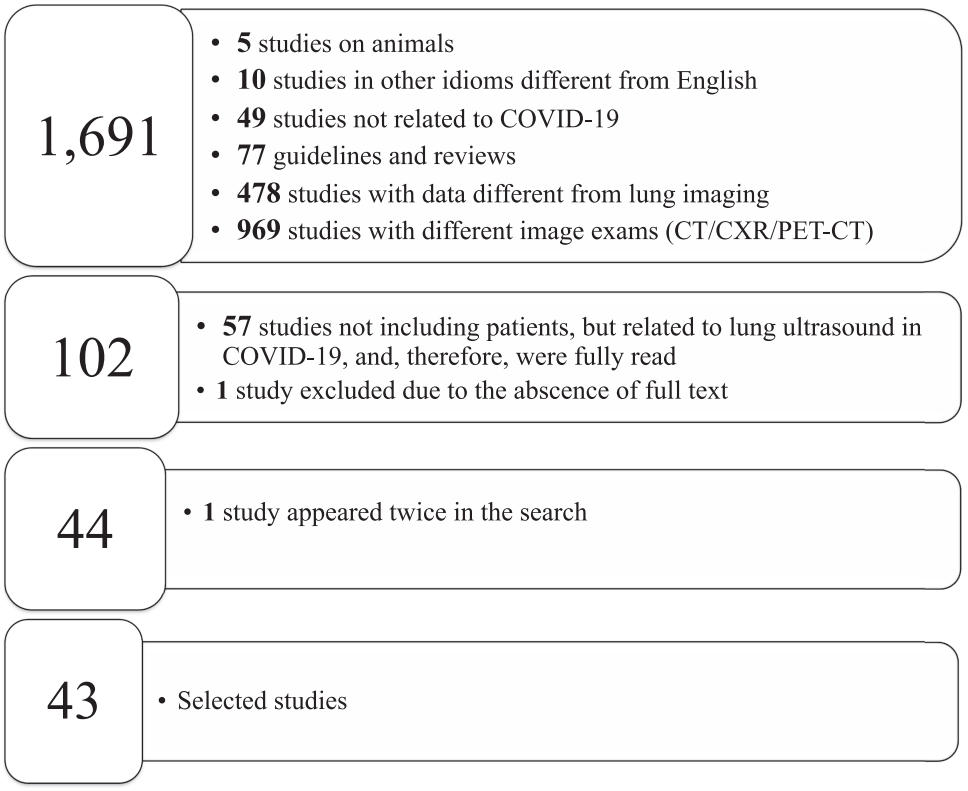

Figure 1 The systematic review flowchart. The systematic review was carried out using the data base PubMed/Medline and according to the preferred reporting items for systematic review and meta-analysis (PRISMA) covering the period from November 2019 to October 2020. The following descriptors guided the search: ((Lung ultrasound OR ultrasound OR lung ultrasonography OR lung US) AND (coronavirus disease-19 OR coronavirus disease OR corona virus OR COVID-19 OR COVID19 OR SARS-CoV-2)). LU = lung ultrasound; CT = computed tomography; CXR = chest X-ray; PET-CT = positron emission tomography combined with computed tomography; COVID-19 = coronavirus disease-2019.

clinical characteristics of the patients, LU findings, use of other imaging exams, scanning areas/LU technique/sort of equipment, patient treatment, the use of individual protection equipment by the professional carrying out the LU, machine cleaning and comments.

Results

Forty-three studies reported lung impairment in COVID-19 evaluated by the LU propaedeutic. Those studies totaled 2,116 patients, including children, adults, elderly and pregnant women, 863 male and 1,210 female individuals, and 43 patients whose gender was not given, the age of the patients ranged from 0 to 106 years. The country with the highest number of reports on the use of this clinical tool was Italy with 15 studies,[12,15,25,27,30,31,34,64,69,71,77,78,82,86,87] followed by China with 8 studies,[29,38,62,67,70,73,76,83] Spain with 6 studies,[35,72,79,80,85,89] France with 5 studies,[32,33,65,68,88] Canada with 2 studies,[18,19] Brazil,[63] Bhutan[81] Germany,[84] Israel,[75] South Korea,[74] Turkey[66] and USA[26] with 1 study each.

The results of the characteristics of the studies investigating LU in COVID-19 are presented in Tables 1 and 2.

Among the articles included, 17 are case reports,[15,18,19,29,30,32,33–35,73,74,80,81,84–86,89] 12 are observational studies,[25,26,27,31,63,65,71,76–78,87,88] 5 are observational prospective,[66,68,69,75,79] and 4 are observational retrospective[64,67,70,83] studies, 1 is a short communication,[72] and 1 is a protocol.[12]

Detection of SARS-Cov2 on RT-PCR assay from the nasopharyngeal swab was found in 34 studies[19,26,27,29,30,31,32,34,35,38,62–75,77–82,85–88] while the infection diagnosis was not specified in the other studies.[12,15,18,25,33,76,83,84]

The clinical picture was described in 39 studies and despite the variability in the signs and symptoms of the disease, fever[15,18,25,26,27,29,30,31,32,34,38,62,63,69,70,74,75,77,78,79,82,84–88] was the most common symptom reported, followed by cough and dyspnea with 6 studies.[15,19,21,25,26,28,29,32] It has been noted that in child populations, from 27 patients evaluated, aged 0–17 years old, 14 (51.8%) had fever, 11 (40.7%) had dry cough, and less commonly 3 (11.1%) had dyspnea, 3 had headache, 3 had odynophagia, 3 had vomiting and diarrhea, 3 had arthralgia and 2 (7.4%) had anosmia.[27,31,72,74,80,89] Among the children evaluated in the studies, 4 were asymptomatic. In the adult and elderly population analyzed, the most common symptoms were fever, cough, and dyspnea, followed by headache, myalgia, nausea, vomiting and abdominal pain. The less common symptomatology included rhinitis, pharyngitis, anosmia and ageusia. Finally, within the sample of pregnant women

Table 1 Clinical characteristics of studies evaluating lung ultrasound in COVID-19.

Study	Country	Type of study	Patients and participants included in the studies	Diagnosis of COVID-19	Clinical picture	Comorbidities	Treatment
Thomas et al.[19]	Canada	Case report	64 years old, female and health professional.	RT-PCR	Productive cough and dyspnea on exertion. After 6 days in O_2 catheter → invasive mechanical ventilaton. 88% SpO_2.	NS	Support: Invasive mechanical ventilation + intubation.
Soldati et al.[12]	Italy	Protocol	30 patients.	NS	NS	NS	NS
Buonsenso et al.[15]	Italy	Case report	1 adult, 52 years old, male.	NS	Fever, asthenia, cough, headache, myalgia, photophobia for 1 week; 90% SpO_2. Dyspnea and bilateral rales.	NS	NS
Kim et al.[18]	Canada	Case report	1 man, 67 years old.	NS	Fever and chills for 5 days, non-productive cough, myalgia and malaise. 80/40 arterial pressure, 38.7°C temperature, 120 cardiac rate, 24 RF, 93% SpO_2 in ambient air.	Hypertension and dyslipidemia.	NS
Denina et al.[25]	Italy	Descriptive observational	8 children and adolescents (0–17 years old), divided into 3 female and 5 male participants.	NS	Fever (6 patients); dry cough (5 patients); dyspnea/tachypnea (3 patients); odynophagia (3 patients); vomit or diarrhea (3 patients) and hypoxemia (2 patients).	NS	Oxygen therapy.
Yasukawa et al.[26]	USA	Analytical observational	10 adults (31–71 years old), divided into 7 male and 3 female participants.	Detection of SARS-CoV-2 in nasopharyngeal swab RT-PCR.	Fever, cough, dyspnea, SpO_2 from 89 to 96%.	Rheumatoid arthritis, SAH, asthma, sleep obstructive apnea, obesity, hyperlipidemia and atrial fibrillation.	Oxygen therapy with mask (4 patients).
Musolino et al.[27]	Italy	Analytical observational	10 children (mean age 11 years).	Nasopharyngeal swab RT-PCR.	Fever (80%), cough (50%), anosmia (10%), arthralgia (30%), chest pain (20%), headache (20%).	NS	Patient did not require hospital treatment or ICU.
Ji et al.[29]	China	Case report	1 female adult (60 years old).	Oropharyngeal swab RT-PCR.	Fever, chills, dry cough, fatigue and dyspnea. RF 30 breaths per minute; 92% SpO_2 in ambient air.	SAH and systemic lupus erythematosus.	Respiratory support and interferon inhalation.

Table 1 (*Continued*)

Study	Country	Type of study	Patients and participants included in the studies	Diagnosis of COVID-19	Clinical picture	Comorbidities	Treatment
Buosenso et al.[30]	Italy	Case report	4 pregnant women (31–42 years old — mean age 37 years). Gestacional periods=17, 24, 35 and 38 weeks.	Nasopharyngeal swab RT-PCR.	NS	No comorbidities.	All patients received hydroxychloroquine, lopinavir/ritonavir, no need for ICU. Tocilizumab was added for the patient based on the pulmonary impairment revealed by the LU.
Inchingolo et al.[31]	Italy	Descriptive observational	1 pregnant woman (age not informed). Gestational period = 23 weeks.	Oropharyngeal swab RT-PCR.	Cough and fever, eupneic, no respiratory discomfort, 98% SpO_2 in ambient air. Bilateral reduced vesicular murmur in bases.	NS	NS
Duclos et al.[32]	France	Case report	1 male adult.	Nasopharyngeal swab RT-PCR.	Dry cough (4 patients); anosmia (1 patient); fever $\geq$38 °C (3 patients) temperature.	NS	NS
Zieleskiewicz et al.[33]	France	Case report	2 older people (65-year-old male; and 72-year-old female participants).	NS	NS	NS	Mechanical ventilation for the 65-year-old patient.
Youssef et al.[34]	Italy	Case report/Letter to the editor	1 pregnant woman, 33 years old, gestational period = 26 weeks.	Positive nasopharyn-geal swab.	Fever, mild chest pain and dyspnea for three days, with normal oxygen saturation.	NS	NS
Tung-Chen et al.[35]	Spain	Case report	35-year-old male adult.	RT-PCR	Abrupt chills and sickness, dry cough after 20 h of isolation, bilateral cephalgia and normal lung auscultation.	NS	Supportive therapy was started with ibuprofen and paracetamol. After confirming worsening of symptoms and LU findings, hydroxychloroquine 200mg twice a day and azithromycin were added to the treatment.
Lu et al. [38]	China	Observational	30 (16 male and 14 female) with mean age of 52 $\pm$ 15 years.	RT-PCR — including two patients with positive results.	Fever: 20 patients (66.7%); cough: 14 patients (46.7%); fatigue: 5 patients (16.7%); muscle soreness: 5 patients (16.7%); nausea: 2 patients (6.7%); no obvious symptoms: 3 patients (10%).	NS	NS

Table 1 (*Continued*)

Study	Country	Type of study	Patients and participants included in the studies	Diagnosis of COVID-19	Clinical picture	Comorbidities	Treatment
Tan et al.[62]	China	Case series	12 (4 male and 8 female), ranging from 52 to 79 years old, mean age 60.5 years.	RT-PCR	Moderate (4 patients): fever, diarrhea or other respiratory tract symptoms. Severe (4 patients) — showing any of the following: RF $\geq$30 times/min OR at rest, peripheral venous oxygen saturation $\leq$93% or PaO_2/FiO_2 $\leq$300 mmHg. Critical (4 patients) — showing any of the following: respiratory failure with mechanical ventilation OR shock OR with other organic failure and need for admission in the ICU.	Hypertension (1 patient), diabetes mellitus (1 patient) and cardiovascular diseases (2 patients).	NS
Mafort et al.[63]	Brazil	Transversal observational	409 (134 male and 275 female), ranging from 35 to 51 years old (mean age 41 years) — all of them health care professionals.	RT-PCR	Cough (84%); fever (69.7%); dyspnea (36.2%).	NS	NS
Veronese et al.[64]	Italy	Retrospective study	48 patients living in nursing homes (women = 81.3%), mean age 84.1 years.	RT-PCR	NS	Dementia and mostly bedridden patients.	NS
Zieleskiewicz et al.[65]	France	Observational study with retrospective analysis	100 (65 male and 35 female), ranging from 54 to 77 years old (mean age 61 years).	RT-PCR	Acute dyspnea (SpO_2 <94% or breathing difficulty).	Body mass index >30 (17%); SAH (24%); coronariopathy (11%); cardiac failure (16%); diabetes mellitus (16%); chronic obstructive pulmonary disease (10%); cancer (7%); chronic kidney disease (2%), hepatopathy (1%) and immunosuppression (1%).	NS
Yassa et al.[66]	Turkey	Prospective cohort	296 pregnant women (23 with positive result for COVID-19), age range from 17 to 43 years old (mean age 26.8 years); gestacional period from 5 to 42 weeks (mean gestacional period 35.18 weeks).	RT-PCR	Pregnant women admitted in Gynecology and Obstetrics unit for any reason were tested for SARS-CoV-2 RT-PCR and examined with LU; 23 pregnant women with positive SARS-CoV-2 RT-PCR result, from whom 11 (3.72%) were symptomatic and 12 (4.05%) were asymptomatic.	NS	NS

Table 1 (*Continued*)

Study	Country	Type of study	Patients and participants included in the studies	Diagnosis of COVID-19	Clinical picture	Comorbidities	Treatment
Zhao et al.[67]	China	Retrospective study	35 (24 men and 11 women) patients divided into 2 groups: refractory (7 patients), mean age 62.14 years and non-refractory (28 patients), mean age 64.14 years.	RT-PCR	1. Severe: respiratory distress with RF $\geq$30, SpO_2 $\leq$93% and PaO_2/FiO_2 $\leq$300 mmHg, at rest. Non-refractory. 2. Critical: respiratory failure requiring mechanical ventilation, shock and another organic failure requiring admission in the ICU. Non-refractory. 3. Refractory: refractory respiratory disease with PaO_2/FiO_2 $\leq$100 mmHg or patients treated with ECMO.	NS	High flow nasal cannula; mechanical ventilation; ECMO.
Dargent et al.[68]	France	Prospective study	10 (8 men and 2 women) ages ranging from 46 to 63 (mean age 56 years).	RT-PCR	Moderate to severe ARDS.	Obesity	Mechanical ventilation.
Bonadia et al.[69]	Italy	Prospective cohort	41 (28 men and 13 women) mean age 60 $\pm$ 22.7 years.	RT-PCR	24 patients (58.5%) with dyspnea; 32 patients (78%) with fever; 27 patients (65.8%) with cough.	NS	Ventilatory support: none in 11 (26.8%); low flow oxygen in 13 (31.7%); high flow oxygen in 2 (4.9%); non-invasive positive pressure ventilation in 9 (21.9%); intubation in 6 (14.6%).
Deng et al.[70]	China	Retrospective study	128* (75 men and 53 women) ages ranging from 55 to 71 years old (mean age 65 years).	RT-PCR	Divided into 4 groups: 1. Light: light symptoms without HRCT alteration. 2. Common: fever and signals of respiratory infection with pneumonia alterations in the HRCT. 3. Severe: any of these symptoms, (a) respiratory distress with RF $\geq$30, (b) SpO_2 $\leq$93% at rest or (c) PaO_2/FiO_2 $\leq$300 mmHg. 4. Critical: (a) respiratory failure requiring mechanical ventilation, (b) shock, (c) admission in the ICU due to multiple organ failure.	44 (34%) patients with hypertension; 22 (17.2%) patients with coronary disease; 19 (14,8%) patients with diabetes melittus; fatigue (96.1%); fever (95.3%) and breathlessness (94.5%); decreased SpO_2 in 99 (77.3%) patients.	Oxygen therapy in all patients. Non-invasive ventilation in 38 patients; mechanical ventilation in 31 patients; ECMO in 4 patients; and 42 patients in the ICU. * Out of the 128 participants, 7 remained in hospital, 84 were discharged and 37 died.

Table 1 (*Continued*)

Study	Country	Type of study	Patients and participants included in the studies	Diagnosis of COVID-19	Clinical picture	Comorbidities	Treatment
Pagano et al.[71]	Italy	Observational study	18 (13 men and 5 women), mean age 69 years.	RT-PCR	Light to moderate ARDS.	NS	Non-invasive CPAP.
Martinez et al.[72]	Spain	Case series	3 (pediatrics age range without specifying the individuals' ages).	RT-PCR	NS	Severe, but not specific.	NS
Yu et al.[73]	China	Case report	Case 1 = 54-year-old man.	RT-PCR	Case 1 = cough.	NS	NS
			Case 2 = 37-year-old woman.	RT-PCR	Case 2 = tightness in chest for a week, solved at admission. Without respiratory symptoms.	NS	NS
Cho et al.[74]	South Korea	Case series	6 (2 men and 4 women) ages ranging from 16 months to 85 years old.	RT-PCR	Case 1 = sore throat, backache, dry cough and fever on the 5th day.	NS	Case 1 = lopinavir/ritonavir.
				RT-PCR	Case 2 = cough and chills for a day, fever >37.5 °C temperature and myalgia.	NS	Case 2 = lopinavir/ritonavir.
				RT-PCR	Case 3 = dyspnea and fever >37.5 °C temperature.	NS	Case 3 = OTI and mechanical ventilation.
				RT-PCR	Case 4 = fever for 8 days, dyspnea.	NS	Case 4 = empirical antibiotic therapy and oseltamivir followed by lopinavir/ritonavir; OTI, methylprednisolone + inhaled nitric oxide and veno-venous ECMO.
				RT-PCR	Case 5 = rhinorrhea, nasal obstruction and sputum.	NS	Case 5 = NS
				RT-PCR	Case 6 = asymptomatic and stable.	NS	Case 6 = no need for treatment.
Lichter et al.[75]	Israel	Prospective study	120 (74 men and 46 women) mean age 64.7 ± 18.2 years.	RT-PCR	Respiratory symptoms; fever; chest pain; fatigue; SpO_2 with 95% median and 89–98% interval.	Found in 81% of the patients: hypertension in 67 (55.8%); diabetes mellitus in 34 (28.3); obesity (not informed %); atrial fibrilation/flutter in 21 (17.5%); ischemic cardiac disease in 21 (17.5%); transient ischemic attack/stroke in 14 (11.7%).	NS

Table 1 (*Continued*)

Study	Country	Type of study	Patients and participants included in the studies	Diagnosis of COVID-19	Clinical picture	Comorbidities	Treatment
Lu et al.[76]	China	Observational study	16 (9 men and 7 women), ages ranging from 47 to 68 years old (mean age 58 years).	NS	Severe COVID-19 consistent with any of the following criteria: respiratory difficulty, RF >30 or SpO_2 <93% in ambient air or PaO_2/FiO_2 $\leq$300 mmHg or pulmonary lesion with over 50% progression in 24-48 h in imaging examination.	NS	High flow cannula, non-invasive ventilation and OTI with mechanical ventilation.
Dini et al.[77]	Italy	Observational study	150 (23 men and 127 women), ages ranging from 72 to 106 years old (mean age 88 years).	RT-PCR	Respiratory symptoms, cough, dyspnea, fever, asthenia.	92 (61.3%) patients with hypertension; 35 (23%) patients with chronic kidney disease; 28 (18.7%) patients with diabetes mellitus; 25 (16.7%) patients with coronary disease; 41 (27.3%) patients with other cardiac diseases; 44 (29.3%) patients with stroke; 28 (18.7%) patients with atrial fibrillation; 12 (8%) patients with cardiac failure; chronic obstructive pulmonary disease in 13 (8.7%) patients.	NS
Iodice et al.[78]	Italy	Observational study	29 (26 men and 3 women), ages ranging from 34 to 79 years old (mean age 60 years).	RT-PCR	Fever: 26 (90%) patients; cough: 15 (52%) patients; dyspnea: 8 (28%) patients; arthralgia: 4 (14%) patients; conjunctivitis: 2 (7%) patients.	15 (62%) patients with hypertension; 5 (21%) patients with diabetes mellitus; 4 (17%) patients with asthma; 6 (21%) smoker patients.	Oxygen therapy in 23 (79%) patients.

Table 1 (*Continued*)

Study	Country	Type of study	Patients and participants included in the studies	Diagnosis of COVID-19	Clinical picture	Comorbidities	Treatment
Tung-Chen et al.[79]	Spain	Prospective study	51 (28 men and 23 women), mean age 61.4 years.	RT-PCR	Dyspnea: 29 (56.9%) patients; fever: 23 (45.1%) patients; myasthenia: 22 (43.1%) patients; gastrointestinal tract symptoms: 10 (19.6%) patients; cough: 22 (43.1%) patients; ageusia/anosmia: 4 (7.8%) patients.	14 (27.5%) patients with cardiovascular disease; 12 (23.5%) patients with pulmonary disease; 10 (19.6%) patients with diabetes mellitus; 6 (11.8%) patients with chronic kidney disease; 8 (15.8%) patients with immunosuppression; 20 (39.2%) patients with hypertension; 13 (25.5%) patients with malignity.	NS
Gregorio-Hernández et al.[80]	Spain	Case report	Case 1 (male newborn)= 2 days old and gestacional period = 38 + 3	RT-PCR	Case 1 = mother with postpartum fever without respiratory symptoms.	Case 1: meconium aspiration syndrome.	Case 1: mechanical ventilation, nitric oxide, vasoactive drugs, cooling therapy and anticonvulsants (due to severe hypoxic ischemic encephalopathy).
			Case 2 (male newborn)=78 days old and gestacional period=39+3.	RT-PCR	Case 2 = asymptomatic, but investigated after case 1 diagnosis.	Case 2: prematurity and bronchopulmonary dysplasia.	Case 2: oxygen therapy.
			Case 3 (male newborn) = 6 days old and gestacional period=39+6 (gestacional period at the moment of the diagnosis).	RT-PCR	Case 3=asymptomatic, but investigated after case 1 diagnosis.	Case 3: Hirschsprung.	Case 3: no need for respiratory support.
LeVine et al.[81]	Bhutan	Case report	A 76-year-old man.	RT-PCR	Swell, loss of appetite, diarrhea and fatigue in the first 48 h. Cough and dyspnea with 78% SpO_2 in ambient air on the 4th day of symptoms.	Hypertension, hyperlipidemia, neuropathy and splenectomy due to mantle cell lymphoma.	Oxygen therapy, OTI and prone position, intravenous immunoglobulin, oseltamivir, ceftriaxone, doxycycline, lopinavir/ritonavir and antibiotic substitution with meropenem and vancomycin.

Table 1 (*Continued*)

Study	Country	Type of study	Patients and participants included in the studies	Diagnosis of COVID-19	Clinical picture	Comorbidities	Treatment
Nouvenne et al.[82]	Italy	Observational study	83 participants (23 men and 60 women), mean age 85 ± 8 years.	RT-PCR	33 (40%) patients with cough; 52 (63%) patients with fever; 33 (40%) patients with dyspnea or light desaturation.	NS	Empirical pharmacological treatment with antibiotics, hydroxychloroquine and corticosteroids.
Yang et al.[83]	China	Observational study	29 participants (18 men and 11 women), mean age 55.2 ± 16 years.	NS	NS	NS	NS
Schmid et al.[84]	Germany	Case report	A 76-year-old man.	NS	Fever for four days; dry cough and diarrhea; tachypnea, respiratory failure, 93% SpO_2 (with O_2 15 L/min in mask).	Absence of comorbidities.	Intensive treatment, not specified.
López Zúñiga et al.[85]	Spain	Case report	Case 1 = 87-year-old man. Case 2 = 53-year-old man. Case 3= 55-year-old man. Case 4 = 35-year-old-man.	Cases 1 = positive RT-PCR. Case 2 = negative RT-PCR with positive serology. Case 3 = positive RT-PCR. Case 4=diagnositc exam not specified.	Case 1 = dyspnea, dry cough, no fever. Case 2 = fever, cough, dyspnea. Case 3 = dyspnea. Case 4 = fever for 3 days.	NS	NS
Giacomelli et al.[86]	Italy	Case report	A 67-year-old man.	RT-PCR	Fever for 7 days, absence of cough or dyspnea; 89% SpO_2 in ambient air.	Hypertension; surgical background of abdominal aorta aneurysm open repair with graft in 2014.	Antiviral therapy (lopinavir/ritonavir); hydroxychloroquine; thrombotic prophylaxis with prophylactic subcutaneous enoxaparin; CPAP and introduction of methylprednisolone and tocilizumab; OTI and prone position. After worsening and evidence of the abdominal aorta graft thrombosis, introduction of sodium heparin and the use of vasoactive drugs.

Table 1 (*Continued*)

Study	Country	Type of study	Patients and participants included in the studies	Diagnosis of COVID-19	Clinical picture	Comorbidities	Treatment
Nouvenne et al.[87]	Italy	Transversal observational	26 participants (14 men and 12 women), mean age 64 ± 16 years.	RT-PCR	25 (96%) patients with fever; 21 (81%) patients with cough; 10 (38%) patients with dyspnea.	Comorbidities in 19 (73%) patients, but not specified.	Oxygen therapy in 17 (26%) patients.
Peyrony et al.[88]	France	Prospective observational cohort	391 participants (241 men and 150 women) ages ranging from 48 to 71 years old (mean age 62 years).	Positive RT-PCR in 225 (57.6%) patients.	Fever in 176 (78.2%) patients; cough in 158 (70.2%) patients; dyspnea in 131 (58.2%) patients; myalgia in 71 (31.6%) patients; rhinitis/pharyngitis in 19 (8.4%) patients; anosmia in 31 (13.8%) patients.	Immunosuppression in 195 (50.5%) patients. Chronic pulmonary disease in 85 (22.1%) patients. Cardiovascular disease in 156 (40.4%) patients. Obesity in 58 (15.2%) participants.	NS
Rodriguez-Gonzalez et al.[89]	Spain	Case report	A 6-month-old male participant.	Negative RT-PCR. Detection of anti-SARS-CoV-2 Immunoglobulin M and anti-SARS-CoV-2 Immunoglobulin G on day 21 of illness.	2-week history of nasal congestion and cough, irritability, tachypnoea (80 breaths per minute), cyanosis (81% SpO_2), tachycardia (170 beats per minute), hypotension (59/32 mmHg), poor perfusion, weak peripheral pulses and hepatomegaly (3 cm).	Short bowel syndrome with fever and cyanosis; cardiogenic shock secondary to severe pulmonary hypertension and right ventricular failure without pulmonary thromboembolism condition labelled as pediatric multisystem inflammatory syndrome.	Prophylaxis with low molecular weight heparin; mechanical ventilation and prone position; inotropic support with milrinone and norepinephrine and broad-spectrum antibiotics (meropenem, vancomycin and fluconazole); Tocilizumab, azithromycin, hydroxychloroquine and methylprednisolone.

COVID-19 = coronavirus disease 2019; RT-PCR = real time polymerase chain reaction; O_2 = oxygen; SpO_2 = oxygen peripheral saturation; ICU = intensive care unit; NS = not stated; RF = respiratory frequency; LU = lung ultrasound; SAH = systemic arterial hypertension; FiO_2 = fraction of inspired oxygen; OTI = orotracheal intubation; CPAP = Continuous Positive Airway Pressure; HRCT = high resolution computerized tomography; ECMO = Extracorporeal Membrane Oxygenation; PaO_2 = oxygen arterial pressure; ARDS = acute respiratory distress syndrome; % = percentage; USA=United States of America; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2.

totaling 17 patients, 6 of them had cough, 5 had fever, 2 had dyspnea, 1 had anosmia, 1 had chest pain and lastly for 11 of them, although symptomatic, their symptoms were not specified.[30,31,34,66]

The results of the studies revealed that patients presenting a clinical condition of dyspnea and hypoxemia showed alterations in the pulmonary aeration evaluated by LU. The evolution of the A line pattern into the appearance of B lines and consolidations was associated with the worsening of the disease and, consequently, of the clinical signals and symptoms.

The related comorbidities reported included hypertension, obesity, asthma and dyslipidemia, obstructive sleep apnea, rheumatoid arthritis, systemic lupus erythematosus, atrial fibrillation, end-stage kidney disease, dementia, diabetes mellitus, cancer and immunosuppression, liver disease, coronary disease, transient ischemic attack and stroke, and chronic obstructive pulmonary disease.

Regarding therapeutic measures, 19 studies did not mention the treatment employed. Some studies mentioned support measures, oxygen therapy and non-invasive ventilation[19,25,26,29,35,67,69,70,74,76,78,80,87] or intubation with invasive mechanical ventilation[19,33,36,67,69,70,76,80,81,86,89] and extracorporeal membrane oxygenation.[67,70,74] The pharmacological interventions reported included the use of hydroxychloroquine, azithromycin, corticosteroids, oseltamivir, favipirapir, lopinavir/ritonavir, tolicizumab, sarilumab (anti-IL6), enoxaparin and broad-spectrum antibiotics,[30,35,74,81,86,89] interferon inhalation therapy appeared in a single study,[29] and another study reported the use of intravenous immunoglobulin.[81]

LU was implemented in the context of the SARS-CoV-2 infection in all studies and in 9 studies it was the only imaging test used in the propaedeutic of lung disease.[12,34,64,67,71,72,77,80,82]

Most of the studies under analysis had LU findings in common in the presence of SARS-CoV-2 infection. The most common finding was B lines, which had very distinct characteristics, 34 of which reported focal, diffuse and confluent B lines.[12,15,18,19,25,26,27,29,30,31,32–35,38,62,67,68,70,72–74,77–88] Twenty-nine studies described consolidations of different types: small, large, linear, subpleural, multifocal and translobar,[12,15,18,19,25,26,27,29,30,33,35,38,62,63,67,68,70,72,73,75,78–80,82–85,87,89] associated with white lung[12,30] and with air bronchograms[18,38]. Nineteen studies described pleural irregularities,[12,15,18,26,27,30,32,33,35,62,70,72,77,79,80,82,84,85,89] and 19 reported pleural and subpleural line alterations, such as thickening or shred sign.[18,19,26,29,31,32,34,38,62,67,70,72,73,75,77,80,85] Ten studies referred to pleural effusion,[38,62,67,70,72,75,77,82–84] 8 reported bilateral findings[15,34,63,79,82,86,87,88] and 3 revealed preponderance of compromise in posterior areas.[79,80,89] Three studies associated appearance of A lines during recovery [35,67,80] and most of the papers reported the LU role in the serial evaluation of patients with COVID-19.[27,29,30,33,35,67,68,70,71,72,74,75–77,80]

Other characteristics found were the presence of glass rockets[38] with or without the Birolleau variant,[26] also known as white lung.[61]

Some studies reported radiological findings agreement between LU and HCRT.[15,18,25,27,29,32,33,35,38,62,63,65,68,70,78,79,83,84,87,89] The main HCRT findings were ground glass opacities, ''crazy-paving'' pattern, consolidations, pulmonary infiltrates and pleural thickening as well as interlobular septal thickening.[18,29,32,33,35,38,62,65,68,70,73,75,78,79,81,83–85,87,89] When comparing thorax HRCT features with those of LU in pneumonia resulting from COVID-19 the findings included (i) correlation of ground glass opacity with B lines (multifocal, discrete or confluent); (ii) presence of thickened pleura in HRCT with thickening of the pleural line in LU; (iii) pulmonary infiltrates as confluent B lines in LU; (iv) pulmonary consolidation in both techniques[20] The finding ''white lung'' was also described as ground glass opacity in HRCT.[15,18,26,27,38,62,78,87]

The areas evaluated during LU presented varied results between studies; with the evaluation from 4 to 7 regions in each hemithorax depending on individual studies,[12,15,30,31,34,35,62–72,74–77,79,80,82,83,87] totaling 8, 10, 12 and 14 assessment areas in these papers. Differences were found in relation to the type of transducer used, whose choice was related to the propaedeutic strategy of better evaluation of superficial regions or smaller thoraces such as in children, using the linear probe, or deeper regions and larger thoraces using the curved probe.[12,15,25,31,34,35,38,62,66,67,69–72,74,76,77–80,82,87] Only one study employed sectorial probe in the pulmonary evaluation, since the institution protocols of that study advocated the point-of-care cardiac evaluation.[75]

Eighteen studies used LU scores.[12,38,62–64,67–71,74–77,79,80,82,87] One study proposed a unified approach to standardize the use of LU in the clinical management of patients with COVID-19,[12] with a score system to classify the seriousness of the lung disease (score): (0 points) presence of A lines with continuous and regular pleural line; (1 point) presence of visible B lines and irregularities in the pleural line; (2 points) presence of discontinuous pleural line with dark areas under the pleura (consolidations) with associations of B lines; (3 points) presence of coalescent B lines with ''white lung'' aspect, dense and widely distributed, with or without consolidations. In that study, 14 thoracic regions were evaluated, using a LU score from 0 to 42 points, in which higher score represented higher severity. Another study[38] applied an LU scoring method ranging from 0 to 36 points in which both hemithoraces were divided into six regions (totaling 12 areas) where: (0) points = presence of pleural line and A-line, <3 B-lines; (1) point = presence of more than 3 B-lines; (2) points = presence of coalescent B-lines; (3) points = presence of pulmonary consolidation signs. The same assay presented a classification of severity of lung lesions: none (0 points); mild (1–7 points); moderate (8–18 points), severe ($\geq$19 points).[40] A third assay showed a scoring system of three items: (a) pleural line involvement, where (0) points = normal; (1) point = thickening ($\geq$0.5 mm) or irregular; (2) points = blurred; (3) points = discontinuous, fragmented; (b) lung parenchymal involvement, where (0) points = no B-line; (1) point = presence of B-line $\leq$3; (2) points = presence of B-lines $\geq$4 or partially merged; (3) points = presence of B-line fully integrated (white lung or waterfall sign); (4) points = presence of pulmonary consolidation or subpleural lesion; (c) complications, where (0) points = none; (4) points = am line (pulmonary balloon); (4) points = pneumothorax or empyema; (4) points = pleural effusion. Pleural line, pul-

Table 2 Characteristics of the lung ultrasound and other image exams findings in COVID-19.

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Thomas et al.[19]	Multifocal B lines; pleural and subpleural thickening; consolidation.	Thorax X-ray with bilateral infiltrates.	NS	NS	LU might be useful to manage COVID-19 suspected patients, even if it does not allow the differentiation of the viral pneumonia causes.
Soldati et al.[12]	Small and large consolidated areas, pleural irregularities, blank vertical areas and extensive blank lung with or without consolidation.	None	LU score:0–3 points in 14 areas (three posterior, two lateral and two posterior in each hemithorax). Portable machines dedicated to exclusive use in patients with COVID-19. Convex or Linear probes, according to the patient's body size.	Yes	Experience of the service in the standardization of COVID-19 assistance with emphasis on the need for a shared data base.
Buonsenso et al.[15]	Irregular pleural line with small subpleural consolidations, blank lung areas, irregular and confluent vertical artifacts (B lines). Bilaterally present preserved areas and mixed with affected areas.	Thorax X-ray with doubtful left peri-hylar hypodiafania and HRCT (ground glass pattern).	A total of 12 areas were evaluated. Portable convex probe (3.5MHz).	Yes	Evaluation using portable LU and two examiners.
Kim et al.[18]	B lines with variable aspect (focal, multifocal and confluent), subpleural consolidations, pleural thickening or irregularity and larger consolidations with occasional air bronchograms.	HRTC with ground glass opacity. POCUS for cardiac scan.	Handheld devices. Without probe description in the article.	Complete +ultrasound protective equipment.	Antisepsis care and preventing contamination during LU.
Denina et al.[25]	Subpleural consolidations (2 patients). Confluent B lines (5 patients). Agreement with radiologic findings in 7 out of the 8 cases. One patient presented B line interstitial pattern, despite the normal thorax X-ray.	Thorax X-ray with consolidation in two patients and ground glass opacities.	Linear transducer from 7.5 to 13 MHz.	NS	LU showing high agreement with thorax X-ray examination; might reduce radiologic exams; able to stratify the patients according to severity into mild, moderate and severe; follow-up, exam repetition before discharge.
Yasukawa et al.[26]	Glass rockets with or without Birolleau variant (white lung); confluent B lines and thick and irregular pleural lines; small subpleura consolidations (5 patients); large consolidation (1 patient).	X-ray and tomography.	NS	Yes	LU might be more sensitive than thorax X-ray in the diagnosis of interstitial syndrome. When resources are limited, where thorax radiograph, tomography and SARS-CoV-2 RT-PCR are not promptly available or the response time is long, LU might help COVID-19 diagnosis.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Musolino et al.[27]	Vertical artifacts, white lung areas, subpleural consolidations and pleural irregularities.	X-ray (unspecified diffuse interstitial thickening), tomography (the findings of one case correlated to the LU findings) and resonance (signs of pneumonia).	Pocket wireless device. Sitting patients. Exam performed by 2 pediatricians with over 5 years of ultrasound experience. LU performed within 12 h of hospital admission.	Yes	Useful tool for the diagnosis and follow-up of COVID-19 related pneumonia. This study aimed at evaluating the LU role in COVID-19 child patients.
Ji et al.[29]	Multiple B lines, small consolidations and pleural line thickening.	Thorax tomography (multiple bilateral and peripheral ground glass opacities).	NS	NS	LU showed reduction of B lines in the evolution (initially they were 88 and reduced to 18) with disappearance of consolidations.
Buosenso et al.[30]	Irregularities in the pleural line. Consolidations with white lung area. Vertical artefacts.	Thorax X-ray was done in two patients only. Patient 1 was compatible with interstitial disease and patient 4 with hyperlucency and basal bilateral alteration. None submitted to tomography.	A total of 14 regions were evaluated. LU was carried out before the positive SARS-CoV-2 RT-PCR result.	NS	LU evaluation along the illness evolution showing improvement of the LU findings with relevant role in the therapeutic decision.
Inchingolo et al.[31]	Diffuse hyperechoic vertical artifacts with thickened pleural liens and white lung with irregular distribution.	Thorax X-ray performed on the same day, did not suggest viral pneumonia.	A total of 14 regions (3 posterior, 2 lateral and 2 anterior in each hemithorax) along the paravertebral, middle axillar and hemiclavicular lines were evaluated. Convex wireless transducer (3.5MHz).	NS	LU was shown to be an accurate imaging method to detect pleural and peripheral pulmonary conditions, including pneumonia, with great accuracy, even in pregnant women.
Duclos et al.[32]	A lines. Focal and confluent B lines. Pleural line thickening and irregularities.	Tomography: multilobar asymmetric lung lesions with peripheral distribution of ground glass opacities, consolidation, and crazy pavement pattern.	NS	NS	Direct comparison between LU and tomography and close time relation.
Zieleskiewicz et al.[33]	Elderly, 72 years old: coalescent B lines and pleural line irregularities alternating with normal area.	Tomography: 72-year-old female patient: bilateral and multilobar ground-glass peripheral opacities.	NS	NS	Comparison between tomography and LU was carried out at the same time. Emphasizes the LU potential to evaluate COVID-19 associated pneumonia in several stages.
	Elderly, 65 years old: pleural line irregularities associated with coalescent B lines, or multifocal subpleural consolidations.	Tomography: 65-year-old male patient: subpleural fibrosis, honeycomb, traction bronchiectasis with anterior distribution and interlobular septal thickening.	NS	NS	

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Youssef et al.[34]	Pleural thickening. Bilateral diffuse coalescent B lines.	Normal obstetric ultrasound.	A total of 6 regions (2 anterior, 2 lateral and 2 posterior in each hemithorax) were evaluated. Linear or convex probes.	NS	Simplified LU systematic approach to motivate its adoption by obstetricians and gynaecologists.
Tung-Chen et al.,[35]	Day 1 = A-lines; day 2 = pleural effusion; day 4 = subpleural consolidation; day 10 = diffuse B-lines; day 14 = irregular pleural lines and resolving B-lines; day 35 = A-lines.	Chest X-ray: local or bilateral patchy shadowing infiltrate. CT: ground glass opacities.	A total of 8 regions were evaluated. Curvilinear probe.	NS	LU guiding monitoring and therapeutic decision.
Lu et al.[38]	3 patients = normal aeration on LU; 27 patients = increased B-lines; 15 patients = coalescent B-lines (<3 mm); 5 patients = wide distance between B-lines (>7 mm) and the lung rocket sign; 3 patients = ''white lung'' sign; 6 patients = pulmonary consolidations including 2 with the presence of air bronchogram and 3 with shred signs; 3 patients = pleural thickening; 1 patient = pleural effusion; 1 patient = pneumothorax.	CT showed patchy ground glass opacities, consolidations, reticular shadows, small amount of pleural effusion.	Six regions (anterior superior, anterior inferior, lateral superior, lateral inferior, posterior superior and posterior inferior in each hemithorax) were evaluated and associated with a score method of 0–3 points in each area. Convex array transducer (2-5MHz) and linear array transducer (5-12MHz).	Yes	Comparison between LU score and tomography score was performed. Bedside ultrasound exhibits relatively low sensitivity with respect to lesions in the vicinity of the pulmonary hilum, which influences the quantitative assessment of lung lesions in patients with COVID-19.
Tan et al.[62]	i. Thickened pleural line (12/12 patients); blurred or irregular (9/12 patients) and fragmented (6/12 patients); ii. Scattered B lines and comet tail signals (4/12 patients); partially diffuse (12/12 patients); completely diffuse with white lung (10/12 patients) or waterfall sign (4/12 patients); iii. Pulmonary consolidations or subpleural focal lesions <1 cm (5/12 patients); iv. Pleural effusion (1/12 patient).	CT with semi quantitative scoring method: ground-glass opacities, irregular pleural margin, septal or subpleural lines, honeycomb, subpleural cyst.	A total of 5 regions in each hemithorax were evaluated. BLUE protocol and BLUE Plus protocol were used in the study. The LU scoring system (i) pleural line involvement, including thickened, blurred, irregular or discontinuous pleural lines; (ii) lung parenchymal involvement, including B lines, partially diffused B lines, completely diffused B-lines (white lung) and lung consolidations; (iii) complications, including pneumothorax, emphysema, and pleural effusion. Portable device with convex array probe 2-5MHz.	NS	The study pointed out some differences in the LU findings in patients with COVID-19 related pneumonia and community-acquired pneumonia. The LU semiquantitative evaluation is viable to assess severity in interstitial pneumonia, including in patients with COVID-19.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Mafort et al.[63]	B lines >2 (72.6%); coalescent B lines (36.2%); subpleural consolidations (8.06%). Unilateral lesions in 204 (49.9%) patients and bilateral in 205 (50.1%) patients.	Most patients were not submitted to CT.	A total of 12 areas (2 anterior, 2 lateral and 2 posterior in each hemithorax) were evaluated. Aeration score: 1 point=presence of >2 B lines; 2 points=presence of coalescent B lines; 3 points=presence of consolidations.	NS	Strong association between consolidation and dyspnea. LU findings can precede the patient clinical condition. LU shows prognostic capability in ARDS before evidence of hypoxemia, LU can define changes that affect the air/tissue relation on the lung surface. There is a correlation between LU and CT results with histopathological findings. In the study, the LU was not carried out in the patient follow-up/evolution and hospitalized patients were not included.
Veronese et al.[64]	The most common findings of the study were not specified.	None.	A total of 12 areas (2 anterior, 2 lateral and 2 posterior in each hemithorax) were evaluated. LU score from 0 to 3 points, in which 1 point = presence of separated B lines occupying <50% of the pleural line; 2 points = presence of separated B lines occupying >50% of the pleural line; 3 points = lung thickening with a tissue aspect.	Complete	LU as mortality predictor = prognostic role. Greater accuracy for the LU when compared to the wrist oximeter. LU can be used in nursing homes or households. Study bias: small sample size and disregard of positive (such as medication therapy) or negative factors (such as comorbidities and polypharmacy).
Zieleskiewicz et al.[65]	High diagnostic accuracy when compared to the X-ray in interstitial syndromes and alveolar consolidations. The most frequent LU findings were not specified in the study.	CT with ground glass opacity, consolidations and interlobular septal thickening.	A total of 12 areas were evaluated, with the posterior ones in the posterior axillary line, rather than accessing via paravertebral.	NS	LU score predictive of pneumonia severity, as evaluated in the CT and clinical characteristics. LU associated to severity evaluated by the CT and clinical parameters, with the possibility of substituting CT in the evaluation of the pulmonary involvement. POCUS for multiorgan evaluation: detection of deep venous thrombosis and acute right cardiac failure signals.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Yassa et al.[66]	NS	Image with ionizing radiation in 1% — X-ray and CT (3 patients out of 296).	Convex transducer. A total of 14 areas (10 seconds per area) were evaluated. The patients were considered negative for SARS-CoV-2 infection suspicion when the LU score was 0 or 1 (in the absence of symptoms) point; however, patients were considered positive for SARS-CoV-2 infection in the presence of score 1 point and with symptoms, and scores 2 points and 3 points.	Complete	LU used to screen SARS-CoV-2 infection concluding that the LU findings were more sensitive than the maternal symptoms in the infection prediction. Potential to be used as a triage tool and in the evaluation of disease severity with the advantage of being used freely during pregnancy reducing exposure to radiation.
Zhao et al.[67]	Most common findings in both groups were the B line patterns and shred sign. More ground glass opacity, consolidations and pleural effusion were observed in the refractory group.	Cites CT as gold standard, but does not explain its use in the patients of the study.	Convex transducer was used. A total of 10 areas (anterosuperior 2nd ICS and anteroinferior 5th ICS in the hemiclavicular line, laterosuperior 2nd ICS and lateroinferior 5th ICS in the mid-axillary line and posterior in the subscapular zone) were evaluated. LU score (from 0 to 40 points): 0 points = normal pattern with pleural sliding, parallel A lines and thin pleural line; 1 point = presence of B line patterns; 2 points = presence of ground glass signal with B lines occupying the whole screen; 3 points = presence of fragmentation signal similar to small subpleural consolidations; 4 points = presence of consolidation/pulmonary hepatization signal or pleural effusion.	Complete	All images were reviewed and scored by 2 medical doctors with over 5 years of experience in LU applied to critical care. LU used in the follow-up for evolution assessment: transformation of B lines into A lines; reduction and disappearance of consolidations; more consolidations and more interstitial syndrome pattern, which might mean disease worsening. LU can be used to evaluate aeration in critical patients.
Dargent et al.[68]	B line patterns and consolidations.	CT: subpleural ground glass opacity with progressive extension and consolidations.	A total of 12 areas were evaluated. LU core from 0 to 3 points, in which 0 points = normal; 1 point =presence of well-defined B lines; 2 points = presence of coalescent B lines and/or subpleural thickening $\leq$15 mm and subpleural consolidations; 3 points = presence of consolidations (pleural thickening $\geq$15 mm), variation from 0 to 36 points.	NS	Higher score in deaths due to refractory hypoxemia and LU helped early diagnosis of pneumonia associated to mechanical ventilation. Good agrement between LU and CT for the presence of consolidations.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Bonadia et al.[69]	Normal LU in three patients and pathological in 38 (92.7%) patients.	Pathological CXR in 34 (82.8%) patients and pathological CT in all patients submitted to examination (n = 17).	Portable, wireless device, with convex transducer. A total of 14 areas (2 anterior, 2 lateral and 3 posterior in each hemithorax) were evalauted during 10 seconds in each area. LU score from 0 to 3 points, where: 0 points = normal; 1 point = presence of regular or irregular pleural line with visible and non-confluent vertical artifacts; 2 points =presence of irregular pleural line with multiple and conludne vertical artifacts and/or subpleural consolidations; 3 points = presence of extensive and dense white lung areas with or without larger consolidations.	NS	Lung global assessment is mandatory, since each pulmonary area might be in distinct stages of the disease. LU carried out at the emergency room in the first evaluation is able to predict the global prognosis, the need for admission to the ICU and identify patients in greater death risk.
Deng et al.[70]	Numerous and coalescent B lines with small multifocal consolidations in several regions — most common.	CT with ground glass opacity (96.1% patients), followed by consolidations (75.8% patients) and crazy paving pattern (ground glass opacity with overlapping of inter and intralobular septal thickening) (60.9% patients).	Convex transducer and adjusted around 10 cm deep. A total of 8 areas (2 anterior and 2 lateral in each hemithorax) were evaluated, in which the superior and inferior zones are delimited by the 3rd ICS. Images analyzed and scored by three blinded medical doctors with 3–6 years of experience.	NS	CT is not suitable for the follow-up of critically ill patients (despite being gold standard) due to transportation and medical team infection risks.
	Presence of pleural line thickening and irregularities.	Most patients with bilateral and multifocal involvement.	LU score (0-24 points): 0 points = presence of A lines with pleural sliding or up to 2 isolated B lines; 1 point = presence of 3 or more spaced B lines restricted to a single ICS; 2 points=presence of multiple B lines (>50% of the area evaluated) with or without consolidations limited to the subpleural space; 3 points=presence of confluent or tissue-like pattern B lines, characterized by dynamic air bronchograms, defined as pulmonary consolidations.		LU carried out every 48 h after admission or when the examiners thought it was necessary. Change in score $\geq$2 points meant improvement, while $\leq$2 points meant worsening and = 1, unchanged condition.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
	Increase in B lines in different degrees and extension. Small and multifocal consolidations limited to the subpleural space. Also, consolidations in mass with dynamic air bronchograms ocurred. Unusual pleural effusion and rare pneumothorax were found.	All patients showed peripheral pulmonary involvement.			The role of semi-quantitative scores in the follow-up of COVID-19 related pneumonia was studied. Positive LU correlation with CT to evaluate the LU accuracy was higher in critical patients when compared to the severe ones. The patients had been diagnosed before the examination; therefore, the LU was used to evaluate the severity of the lesions, but not to diagnose the disease. The LU was more accurate in the evaluation of the worsening than the improvement or maintenance of the condition.
Pagano et al.[71]	LU used to verify alveolar recruitment after non-invasive CPAP. It was carried out before and after CPAP.	CT is considered gold standard in the quantitative evaluation of recruitment and pulmonary aeration, but it is not carried out due to certain issues such as transport logistics, contamination, instability of critical patients, among others.	A total of 12 areas (anterior, lateral and posterior, divided into upper and lower sections in each hemithorax) were evaluated. LU score from 0 to 3 points: 0 points = presence of A lines or below 3 isolated B lines; 1 point = presence of multiple and well-spaced B lines; 2 points = presence of coalescent B lines with or without small subpleural consolidations; 3 points = presence of pulmonary consolidation. Convex transducer.	NS	LU is a valid technique to assess alveolar recruitment, evaluation of extra-vascular pulmonary water and improvement after CPAP application. Patients that improved the PaO_2/FiO_2 relation after 1 h of CPAP showed lower mortality.
Martinez et al.[72]	Pleural effusion in all patients, followed by diffuse and translobar subpleural consolidations, coalescent B lines and pleural line irregularities. No A line patterns were observed. Also, after a 3-month follow-up, all patients were asymptomatic, presented normal echocardiogram, no effusion and persistence of pleural thickening.	Cites CT as gold standard, but also the need for transfer of the critical/unstable patient, high infection risk and the ionizing radiation limits its use in children.	Linear transducer. A total of 10 areas (4 anterior — between the sternal and anterior axillary lines; 2 lateral — between the anterior and posterior axillary lines; 4 posterior — between the paravertebral and posterior axillary lines) were evaluated.	Cites sanitation/sterilization of transducers and the use of protection covers.	Infection in children is unusual and less severe.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Yu et al.[73]	Case 1 = increased B lines and focal pulmonary consolidation.	Case 1 = thorax X-ray indicating pulmonary infection. CT with irregular shadows of high density and bilateral ground glass opacity.	Using remote ultrasound robotic device assisted by the 5G technology.	NS	Real time robotic scan using big data, cloud storage and artificial intelligence. A robotic arm provided the examiners with protection and reduced the number of professionals in contact with the patients with COVID-19.
	Case 2 = partially thickened pleural line, intensive B lines, consistent with pneumonia signs.	Case 2 = multiple nodes with bilateral inflammatory appearance.			CT limitation in general application to all population groups (such as pregnant women and children).
Cho et al.[74]	Early detection of B lines, in patients with normal X-ray, corresponding to the ground glass opacities in the CT.	CXR and CT at hospital admission, however, no findings were specified.	Microconvex transducer was used to evaluated 12 areas. BLUE protocol was applied and it was done the use of the Venice self-learning system with automatic identification of B lines (distinction from artifacts). LU score: 0 points = presence of $\leq$2 B lines; 1 point= presence of 3 or 4 B lines (B1 lines); 2 points= presence of $\geq$5 B lines (B2 lines); 3 points = presence of consolidation(s).	Not specified, but exemplifies complete garments	LU proved useful in the monitoring of the disease evolution. Also, LU in the triage of SARS-CoV-2 infected patients was able to indetify greater risk of respiratory failure.
Lichter et al.[75]	Fragmented pleural thickening in 100 (83%) patients; irregular subpleural consolidations in at least one zone in 93 (78%) patients and pleural effusion in 9 (8%) patients.	CT with bilateral pulmonary infiltrates. CXR with bilateral infiltrates (39%); pleural effusion and rare lobar infiltrates (<15%).	Tranducer used for cardiac evaluation. A total of 12 areas (anterior, anterolateral and posterolateral in each hemithorax) were evaluated. LU score from 0 to 36 points: 0 points= presence of A lines; 1 point= presence of B1 lines (separated = moderate loss of pulmonary aeration); 2 points = presence of B2 lines (coalescent = severe loss of pulmonary aeration); 3 = presence of consolidation (complete loss of aeration). The pleural thickening was determined qualitatively.	Complete	LU identifies quickly the pulmonary involvement allowing stratification and prediction of the need for mechanical ventilation, mortality and outcome. The main factor responsible for the LU worse score was a new or greater involvement of the anterior pulmonary segments, a finding that can be used clinically as an alert of imminent clinical deterioration.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Lu et al.[76]	NS	NS	Convex transducer (2-4MHz). A total of 12 areas were evalauted with LU score from 0 to 3 points for each of them (0–36 points in total). LU score: 0 (normal aeration) points= presence of pleural sliding with A lines or less than 2 vertical isolated B lines; 1 (moderate loss of pulmonary aeration) point= presence of spaced or coalescent B1 lines, multiple, well-defined or small juxtapleural consolidations; 2 (severe loss of pulmonary aeration) points= presence of multiple vertical coalescent B2 lines or juxtapleural consolidations found in the whole area of one or two intercostal spaces and corresponding to alveolar edema; 3 points = presence of pulmonary consolidations with static or dynamic air bronchograms up to the complete loss of aeration.	NS	LU can be a more precise indicator of the ideal moment of intubation than the oxygenation index and the respiratory rate.
Dini et al.[77]	Non-coalescent B lines in >3 zones (36 patients); coalescent B lines in >3 zones (32 patients); not consolidated hyperdense condition (30 patients); pleural effusion (11 patients). Pleural line abnormalities in 90% (irregularities, discontinuities and fragmentations).	None	Linear or convex portable wireless transducer. A total of 8 to 12 areas were evaluated. LU score from 0 to 3 points, where: 0 points=presence of normal pattern; A lines or insignificant B lines; 1 point=presence of non-coalescent B lines in >3 zones; 2 points=presence of coalescent B lines in >3 areas; 3 points=presence of not consolidated hyperdense condition.	Sanitation and disposable plastic packaging. Personal/Individual protection equipment not specified.	Serial evaluation strategy in population of older people in nursing homes and support institutions.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Iodice et al.[78]	Multiple B lines and consolidations. White lung.	CT: bilateral multiple lesions; 80% showed bilateral ground glass opacity; 62% showed evidence of consolidation in the left lung and 69% had consolidation in the right lung; crazy paving pattern in 17%.	LU score were not informed. Convex (3-5MHz) and linear (9-12MHz) transducers.	NS	LU and CT carried out on the same day. Ground glass opacity showed correlation with the presence of B lines in LU and the crazy paving pattern correlated with white lung in LU.
Tung Chen et al.[79]	Bilateral, isolated or confluent B line pattern, pleural irregularity, presence of linear and subpleural consolidations.	CT in 51 patients: pleural thickening in 2 (1%); ground-glass opacity in 37 (72.5%); septal thickening in 18 (35.2%); crazy paving in 10 (19.6%); subpleural consolidation in 10 (19.6%); pleural effusion in 12 (23.5%).	convex (3.5-5 MHz) and linear (9- A total of 12 areas with score from 0 to 3 points for each region evaluated (score from 0 to 36 points): 1 point= presence of irregular or isolated B lines; 2 points =presence of confluent B lines; 3 points = presence of consolidations or pleural effusion.	NS	Excellent correlation between CT and LU was observed.
	Subpleural consolidations in posterior regions of the basal lobes were the most common finding.	CXR in 28 patients: ground-glass opacity in 12 (42.9%); interstitial pattern in 13 (46.4%).	Portable device and convex transducer (1.5−4.5 MHz).		LU showed accuracy similar to that of the CT to detect pulmonary abnormalities in patients with COVID-19.
Gregorio-Hernández et al.[80]	Case 1 = LU in 3-day old patient without consolidation or coalescent B pattern; during evolution, presence of coalescent B lines and consolidation in the lateral and posterior areas. Case 2 = along the SARS-CoV-2 infection, more evident B pattern, mainly posterior with the appearance of consolidation. Blurred and thickened pleural line with normal pleural sliding. Case 3 = most areas with A pattern and thin pleural line with normal pleural sliding and isolated B lines; in posterior regions, thickened and blurred pleural line with coalescent B lines and millimetric pleural consolidation; during the evolution, the findings disappeared.	NS	Portable device with linear transducer. A total of 6 areas were evaluated. LU score from 0 to 3 points (score from 0-18 points): 0 points = presence of A pattern; 1 point=presence of $\geq$3 B lines; 2 points= presence of agglomerated and coalescent B lines; 3 points = presence of extensive consolidation.	NS	LU use in the follow-up, repeated 48/48 h in the first week after diagnosis. Apperance of consolidations and coalescent B lines did not follow the respiratory deterioration.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
LeVine et al.[81]	B lines	CXR: light bilateral irregular infiltrates. CT: ground glass opacities consistent with acute respiratory distress syndrome.	NS	NS	LU and other imaging methods allowed early diagnosis of COVID-19 despite its atypical clinical presentation.
Nouvenne et al.[82]	Normal LU in 27 (33%) patients; bilateral multiple subpleural consolidations in 32 (39%) patients; diffuse bilateral B lines or white lung in 24 (30%) patients; focal B lines in 17 (20%) patients; pleural effusion in 3 (4%) patients; isolated abnormalities in the pleural line in 3 (4%) patients.	NS	Portable device with convex transducer (panoramic exploration) and linear (detailing the pleural line and subpleural alterations). A total of 8 areas were evaluated with LU score from 0 to 3 points (score 0–24 points): 0 points=presence of regular pleural line, presence of A lines; 1 point=presence of discontinued pleural line, focal B lines; 2 points=presence of fragmented pleural line, subpleural consolidations; 3 points=presence of white lung with or without consolidations.	NS	Bedside LU as auxiliary diagnosis in extra-hospital situations. Integration of anamnesis with clinic and LU allow the refinement of the diagnosis of respiratory diseases in the elderly, and might eliminate the need for avoidable hospital admission.
Yang et al.[83]	540 pulmonary regions were evaluated: multiple B lines in 324 regions; consolidations in 220 regions; pleural effusion in 67 regions.	CT showing 209 abnormal regions: ground glass opacities in 208 regions; consolidations in 16 regions; pleural effusion in 14 regions.	A total of 12 areas were evaluated. Considering regional alveolar-interstitial patterns such as multiple B lines ($\geq$3) within the region evaluated using LU or the presence of ground glass opacities in the CT. Alveolar-interstitial syndrome was defined as the presence of $\geq$2 regions with alveolar-interstitial pattern per side and bilateral positivity.	NS	LU and CT carried out in an interval $\leq$12 h. LU was more sensitive tha CT in the diagnosis of regional alveolar-interstitial pattern, alveolar-interstitial syndrome, consolidation and pleural effusion.
Schmid et al.[84]	Irregular pleural line with partially confluent B lines, mainly anterior and above the left lung. Presence of pleural sliding. Consolidation with hepatic echogenic texture, air bronchogram and pleural effusion in the right costophrenic sinus.	CT with ground glass opacities in the left apical lobe and consolidations in the right basal lobe.	NS	NS	Patient developed ARDS and multiple organ failure and died on the 14th day of evolution.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
López Zúñiga et al.[85]	LU use only in case 4: pleural line thickening and irregularity. Diffuse B lines and consolidations.	CXR in cases 1 and 2: unequal, diffuse alveolar-interstitial opacities, with peripheral predominance and pulmonary bases. CXR in case 4: no abnormalities found. CT in case 3: density diffusely increased with mainly ground glass peripheral bilateral distribution pattern, thickening of the interlobular sept or bronchiectasis.	NS	NS	LU proposed as an alternative for the diagnosis and monitoring of patients with COVID-19 with higher sensitivity than CXR, despite its low specificity.
Giacomelli et al.[86]	Bilateral moderate B lines, without pleural effusion.	CXR with interstitial thickening in the right mid and basal field.	NS	NS	SARS-CoV-2 associated to increased risk of thromboembolism due to inflammation, stasis and hypercoagulability condition. Patient with no signs of distal hypoperfusion at admission and ultrasound examination confirming graft patency, the only possible explanation would be hypercoagulability and COVID-19 related inflammation. Patient died.
Nouvennea et al.[87]	Bilateral involvement in 26 (100%) patients with predominance of basal, medial, or apical lobe involvement in 3 (12%) patients. Pattern of alveolar-interstitial syndrome: (i) with distinct B lines in 7 (27%) patients; (ii) with confluent B lines (white lung) in 17 (73%) patients; (iii) subpleural consolidations in 17 (73%) patients; (iv) parenchymal consolidations in 13 (50%) patients. LU score 15±5 points.	CT with, n (%): 26 (100) bilateral involvement, 21 (81) mixed axial distribution, 23 (88) involvement of 6 pulmonary lobes; 6 (23) predominance of basal, medial, or apical lobe involvement, 26 (100) Ground-glass opacities, 13 (50) subpleural lines, 15 (58) fat vessel sign, 4 (15) crazy paving sign, 2 (8) basal consolidations, 1 (4) centrolobular nodules, 1 (4) pleural effusion, 2 (8) lymphadenopathy.	Convex transducer for panoramic view and linear for abnormalities in the pleural line. A total of 8 areas were evaluated. LU score from 0 to 3 points, scores 0–24 (points): 0 points=regular pleural line and presence of A lines; 1 point=presence of fragmented pleural line, focal B lines; 2 points=presence of irregular pleura line, subpleural consolidations; 3 points=white lung with or without consolidations.	Exclusive transducers, machine and operator protection with IPE.	34% deaths of patients in hospital treatment. LU score, according to type, extension and severity of the alterations, presented statiscally significant correlation with the CT severity score and SpO_2 in ambient air.

Table 2 (*Continued*)

Study	Lung ultrasound findings	Other image exams	Scanning areas/LU technique/sort of equipment	IPE and machine cleaning	Comments
Peyrony et al.[88]	LU was used in 48 (21.4%) patients and bilateral B lines were identified in 36 (76.6%) patients.	CXR carried out in 80 (35.6%) patients. Findings consistent with normality in 19 (84%) patients.	Scores and evaluation technique are not mentioned, portable device.	NS	In COVID-19 suspected patients, anosmia, high clinical probability and presence of bilateral B lines in LU increased the probability of disease identification.
Rodriguez-Gonzalez et al.[89]	Irregular pleural line, B-lines, some coalescent, with bilateral patchy distribution, and small peripheral consolidations, which were larger in posterior-basal areas.	Thoracic angioCT-scan ruled-out massive pulmonary thromboembolism but showed a pattern of ground glass and numerous consolidations of predominance in the posterior-basal segments of both lungs.	NS	NS	A concerning association between COVID-19 and the novel multisystem inflammatory syndrome has been recently noticed and increasingly reported. A severe cardiovascular involvement associated with pediatric COVID-19, even without previous heart disease. The screening of myocardial dysfunction and pulmonary. Hypertension through cardiac biomarkers or echocardiography could be beneficial in severe COVID-19 pediatric cases. Some SARS-CoV-2-infected patients who became critically ill suffered a generalized thrombotic microvascular injury mediated by intense complement activation involving the lung.

COVID-19 = coronavirus disease 2019; NS = not stated; IPE = individual protection equipment; HRCT = high resolution computed tomography; CT = computed tomography; LU = lung ultrasound; CXR = chest-X ray; SpO_2 = oxygen peripheral saturation; ARDS= acute respiratory distress syndrome; FiO_2 = fraction of inspired oxygen; CPAP = Continuous Positive Airway Pressure; POCUS =point of care ultrasound; ICS = intercostal space; RT-PCR=real time polymerase chain reaction; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2; ICU=intensive care unit; PaO_2=oxygen arterial pressure; BLUE=Bedside Lung Ultrasound in and Emergency.

monary parenchyma and complications were observed and scored respectively in each of the 10 examined sections.[62] Also, Zhao et al. proposed a scoring system from 0 to 4 points imputed to 10 lung sonographic areas, as described below: (0) points = presence of normal pattern with lung sliding, parallel A-lines and thin pleural line; (1) point =presence of B-lines pattern; (2) points = presence of ground glass sign with B-lines occupying the entire screen; (3) points = presence of shred sign suchlike small subpleural consolidations; (4) points = presence of consolidation/pulmonary tissue-like aspect or pleural effusion.[67]

Other particularities and LU scores found in the studies listed above are detailed in Table 2.

The description of individual protection equipment use during LU examinations was carried out in 14 studies only.[12,15,18,26,27,38,64,66,67,72,74,75,77,87] The common strategy to minimize the risk of transmission was making a LU machine available exclusively for COVID-19 exams combined with the use of protective covers for the probe and equipment. The LU examination had to be carried out, if possible, by 2 professionals, one of whom would be in direct contact with the patient and the other with the screen, the keyboard and the image acquisition and recording.[12,27,67] Another strategy employed to reduce the occupational risk when dealing with patients with COVID-19 was the use of portable wireless transducers, making it easier to clean and handle the equipment.[12,27,31,62,69,73,77,79,80,82,88]

Fig. 2 shows the main findings of the LU imaging described in the study.

Discussion

In the COVID-19 pandemic, it is necessary to seek tools that enable the evaluation of lung impairment by the disease, minimizing the involvement of multiple teams and the exposure of professionals in the health area to the SARS-CoV-2. The LU examination is an alternative in the respiratory system propaedeutic as it is a low-cost technique, highly portable and allows for repetition of exams, and can be performed at the patient's bedside.[12–14,20,22,55] The LU may be used in several moments of the natural history of the SARS-CoV-2 colonization/infection as it can identify the pulmonary involvement and seriousness of the disease in patients with suspected or confirmed COVID-19. It can also help to reduce the use of X-ray and/or thorax HRCT.[17,62,66,74,85] In addition, LU is a low-cost tool that can be used in low- and average-income countries where HRCT might not be available,[12] however, specialization in the area is necessary to use this technique.

The application of LU in the screening of COVID-19 symptomatic patients in the pre-hospital phase through pneumonia evaluation was described.[13,63,64,82] Dini et al. (2020) proposed a flowchart of the intervention carried out employing LU in the evaluation and triage of older individuals living in nursing homes that presented symptoms consistent with the SARS-CoV-2 infection and those exposed to the infection from having contact with patients with COVID-19. Those exposed to patients with COVID-19 were submitted to LU and when the result was negative, pneumonia was excluded. When the LU result was altered, nasopharyngeal material was collected for RT-PCR. Whenever the result was positive, isolation and treatment were started; in addition, LU was carried out every 5–7 days and if the symptoms worsened, hospital admission was indicated. Patients that presented clinical symptoms consistent with COVID-19 and whose LU showed altered results, were isolated, treated and their pulmonary condition was monitored with ultrasound. Those showing unaltered LU were subject to SARS-CoV-2 RT-PCR collection and when the result was negative, other etiologies were considered for a differential diagnosis.

Other studies also showed LU applicability in the home assistance of older people and helping prevent unnecessary hospital admission, since LU integrated to the clinic and physical examination resulted in more accurate diagnosis of COVID-19 and other respiratory disease in older populations. In addition, due to the overload of the health service caused by the pandemic, some countries implemented home care for the older population whenever possible.[64,82]

Additionally, LU can be used in suspected diagnosis and in the prognostic stratification of individuals with pneumonia through the extension of specific patterns and their evolution to the consolidation phase in emergency assistance; it makes possible the management of patients in intensive care in relation to the mechanical ventilation and ventilator weaning; it can also monitor the effect of the therapeutic measures, like alveolar recruitment maneuvers, implemented in seriously affected patients submitted to invasive mechanical ventilation with orotracheal intubation.[30,71,75]

In clinical practice, when managing patients with acute hypoxemic respiratory failure due to COVID-19, deciding whether to proceed with the invasive mechanical ventilation and intubation might be a challenge; LU might be a helpful and accurate indicator of the ideal moment for intubation.[76]

Lu et al. investigated the role of LU role in the evaluation of the severity of the pulmonary aeration loss in intubated patients due to pneumonia by SARS-CoV-2 and those that were not intubated. The study carried out LU evaluations at different moments in the hospital care, within the period of one week after the patients had been admitted in the intensive care unit. The author pointed out that the LU could evaluate dynamically the ventilation condition of the two groups of patients in the study during the treatment and enable the prediction of the disease decline.[76]

Since a LU negative result, that is, without visible alterations, does not rule out a SARS-CoV-2 infection, LU cannot be considered a tool that substitutes the physical examination or the SARS-CoV-2 RT-PCR, but, it should be considered a complementary tool to be used in the screening of patients to detect mild symptoms and allow a fast and efficient decision.[82] However, it has become clear that in the COVID-19 pandemic, the characteristics suggesting alterations provoked by the disease appearing in a LU or in the HRCT, even in the event of a negative SARS-CoV-2 RT-PCR test, might be highly suggestive of a SARS-CoV-2 infection.[35]

Antúnez-Montes et al. emphasized LU usefulness in the evaluation and triage of patients that presented respiratory complaints in the context of the SARS-CoV-2 pandemic.[41] Abnormal LU findings would lead to a possible early admission into emergency units or intensive care units, while the identification of normal ultrasound patterns would categorize those patients as low risk patients. Fox et al. pointed out

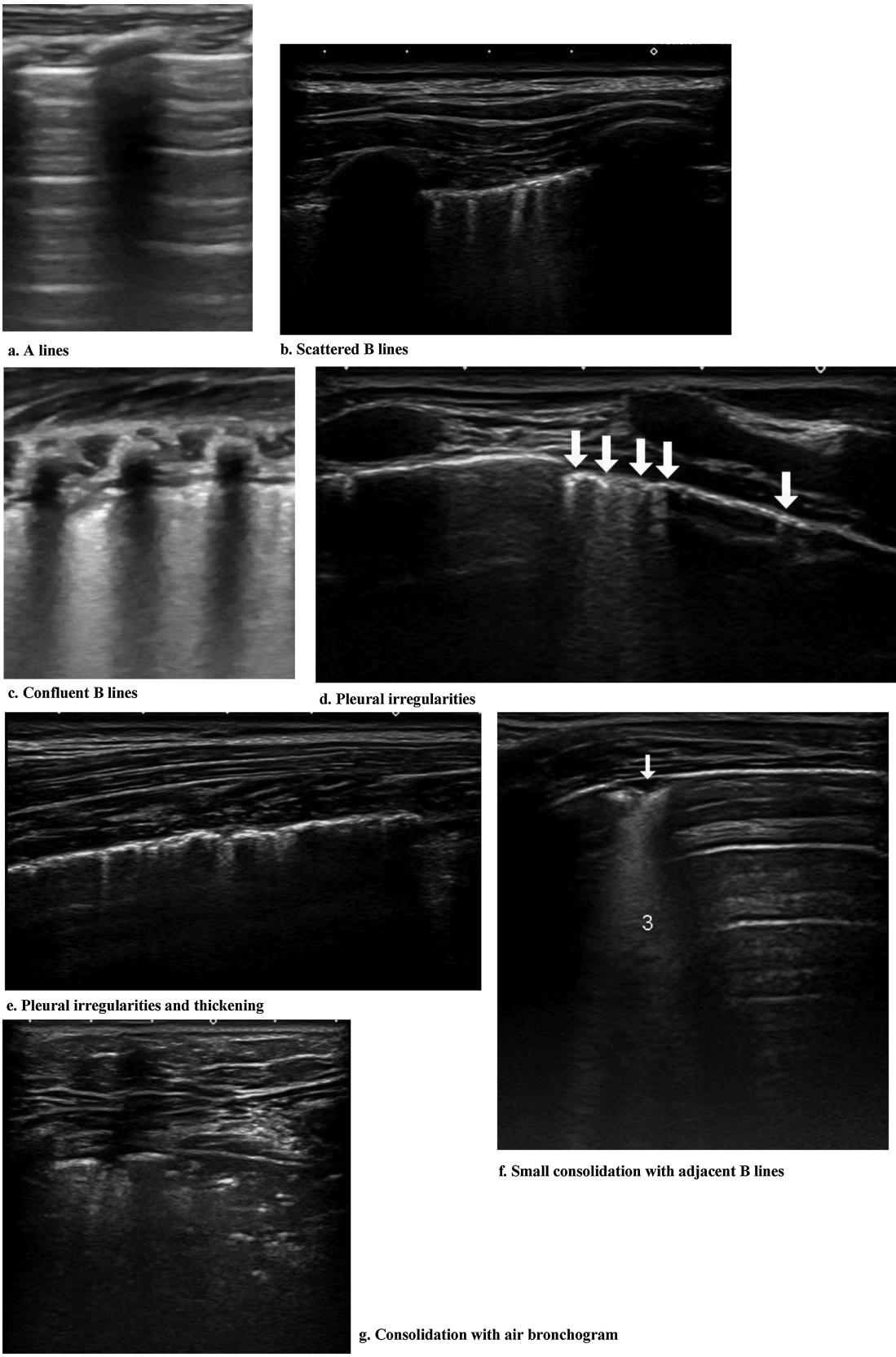

Figure 2 Findings of the LU imaging described in the study.

that LU presented a potential role in the triage of patients infected with the SARS-COV-2 and suggested an association between the more noticeable LU alterations and clinical deterioration.[42,63,66,69]

The existing literature suggests using of HRCT for the COVID-19 diagnosis and as a triage tool to identify SARS-CoV-2 infection, because, although the nasopharynx swab presents a definite etiological diagnosis, this test also presents limitations, mainly due to its low sensitivity,[27,43] which is lower than HRCT.[44] However, the HRCT is represents high cost, low availability, exposure to ionizing radiation that limits its use in some populations such as pregnant women, and the need for sedation in lower age groups.[16,27,66] Therefore, LU becomes an important tool for the triage and evaluation of patients presenting COVID-19 symptoms.[45,66,74]

Pulmonary abnormalities might occur before clinical manifestations and some specialists recommend HRCT for patients with clinical suspicion of COVID-19.[20,47] However, the high contagiousness of this virus and the risks of transporting patients in hemodynamically unstable and invasive mechanical ventilation to where radiography can be performed, results in the need for alternatives to evaluate lung damage. In such a context, LU is a positive choice as it provides similar results to those of the HRCT and is a more advanced method than thorax radiography for the evaluation of pneumonia and/or respiratory distress syndrome in adults, with the advantage of being an ionizing radiation free method.[22,26,31] The LU findings in pneumonia and respiratory distress syndrome in adults caused by the SARS-CoV-2 are related to the illness phase, the seriousness of the pulmonary lesion and the presence of comorbidities. The predominant pattern is of varied degrees of interstitial syndrome and alveolar consolidations, related to the seriousness of the pulmonary lesion.[20,26,30,82,83]

Earlier quantification of the severity of the pulmonary impairment in patients with COVID-19 might be obtained by estimating the total number of pulmonary areas detected as pathological in LU.[48,83] In a prospective study with 10 patients during a 15-day investigation period, the author demonstrated the LU score as a bedside non-invasive monitor of the pneumonia evolution in the COVID-19 disease by the graphical description of the evolution of the scores in the LU. Successfully extubated patients showed lower scores than those found before the intubation. The scores tended to increase in deaths caused by refractory hypoxemia, as a result of the progressive component of the pulmonary aeration failure characteristic of COVID-19. In addition, the score enabled early diagnosis of pneumonia associated with mechanical ventilation through the increase in new consolidations. Good agreement was observed between the thorax HRCT and LU to detect the presence of consolidations.[68]

In an observational series, LU was shown to be a useful tool to evaluate and monitor lung impairment in pregnant women with COVID-19, playing an important role in the treatment decision. All the patients presented ultrasound characteristics indicating COVID-19 at admission and 3 patients obtained resolution of the ultrasound pulmonary alterations.[30] The use of LU in the follow-up and evolution evaluation has been described in several studies.[67,70,80] Zhao et al. evaluated 35 patients with different clinical conditions and divided them into two groups that were classified according to clinical severity. Patients feeling uncomfortable and with respiratory failure were called non-refractory, while those presenting refractory respiratory failure with PaO_2 (oxygen partial pressure)/FiO_2 (oxygen inspired fraction) $\leq$100 or patients treated with extracorporeal membrane oxygenation, were classified as refractory group. The ground-glass opacity pattern and the consolidations were more frequent in the refractory group. In the follow-up, B lines were seen to transform into A lines, with reduction in and disappearance of consolidations. Therefore, it seems relevant to emphasize that the presence of more consolidation areas and interstitial syndrome might imply disease worsening. In addition, the study showed one more use for the LU to spot, with high specificity ($\sim$90%), patients that might need extracorporeal membrane oxygenation.

When evaluating the child population, a study with 8 individuals from 0 to 17 years old documented improvement of radiological alterations throughout clinical evolution and resolution of the pulmonary disease caused by the COVID-19. One of the patients that presented a severe clinical situation was examined repeatedly with LU on alternate days and a reduction was noticed in the B lines pattern bilaterally one day before the clinical and radiographic improvement. In the same study, LU repeated before the hospital discharge showed improvement in the resolution of consolidations and interstitial patterns, consistent with the concomitant radiologic findings.[25] The reappearance of A lines was reported in the illness recovery phase.[35,56,80]

Gregorio-Hernández et al., described LU findings in newborns infected by SARS-CoV-2, carried out every 48 h in the first week after diagnosis, and ascribed a score according to the severity of the pulmonary sound involvement and applied the score (from 0 to 3 points) to the 6 anatomical regions under evaluation. Newborns with an initial score from 3 to 4 points presented some degree of interstitial alveolar syndrome, and the newborn with the highest score evolved with the worst respiratory outcome.

Dudea et al. proposed a severity classification through the evaluation of the pulmonary damage using LU, in which mild to moderate damage was seen as B lines in growing number and distribution, irregular pleural line with interruptions, heterogeneous mixture of B and A lines A and pleural areas with normal sliding and small subpleural consolidations (<1 cm); the severe damage involved several B lines, stretching in superior and anterior directions, with confluent areas and increase in the number and size of the subpleural consolidations, and critical damage presenting coalescent B lines, extensive damage to the anterior and superior pulmonary areas, numerous small consolidations, areas of bilateral alveolar filling syndrome with or without air bronchogram and rare pleural collections.[46] The topographic analysis of lung regions by LU and the application of scores seem to be efficient strategies for patients that require intensive care. LU scores are important to evaluate the seriousness of the structural impairment and enable the establishment of correlations with clinical deterioration.[12,17,38,67,69,70] A step-by-step approach to safely performing LUS was described in several studies and recommended a systematically scanning of different zones in both hemithoraces proposing a point-awarding system to the LU findings and their correlation to the severity of the lung impairment.[17,49,69] Several studies reported scanning of

three areas of the thorax: anterior, lateral and posterior segments and, next, superior and inferior. Thus, 6 regions were defined for each lung.[15,17,34,38,63–65,68,71,74–76,79,83] Points were awarded according to the region and the distinct aeration patterns [point(s)]: [A lines] = 0 points; [B1 lines — are associated with an interstitial syndrome and diminished lung aeration] = 1 point; [B2 lines — confluent lines appearing as a ''white lung'' (called also glass-rockets), equivalent to computed tomography (CT) ground-glass opacities] = 2 points; [consolidations] = 3 points. Therefore, the LU score ranged from 0 (normal) to 36 (worst pulmonary aeration).[17]

A retrospective study by Yan et al. analyzed 540 pulmonary regions of 29 patients with COVID-19 related pneumonia confirmed in China. The patients were submitted to simultaneous LU and HRCT in intervals of time under 12 h. That author defined two patterns of how the disease affected the pulmonary system: the interstitial alveolar pattern, defined by multiple B lines ($\geq$3) within a region found in the LU or the presence of ground-glass opacity in the HRCT; and the Interstitial Alveolar Syndrome, defined by two or more regions with interstitial alveolar pattern per side, in which both should be found bilaterally. LU was seen to be highly sensitive to alterations in the air/pulmonary liquid interface, showing clearly the interstitial alveolar damage with inflammatory exudates and edema caused by the COVID-19. Therefore, LU showed higher sensitiveness than the thorax CT in the identification of alveolar and interstitial disorders, consolidations and pleural effusion.[83]

Another study adopted a new protocol called CLUE (COVID-19 Lung Ultrasound in Emergency) involving an anatomical parameter,[49] a LU scoring system and oxygen requirement at the time of examination, in order to help the emergency clinician to make therapeutic decisions. The LU scoring system was reported as a valid tool for assessing regional and global lung aeration in Acute Respiratory Distress Syndrome in other studies,[50,51] one that can be used in COVID-19 pneumonitis with several similar sonographic features.[20] LU scoring system points ranged from 0 to 3 points, in each zone, totaling 12 zones, with higher points allocated to severe lung changes. The severity was classified as mild (score 1–5), moderate (6–15) and severe (>15). Employing the CLUE protocol could help risk-stratify suspected patients with COVID-19 and may decrease reliance on chest X-rays or HRCT chest during the initial clinical evaluation of suspected patients.

Two studies have evidenced LU accuracy in detecting acute illnesses and its non-inferiority in relation to thorax radiography in the differential diagnosis of pneumonias, pulmonary edema and pleural effusion;[15,23] the use of this tool in chronic diseases such as cystic fibrosis was also evaluated.[24] This demonstrates the advancement of ultrasound technology for pulmonary evaluation in the last few years and the relevance of this tool being disseminated in the management of COVID-19, not only for risk groups (elderly, pregnant women and adults with comorbidities) but also in the pediatric community.

When evaluating the findings of interstitial pneumonia in COVID-19, it is possible to obtain images that help the cardiovascular semiologic evaluation by providing information on the presence of morbidities such as cardiopathy and becoming a guide to fluid therapy and hemodynamic stability. Based on Point of Care Ultrasound (POCUS) findings in several organs, there are reports in which the patients received intravenous bolus injection of saline solution for hemodynamic resuscitation. The cardiac and inferior vena cava evaluations are easily obtained, and this approach aids determination of other dyspnea causes. Therefore, ultrasound might guide the amount of intravenous fluid to be used and also evaluate the right ventricular function when there is suspected cardiac insufficiency, in cases where COVID-19 might be co-occurring with cardiovascular comorbidities.[57,65,72,75]

POCUS can be used to quantify the illness course by counting the number of B lines in different lung regions, consolidation size or pleural effusion and development or resolution of any other lung abnormalities.[53] Ji et al. used the B line count as a semi-quantitative index representing series of alterations in the pulmonary lesions before and after treatment,[29,58,62] however, with some reservation, since B lines might be found in other cardiac and pleuropulmonary diseases.[26,52] Other POCUS applications listed were the evaluation of deep venous thrombosis, assessment of endotracheal tube, mechanical ventilation weaning with evaluation of edema in the airways and diaphragm mobility, tracheostomy and sleep-guided deep vascular access.[53,54,57,71,89]

Despite the LU nonspecific findings that can occur in other illnesses including other viral pneumonias and a broad spectrum of non-infectious diseases (chronic obstructive pulmonary disease, neoplastic lymphangitis, pulmonary fibrosis and interstitial pulmonary disease), the homogeneous interstitial pattern seems to suggest the cardiogenic edema diagnosis, while a heterogeneous interstitial pattern, mainly in combination with subpleural consolidation and/or pleural thickening might suggest, in the pandemic clinical and epidemiological environment, pneumonia caused by the SARS-CoV-2.[59] One study investigated ultrasound particularities that could help the distinction of bacterial pneumonia and the pneumonia caused by SARS-CoV-2. The differentiation by LU between viral and bacterial pneumonia is a challenge, however, in that assay the finding of B line artifacts, or partial or confluent B lines, small consolidations and pleural alterations was suggestive of the COVID-19. These findings are described in other interstitial pneumonic processes of viral etiology.[62] Isolated large lobar consolidation with or without pleural effusion and with dynamic air bronchograms indicates bacterial infection.[60]

Some studies used the contrast-enhanced ultrasound to evaluate lungs regarding the presence of an underlying thrombosis process. Bedside contrast-enhanced ultrasound was indicated due to the presence of small and cuneiform pulmonary consolidations with a central echogenic point (signal described in pulmonary embolism patients) associated to the discovery of high levels of D-dimer and the impossibility of performing contrast-enhanced HRCT. Large delimited perfusion defects were demonstrated in relation to the normally perfused parenchyma. These areas were solved with the clinical improvement.[37,39,46]

Limitations

The point of the disease development at which the ultrasound evaluation is performed is extremely important since the structural damage might precede clinical alterations.

The observation studies were seen to present small samples and experimental clinical studies were scarce.

Besides the high number of studies, the use of LU as a triage tool still lacks specific protocols, operator experience as well as reproducibility and inter-operator agreement.[42,45,46] Further studies are needed to determine the role of LU as a triage tool and its use in the prognostic and monitoring of hospital patients.[47]

Due to the model of register of papers on the PubMed, some studies that might possibly include data collected from patients might have been overlooked in the filter analysis.

Highlights

LU findings presented correlation with HRCT images.

LU can be used in respiratory system propaedeutics as an alternative to the ''stethoscope use''. Special clothing and individual protection equipment are indispensable, since the manipulation of the stethoscope in pulmonary evaluation might create contamination risks for the health professionals and patients.

COVID-19 normally induces a bilateral and diffuse interstitial pneumonia with asymmetric lesions and uneven distribution, mainly involving the lung periphery, which makes it particularly suitable for investigation using LU.[60]

Studies have identified potential correlation between the LU patterns and the patients' clinical outcome. One of the assays in this study reported that each pulmonary area could be in a different stage of the disease, therefore, the global evaluation of the lungs is fundamental.[69]

The POCUS allows for hemodynamic, cardiac and vascular evaluations (thromboembolic phenomena — deep venous thrombosis).

LU should be associated to the multisystem point-of-care exam, since the SARS-CoV-2 infection might be linked to myocarditis and a high incidence of thromboembolic events. Thus, multiorgan ultrasound evaluation in early treatment is useful to screening these complications at the bedside.

Perspectives

More studies on LU application in the pediatric population are necessary.

LU in COVID-19 score standardization.

Improvement of reading/automatic identification of B line software, as reported in this study is still needed.[74]

The advancement of the remote robotic ultrasound scanning technology assisted by the 5G network in real time by the use of big data, cloud storage and artificial intelligence must be improved.[73]

Conclusions

LU can be employed in different age groups to evaluate the seriousness and the response to treatment for the COVID-19 control. The main characteristics of LU in COVID-19 are focal, multifocal and/or confluent B lines, corresponding to the ground glass opacity of the thorax HRCT, in addition to the evidence of pleural thickening and irregularities. The fact that findings correspond shows the potential of LU as a radiation free, low cost, safe, reproducible method, with easy-to-sanitize equipment. Another advantage is the reduced need to manipulate the patient compared to the HRCT, avoiding transportation of the patient to the X-ray room and reducing the risk of contamination of other patients and the health professionals directly or indirectly involved with the patient. With the increase in the number of studies on the application of ultrasound, LU has been shown to be a useful tool for evaluating the progression, therapeutic response and follow-up of pulmonary disease in COVID-19.

Conflict of interest

The authors have no conflicts of interest to declare.

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Authors' contributions

[AOP, RMC, RU and FALM] participated in data collection; [AMAF, JDR and FALM] supervised, performed and validated data based on reproducibility. All authors conducted the writing and critical review of this study. Also, all authors read and approved the latest version of the manuscript prior to submission.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pulmoe.2021.02.004.

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LETTER TO THE EDITOR

Predictors of reduced 6-minute walk distance after COVID-19: a cohort study in Mexico

Clinical sequelae after COVID-19 have been well described, including abnormalities in pulmonary function tests, chest imaging, and patient-reported outcome measures.[1,2] However, functional outcomes after COVID-19 are not well understood. We sought to identify the presence and underlying mechanisms of functional impairments after COVID-19. We hypothesized that patients with more severe COVID-19 would have a lower 6-minute walk distance (6MWD) at follow-up and that exertional dyspnea, fatigue, and hypoxemia would independently predict a lower 6MWD.

This was a consecutively-enrolled prospective cohort study. Patients who were seen in a hospital in Yucatan, Mexico with SARS-CoV-2 confirmed by real-time polymerase chain reaction were referred to a COVID-19 clinic for follow-up. Patients who were able to complete surveys, pulmonary function tests (PFTs), and 6-minute walk tests (6MWTs) were included. There were no exclusion criteria. PFTs and 6MWTs were conducted according to international guidelines.[3–5] Patients did not receive formal physical rehabilitation during their recovery. This study received institutional ethics approval.

COVID-19 severity was categorized as mild (no hypoxemia), moderate (hypoxemia without mechanical ventilation), or severe (hypoxemia with mechanical ventilation). The association between COVID-19 severity and 6MWD was determined using multivariable linear regression, and underlying mechanisms for reduced 6MWD were then explored. Unadjusted and adjusted linear regression models were used to determine the association between potential predictor variables (Borg dyspnea, Borg fatigue, and end-exercise SpO_2) and 6MWD, first in separate models and then in a final model with both Borg dyspnea and end-exercise SpO_2 as co-primary endpoints to explore the independent relationship of these two predictors with 6MWD. All models were adjusted for age, sex, smoking, body mass index (BMI), and time from symptom onset. Statistical analyses were performed using R version 3.6.3 (R Foundation).

A total of 295 patients were referred to the COVID-19 clinic between May and August 2020, of whom 225 were enrolled (65 patients declined and 5 were lost to follow-up). The overall cohort had 62% males and 19% ever-smokers, with a mean age of 47 ± 13 years and BMI of $32 \pm 7\,kg/m^2$ (Table 1). There were 63 patients with mild, 144 with moderate, and 18 with severe COVID-19. The median follow-up time was 61 days (interquartile range [IQR] 50–75), with fatigue on effort (68%) and dyspnea (39%) being the most common symptoms.

Patients with moderate or severe COVID-19 had a lower 6MWD compared to patients with mild disease (−51 m [95%CI −85, −17], $p = 0.004$ or −68 m [95%CI −134, −3], $p = 0.04$ respectively), with no difference between moderate and severe groups ($p = 0.55$). 6MWD was associated with both Borg dyspnea (coefficient −17 m per unit increase in Borg dyspnea [95%CI −27, −8]) and end-exercise SpO_2 (coefficient 8 m [95%CI 4, 12]) (both $p < 0.001$). A sensitivity analysis using the delta SpO_2 (i.e., end-exercise SpO_2 — baseline SpO_2) demonstrated similar results (coefficient 7 m per unit increase in delta SpO_2 [95%CI 2, 13; $p = 0.004$]). Borg fatigue was not associated with 6MWD. When Borg dyspnea and end-exercise SpO_2 were included as co-primary predictors in a single model, both variables remained independently associated with 6MWD with coefficients of −13 m (95%CI −22, −3) and 7 m (95%CI 3, 10), respectively, after adjusting for covariates (Table 2).

A lower 6MWD was independently associated with exertional dyspnea and hypoxemia, suggesting that dyspnea and hypoxemia may have distinct mechanisms through which they impact functional capacity. Of the patients who had exertional hypoxemia (i.e., SpO_2 decline ≥4%), 45% had a walk distance less than the lower limits of normal (LLN) and 100% had a $DL_{CO} < LLN$, which suggests that desaturation during exercise is associated with parenchymal and/or pulmonary vascular phenomena. Although dyspnea is typically accompanied by hypoxemia during acute COVID-19 illness,[6] our study found that exertional dyspnea predicted reduced functional capacity, regardless of whether end-exercise hypoxemia was present or not. The underlying mechanisms of persistent dyspnea after COVID-19 remain

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Table 1 Patient characteristics. Patients with mild (no hypoxemia), moderate (hypoxemia without mechanical ventilation), and severe (hypoxemia with mechanical ventilation) are shown. An obstructive pattern was defined as $FEV_1/FVC < LLN$. A restrictive pattern was defined as normal FEV_1/FVC with FVC-% predicted <LLN. Lung volumes using body plethysmography were unavailable.

	Overall (n = 225)	Mild (n = 63)	Moderate (n=144)	Severe (n = 18)
Age, years	47 ± 13	42 ± 11	49 ± 14	51 ± 8
Male sex, n (%)	139 (62)	31 (49)	92 (64)	16 (89)
BMI, kg/m^2	32 ± 7	30 ± 7	33 ± 7	33 ± 10
Current or former smoker, n (%)	43 (19)	17 (27)	24 (17)	9 (50)
Comorbidities, n (%)				
Obesity	115 (51)	24 (38)	82 (57)	9 (50)
Hypertension	47 (21)	8 (13)	32 (22)	7 (39)
Diabetes	32 (14)	3 (5)	27 (19)	2 (11)
Other[a]	15 (7)	3 (5)	11 (8)	1 (6)
Symptoms at follow-up, n (%)				
Fatigue on effort	153 (68)	37 (59)	102 (71)	14 (78)
Dyspnea	87 (39)	20 (32)	58 (40)	9 (50)
Chest pain	68 (30)	12 (19)	53 (37)	3 (17)
Myalgias	70 (31)	18 (29)	46 (32)	6 (33)
Cough	69 (31)	18 (29)	43 (30)	8 (44)
Sore throat	40 (18)	8 (13)	27 (19)	5 (28)
Sputum production	38 (17)	7 (11)	26 (18)	5 (28)
Headache	32 (14)	12 (19)	19 (13)	1 (6)
Rhinitis	32 (14)	10 (16)	22 (15)	0 (0)
Anosmia/ageusia	23 (10)	6 (10)	16 (11)	1 (6)
Dermatological symptoms	23 (10)	6 (10)	17 (12)	0 (0)
Diarrhea	6 (3)	2 (3)	4 (3)	0 (0)
Pulmonary function				
FVC, %-predicted	82 ± 19	95 ± 13	79 ± 18	61 ± 19
FEV_1, %-predicted	87 ± 19	97 ± 13	85 ± 19	68 ± 21
FEV_1/FVC, %	85 ± 7.4	83 ± 5	86 ± 8	88 ± 4
D_{LCO}, %-predicted	97 ± 29	112 ± 20	93 ± 27	65 ± 34
Restrictive pattern, n (%)	87 (39)	7 (11)	66 (46)	14 (78)
Obstructive pattern, n (%)	5 (2)	2 (3)	3 (2)	0 (0)
6- min walk test				
Distance, m	447 ± 104	491 ± 72	433 ± 111	425 ± 94
Distance, %-predicted	83 ± 20	83 ± 14	83 ± 21	86 ± 21
Baseline SpO_2, %	96 ± 2	97 ± 1	96 ± 2	96 ± 1
End-exercise SpO_2, %	95 ± 4	97 ± 2	95 ± 2	93 ± 5
Peak dyspnea, Borg 0–10	2 (1–3)	2 (1–3)	2 (1–3)	3 (2–4)
Peak fatigue, Borg 0–10	2 (0–3)	2 (1–4)	2 (0–3)	0 (0–2)

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; SpO_2, oxygen saturation by pulse oximetry.

[a] Other comorbidities include asthma, malignancy, dyslipidemia, and HIV. Values represent mean ± standard deviation or median (interquartile range), unless otherwise specified.

unclear; however, it is likely that physiologic sequelae contribute to this lingering symptom. In a previous study using the same cohort, we demonstrated that patients with persistent dyspnea had lower FVC, forced expiratory volume in 1 s, and higher proportion of restrictive ventilatory pattern compared to patients without persistent dyspnea.[6] Furthermore, patients with abnormal DL_{CO} at follow-up are more likely to have an elevated D-dimer on admission, suggesting that microangiopathies could contribute to dyspnea.[7]

This study had several limitations. First, our data did not include validated tools such as the Charlson Comorbidity Index to assess how comorbidities impact 6MWD. Second, this study was from a single Mexican center. However, this unique population adds to the understanding of COVID-19 recovery in diverse patient backgrounds. Third, we did not have information on treatment during the acute illness which could impact outcomes.

We demonstrate the impact that persistent dyspnea and hypoxemia have on functional capacity in patients after COVID-19. Further research to understand the underlying mechanisms of persistent symptoms, particularly dyspnea that is disproportionate to physiologic and radiologic findings, is needed in order to help patients recovering from COVID-19.

Table 2 Mechanisms of reduced 6-min walk distance after COVID-19 illness.

	Unadjusted analysis		Adjusted analysis						
Model	Outcome	Primary predictor(s)	Coefficient	95%CI	P-value	Coefficient	95%CI	P-value	Prespecified covariates
1a	6MWD	BORG dyspnea	−22	−33, −12	<0.001	−17	−27, −8	<0.001	Age, sex, smoker, BMI, time[a]
1b	6MWD	BORG fatigue	−5	−13, 4	0.277	−4	−11, 4	0.298	Age, sex, smoker, BMI, time
1c	6MWD	End-exercise SpO_2	8	4, 11	<0.001	8	4, 12	<0.001	Age, sex, smoker, BMI, time
2	6MWD	BORG dyspnea	−18	−29, −7	<0.001	−13	−22, −3	0.009	Age, sex, smoker, BMI, time
		End-exercise SpO_2	6	2, 10	0.004	7	3, 10	<0.001	

Abbreviations: 6MWD, 6-min walk distance; BMI, body mass index; CI, confidence interval, SpO_2, oxygen saturation by pulse oximetry.
[a] Time from symptom onset.

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Conflict of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Late-onset Pompe disease (LOPD): May axial myopathy influence respiratory dysfunction?

Clinical note

Late-onset Pompe disease (LOPD) is an autosomal recessive disease caused by acid alpha−glucosidase deficiency. The phenotype is a progressive proximal myopathy. Respiratory failure is the main life-threatening complication, usually resulting from diaphragm weakness,[1] which may be independent of the severity of motor involvement. Screening for diaphragm function include the assessment of postural drop in forced vital capacity (FVC) moving from sitting to supine position (ΔVC),[2] and measurement of Maximal Inspiratory Pressure (MIP).

We previously observed by Magnetic Resonance Imaging (MRI) that axial muscles involvement (posterior trunk, abdominal wall) represents a feature peculiar to LOPD, otherwise uncommon in other myopathies. Axial involvement may be suspected in patients with chronic lumbar pain, hyper-lordosis, and abdominal prominence, but axial muscles are difficult to assess by clinical examination alone: thus, imaging fills a clinical need.[3] What is the clinical impact, if any, of axial muscles involvement? Are there any functional correlates, beyond lumbar pain and postural changes? Indeed, trunk muscles may be involved in respiration, with posterior muscles participating in inspiration, and anterior abdominal wall muscles contributing to forced expiration.[4] Our hypothesis is that axial involvement may be a sentinel sign of respiratory dysfunction, and that MRI of the axial muscles may represent an effective approach to screen for respiratory impairment in LOPD, to optimize pulmonary evaluation and treatment strategy for these individuals.

We investigated prospectively 19 patients (8 females) aged 54.6 ± 18.2 years (range 25−76) with genetically confirmed LOPD. Clinical, demographic, genetic data are in **Supplementary Table 1**.

Muscle MRI was performed as previously described[3] by a 1.5T MRI scanner (1.5T Philips Intera and 1.5T Philips Ahieva XR Realeas) using T1-weighted spin-echo axial images from the mid-dorsal segment to the sacrum, using the same parameters (TR=300 ms, TE=10 ms, thickness =10 mm, matrix=640 × 640, in plane resolution 0.6 × 0.6 mm). Muscles were graded qualitatively according to the Mercuri score.[3] We considered two muscles of the posterior wall of the lower trunk (*Quadratus lumborum, Iliocostalis lumborum*), and seven anterior wall muscles (*Multifidus, Longissimus, Iliopsoas, Rectus abdominis, Transversus abdominis, Obliquus externus abdominis, Obliquus internus abdominis*). Two independent observers blinded to clinical data examined all scans.

Respiratory assessment was performed within 48 h ofm MRI, according to standard guidelines.[5] A postural drop of FVC (ΔVC) ≥30% was considered expression of diaphragmatic weakness;[5] MIP was measured from the Functional Residual Capacity in the upright position; Maximal Expiratory Pressure (MEP) was measured at the Total Pulmonary Capacity. Both MIP and MEP were repeated at least three times or until two identical readings were obtained, with patients receiving strong verbal encouragement; the best value of both measurements was used.[6]

Deviations of quantitative variables from normality were calculated by the Shapiro-Wilk test ($p<0.05$). Quantitative variables with normal distribution are described as mean ± standard deviation or by median (25th−75th percentiles) otherwise. To test for significant differences in terms of normally distributed variables between binary conditions we used the Welch's *t*-test, and the Wilcoxon rank-sum test to test for differences in terms of variables deviation from the normal. Pairwise correlations were estimated by the Spearman test, associations between categorical variables by the Fisher's exact test. The significance threshold was set to $p<0.008$ based on the Bonferroni correction accounting for the number of muscles for which the MRI score was evaluated (α=0.05/6 tests). Univariate tests were applied to evaluate: a) significant correlations between MRI measurements and: MIP, MEP, FVC, ΔVC, FVC%; b) presence of significant associations between MRI measurements corresponding to the analyzed muscles and: Diaphragm ≥20 or Diaphragm ≥30. Statistical tests were performed by the R software v. 3.1.0 (www.r-project.org/).

Summary statistics reporting the characteristics of the analyzed patients are in **Supplementary Table 2** (quantitative variables) and **3** (categorical variables). **Fig. 1** shows three different patterns of severity of trunk involvement. Involvement of the *Internal Oblique* and *Multifidus* correlated with worse MIP (rho=0.85, $p = 0.004$ and rho=0.75, $p = 0.003$ respectively). Similarly, *Internal Oblique*, *Multifidus* and *Longissimus* muscles were positively correlated with ΔVC values (rho=0.86, $p<0.001$; rho=0.80, $p<0.001$ and rho=0.73, $p<0.001$

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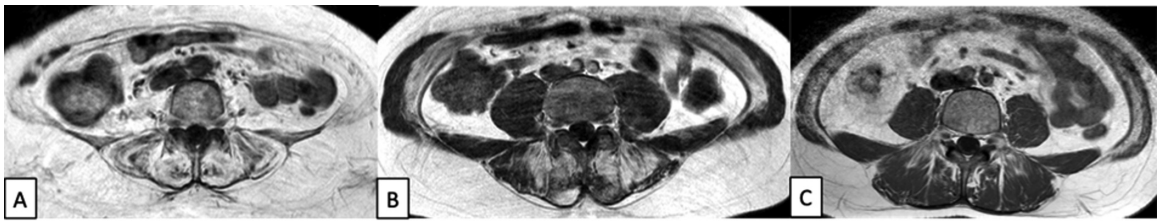

Figure 1 Muscle MRI with T1-w images at the level of the lumbar region showing three patients with different degrees of paraspinal muscle atrophy, in particular involving *Quadratus Lumborum*, *Multifidus*, *Longissimus* and *Iliocostalis Lumborum*. The first patient (A) shows a severe muscle atrophy, while the second (B) and the third (C) show respectively a moderate and a mild atrophy.

respectively) (**Fig. 2**). Increased MRI scores for *Multifidus* were associated with increased probability of diaphragm $\geq$20 ($p = 0.006$) and diaphragm $\geq$30 ($p = 0.005$). Similarly, higher MRI scores for *Longissimus* were associated with increased probability of diaphragm $\geq$30 ($p = 0.002$). A weaker but still consistent correlation was found with *Internal Oblique* ($p = 0.015$).

Thus, posterior trunk atrophy was associated with decreased MIP, and both anterior and posterior trunk atrophy to postural drop; forced expiration (MEP) and upright FVC were not influenced by trunk muscles status. Indeed, posterior trunk muscles contribute to inspiration[4] and are thus expected to influence postural drop and MIP.

The role of anterior/abdominal atrophy on postural drop may rather seem unexpected, given that abdominal muscles are essentially expiratory. We suggest that -in LOPD patients with diaphragm weakness- abdominal muscles may contribute to inspiration also, even during tidal breathing. At present, abdominal muscles contraction during expiration is conventionally regarded as beneficial to the act of breathing, because the consecutive rise in abdominal pressure induces diaphragm lengthening, placing diaphragm fibers on a more advantageous portion of their length-tension curve, and hence improving the force-generating ability of the diaphragm during the subsequent inspiration. Expiratory contraction of the abdominal muscles is a natural (automatic or spontaneous) component of the response of the normal respiratory system to greater than resting stimulation.[7] When normal subjects increase their ventilation or breathe against inspiratory mechanical loads, they recruit the abdominal muscles, particularly the transversus, during expiration[8]: the associated reduction in end-expiratory lung volume allows the increased work of breathing to be shared between the inspiratory and the expiratory muscles. It is possible that in LOPD patients with diaphragm weakness, this "automatic" response to the imbalance of the inspiratory load/capacity relationship is already triggered during resting breathing, even though it may be useless and induce additional energy expenditure.

A limitation of our study is the lack of a control population. Further studies confirming our results are needed. Detection of axial involvement on MRI may be a warning sign of initial diaphragm weakness and respiratory dysfunction in clinostatism, since trunk weakness (and mainly abdominal weakness) is likely to impair the ability to compensate for diaphragmatic dysfunction in the supine position. Detection of trunk muscle damage by MRI may thus suggest the need of a closer respiratory follow-up or more extensive respiratory assessment, i.e. by polysomnography, even when upright FVC is still within normal ranges.

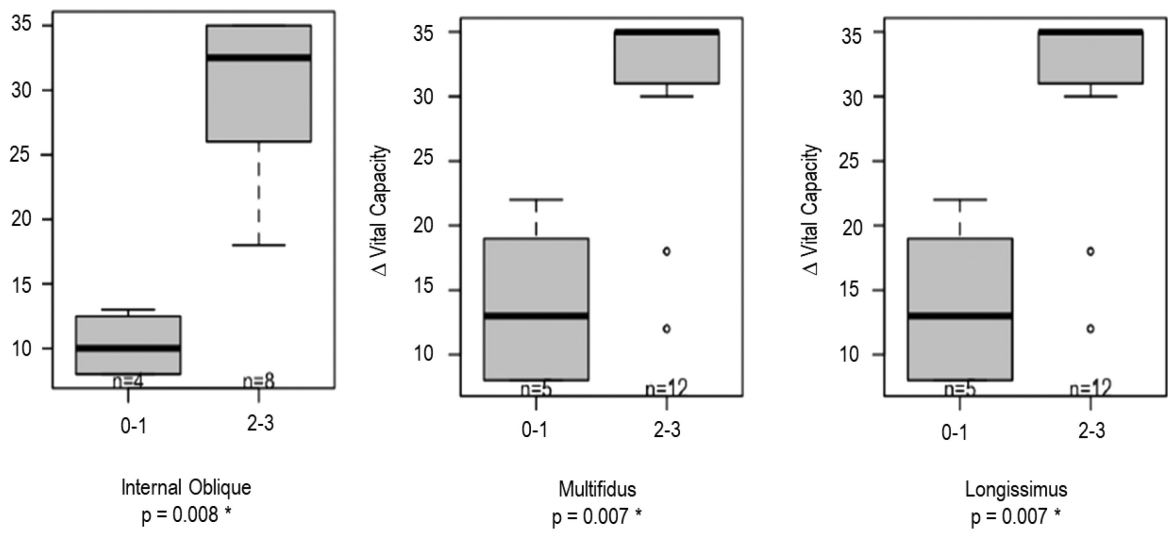

Figure 2 *Internal Oblique*, Multifidus and Longissimus muscles are positively correlated to ΔVC values. In particular, patients having MRI values $\geq$ 2 for these three parameters are characterized by a statistically significant increase in terms of ΔVC values with respect to those having MRI values $\leq$ 1 ($p < 0.008$).

Declarations

Ethics approval and consent to participate:

The data collected are part of the regular follow-up of patients with Pompe disease. Data collection and consent to participate was approved by the Pavia Ethical Committee (IRCCS San Matteo Foundation), reference number p-20,160,022,743

Consent for publication

All patients gave consent to collect their demographic and clinical data and to perform clinical and MRI investigations.

Availability of data and material

Database of clinical data is available to any scientist wishing to use them (Sabrina.ravaglia@mondino.it)

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Authors' contribution

The Author's contributions are as follows: AC, SR, CD: methodology, conceptualization of results, manuscript writing and editing; NB: interpretation of physiological data; CD, PdF: genetic analysis; AM statistical analysis; SC: respiratory examinations and acquisition of data; AP: muscle MRI. All Authors read and approved the final manuscript.

Declaration of Competing Interests

The Authors declare that they have no competing interests.

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LETTER TO THE EDITOR

Implementing nitrogen multiple breath washout as a clinical tool − A feasibility study

KEYWORDS
Multiple breath washout;
Lung clearance index;
Cystic fibrosis;
Primary ciliary dyskinesia;
Children

Dear editor,

The multiple-breath inert gas washout (MBW) test involves recording an inert tracer gas being cleared from the lungs during normal tidal breathing. In nitrogen (N_2) MBW resident nitrogen is washed out by inhaling 100% oxygen. MBW allows us to calculate the lung clearance index (LCI), defined as the number of lung turnovers required to washout an inert gas to 1/40th of its initial concentration.[1−3] It offers complementary information to standard lung function tests, such as spirometry[1]

The procedure is strongly dependent on skilled operators and a relaxed testing environment is key to obtaining good quality measurements.[4] Operator training and certification in performance of the MBW measurement is imperative to achieving high-quality data, and standardization of LCI is part of an ongoing collaborative, multicentre process.[2]

Aim: to assess the feasibility of N_2MBW in a paediatric lung function laboratory in children with different clinical conditions [Cystic Fibrosis (CF), primary ciliary dyskinesia (PCD) and healthy controls].

School-aged children with a confirmed diagnosis of CF or PCD were recruited from a Paediatric Pulmonology clinic in a tertiary-care hospital, and healthy controls from the community, throughout December/2018-November/2019. Patients were clinically stable at inclusion and the study procedures were performed during the patients' routine clinic visits. Height and weight were measured prior to the lung function assessments, and BMI z−scores standardized using WHO reference values.

Exhalyzer® D and the associated software Spiroware® version 3.1 (EcoMedics AG, Duernten, Switzerland) were utilized for the N_2MBW measurements and calculation of the N_2MBW indices. The means of the N_2MBW indices from intentionally three and at least two technically acceptable measurements performed at each test occasion were reported in absolute values.[1] Prior to implementing this technique in our setting, three operators completed a European standardization and certification process for measuring LCI through N_2MBW with a commercial device (specific training and sharing of data for central over-reading).

Static and dynamic lung volumes were measured by body plethismography and spirometry (Jaeger MasterScreen Body, CareFusion, Hoechberg, Germany) after the N_2MBW procedure. Absolute values for static lung volumes and z-scores for dynamic lung volumes and flows were recorded and performed according to the ERS/ATS standards.

Patient characteristics were presented by medians (ranges) or numbers and percentages of total. Patients with CF and PCD were grouped for comparison with healthy controls. Group differences were analysed using the independent *t*-test, Mann−Whitney *U*-test, and Chi-squared test as appropriate; $p < 0.05$ was accepted as statistically significant. Data analyses were performed using Microsoft Excel for Office 365 MSO and SPSS 24.0.

The study was approved by a local ethics community (*Comissão de Ética para a Investigação Clínica*). Informed consent for participation was obtained.

During the study period 34 children were assessed, five were excluded due to invalid MBW readings and two successfully repeated the procedure in a different testing session. The success rate for performing N_2MBW for the first time was 75% (22 out of 29). Additionally, all healthy controls were naïve to lung function testing, and one was unable to perform spirometry properly.

We analysed data from 29 children: ten CF, six PCD and thirteen healthy controls (Table 1). There were no differences between patients and healthy children regarding gender, age, or BMI. The diseased group had higher LCI [10.8 (7.6; 15.3) vs 6.9 (6.5; 7.5)], and lower FEV1 [-0.8(-2.8; 0.4) vs. 0.7(-0.9; 1.8)] and MMEF [-1.0 (-2.6; 0.3) vs. 0.03 (-0.5; 2.4)] when compared to healthy controls ($p < 0.001$).

Executing MBW took 28 (16; 76) minutes [patient group 29 (16; 76) minutes; healthy controls 22 (16; 53 min], and it was attempted for 5 (3; 15) trials in each testing session (Table 2). For nine individuals (four healthy controls, two CF and three PCD), only two technically acceptable trials were achieved.

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Table 1 Participants' characteristics and lung function results.

		Healthy controls (n = 13)*	CF (n = 10)	PCD (n = 6)	Controls *vs.* Patients (p-value)
	Gender ♂ [n (%)]	10 (77%)	4 (40%)	2 (33%)	0.034
	Age [years (min; max)]	12.2 (8; 17.3)	13.9 (7.7; 16.8)	13.8 (11; 19.2)	0.195
	BMI z-score (min; max)	-0.4 (-1.5; 2.7)	-0.4 (-2.2; 1.0)	-0.3 (-1.5; 0.5)	0,376
N_2MBW	**LCI** (min; max)	**6.9 (6.5; 7.5)**	**10.9 (7.6; 15.3)**	**10.7 (8.6; 13.2)**	<0.001
	FRC [L (min; max)]	1.9 (1.3; 4.9)	2.1 (1.0; 3.6)	2.6 (1.6; 2.8)	0.656
Plethis.	ITGV [L (min; max)]	2.1 (1.2; 3.7)	2.3 (1.2; 3.4)	2.6 (1.7; 3.2)	0.405
	RV/TLC (min; max)	**0.25 (0.22; 0.32)**	**0.31 (0.23; 0.36)**	**0.33 (0.26; 0.52)**	0.005
Spirometry	FEV_1 z-score (min; max)	**0.7 (-0.9; 1.8)**	**-0.5 (-1.8; 0.4)**	**-1.0 (-2.8; -0.3)**	<0.001
	FVC z-score (min; max)	0.4 (-0.9; 1.4)	0.1 (-1.5; 0.8)	-1.3 (-2.7; 0.2)	0.014
	FEV_1/FVC (min; max)	0.88 (0.83; 0.98)	0.82 (0.75; 0.90)	0.84 (0.74; 0.95)	0.021
	MMEF z-score (min; max)	**0.03 (-0.5; 2.4)**	**-0.9 (-2.2; 0.3)**	**-1.5 (-2.6; 0.2)**	<0.001

* Performed spirometry n = 12

CF: Cystic Fibrosis, PCD: Primary Ciliary Dyskinesia, BMI: Body Mass Index, N_2MBW: nitrogen multiple breath washout, Plethis: plethismography.

Table 2 Nitrogen multiple breath washout feasibility.

	Healthy controls (n = 13)	CF (n = 10)	PCD (n = 6)
Median duration [minutes (min; max)]	22:20 (15:48; 52:50)	25:18 (15:54; 70:46)	41:22 (16:24; 76:24)
Total of trials (min; max)	5.0 (3; 12)	4.0 (3; 10)	7.5 (5; 12)
Trials aborted (min; max)	1 (0; 8)	1 (0; 3)	4 (1; 10)

CF: Cystic Fibrosis, PCD: Primary Ciliary Dyskinesia

We have shown that LCI is feasible with a high success rate on first attempt (75%) in school-age children, and throughout the first year of implementing N_2MBW. Nevertheless, the procedure is time-consuming and largely dependent on specialized technicians.[2] Also, N_2MBW takes more time than routine spirometry and the time needed increases relative to the increase of LCI. In our setting, the duration of the test was influenced by the pathology and cooperation, and these challenges were concordant with guidelines and recommendations regarding this technique.[1,5]

Even though N2MBW tests were done as part of a research project, they were included in the patients' clinic visits, allowing us to estimate its burden on routine lung function assessments, if we were to add this tool to the evaluation of children with chronic, progressive, obstructive lung disease.

In agreement with published data,[6,7] we found that LCI was raised in children with CF and PCD compared to healthy controls, even in those with FEV1 within normal range. This is important as it shows that LCI in a clinical setting provided reliable data that reflects previous findings from studies in which the test had been undertaken in a research setting. Additionally, children with well-preserved spirometry, are those for whom monitoring with LCI will be most useful, and it is increasingly being adopted in CF centres for clinical decision making.[2]

Accordingly, anticipating the success rates within a clinical setting and assigning appropriate time slots for its inclusion is crucial when planning to implement this technique.

This brief, pragmatic report, provides information about the feasibility of N_2BMW in children during routine visits, using the Exhalyzer®D.

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LETTER TO THE EDITOR

Organizing pneumonia associated with optic neuromyelitis: Coincidental occurrence or causal association?

Dear Editor,

Optic neuromyelitis (NMO) is an autoimmune inflammatory disorder of the central nervous system characterized by episodes of immune-mediated demyelination and axonal damage mainly involving optic nerves and spinal cord.[1] Immunoglobulin (Ig)G antibodies against the water channel protein aquaporin 4 (AQP4) play a pivotal role in the pathogenesis of the disease. Although most commonly an idiopathic autoimmune condition, it may also occur as a paraneoplastic syndrome and/or associated with other autoimmune diseases such as Sjögren's syndrome, sarcoidosis, antiphospholipid syndrome and systemic lupus erythematosus. An unusual case of organizing pneumonia in a patient with NMO is reported herein. These clinical entities might share common pathogenic mechanisms, as suggested by the present study which could explain their co-existence in the patient.

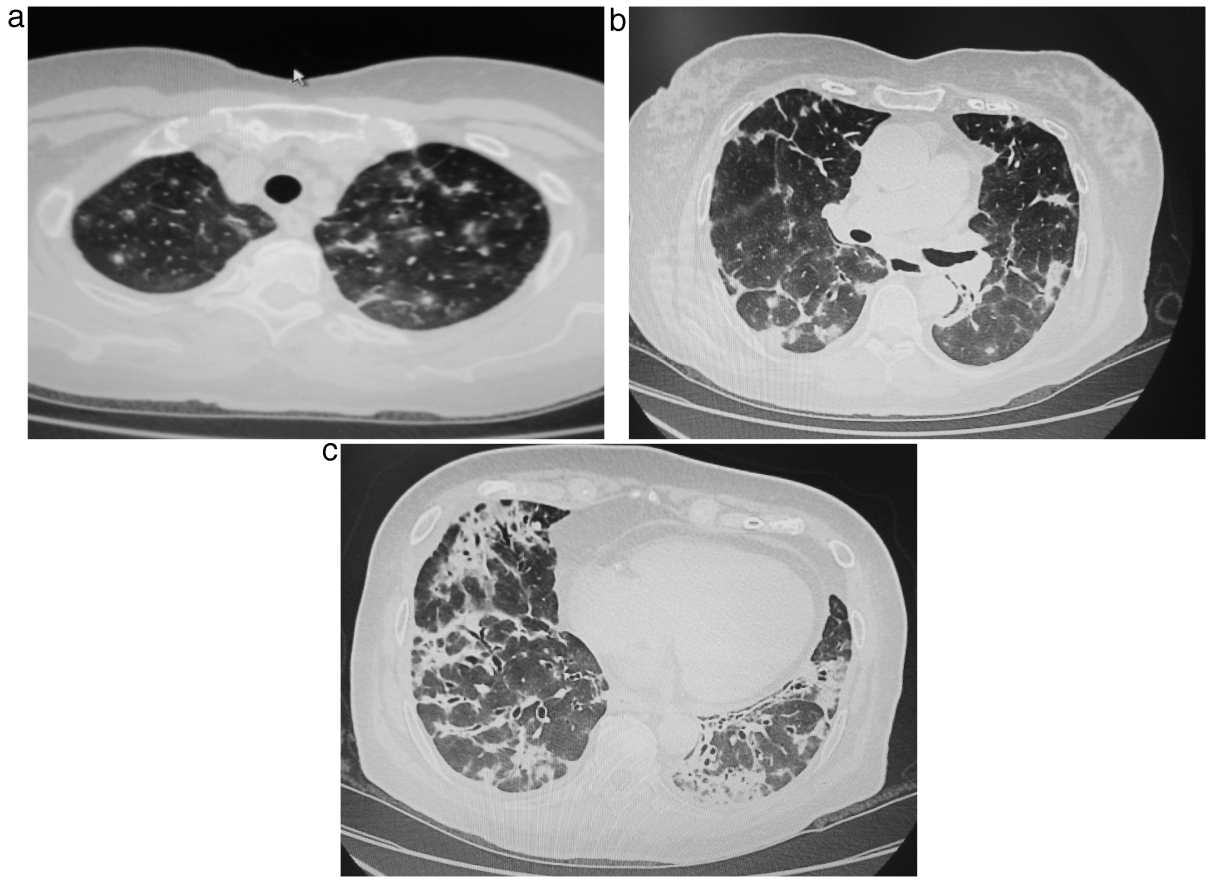

Figure 1 (a, b) Chest CT showing bilateral multiple consolidations with distribution accompanied by ground glass opacities throughout the upper and middle lung fields. (c) Bilateral consolidations with peribronchovascular distribution and dilated airways within them are visible in the lower lung fields.

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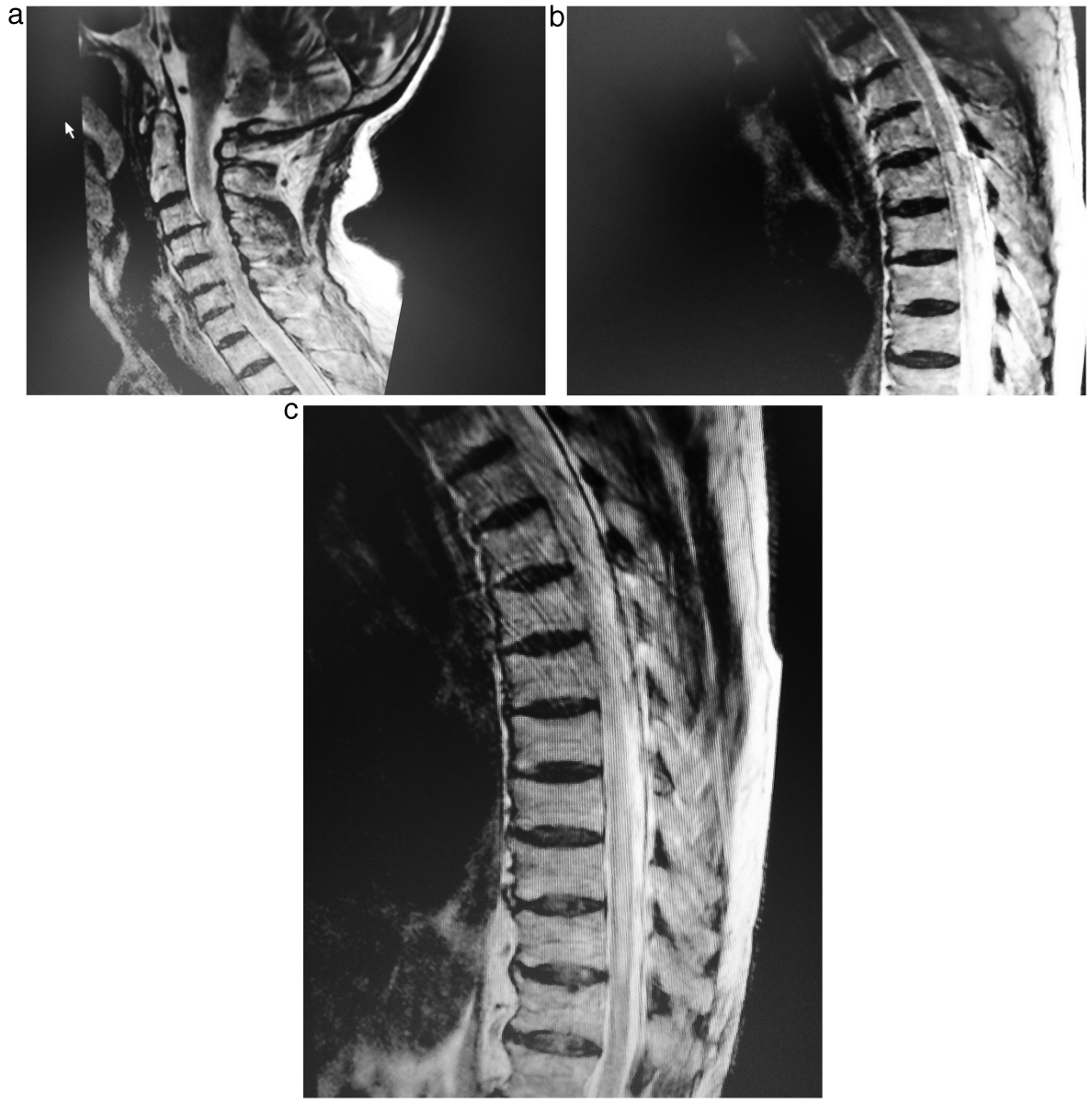

Figure 2 (a–c) Cervical and thoracic spine MRI demonstrating high intensity signals at the C1–2, C4–7 levels and T6–9 on T2-weighted imaging.

A 77 year old woman, non-smoker, was admitted to our department presenting dyspnea on exertion, productive cough and low-grade fever (37,8 °C) for two months before her admission. Physical examination of the chest revealed fine crackles throughout the lung fields. Upon admission, a chest CT showed bilateral multifocal asymmetric consolidations with predominantly subpleural distribution, especially in both upper and middle lung fields. Ground glass appearance is also evident (Fig. 1a, b). In addition, bilateral consolidations with strongly peribronchovascular distribution and dilated airways within them were noticeable in the lower lung fields (Fig. 1c). Standard laboratory results demonstrated mild leukocytosis and hypoxemia (WBC count: 12,200/μL, neutrophils: 10,600/μL, pO_2: 68 mmHg), as well as severely elevated creatine phosphokinase levels (2048 IU/L).

Fiberoptic bronchoscopy was performed and BAL fluid analysis revealed a mixed cellularity pattern with 28% lymphocytes, 16% neutrophils, 12% eosinophils, 4% mast cells, 40% macrophages and CD4/CD8 ratio of 0.12. Microbiological and cytological examinations were negative. Conventional transbronchial lung biopsies were non-diagnostic. However, BAL findings were highly suggestive of organizing pneumonia.[2]

Furthermore, the patient experienced numbness, paresthesia and partially affected mobility of both lower limbs and left upper limb on the second day of hospitalization. Neurologic examination revealed a sensitive thoracic level T6—9, hyperactive bilateral patellar tendon reflexes and a 4/5 grade muscle strength. Lumbar puncture disclosed lymphocytic pleocytosis and absent oligoclonal bands. PCR test for detecting viruses in the cerebrospinal fluid was negative. Cervical and thoracic spine MRI showed high intensity signals at the C1–2, C4–7 levels and T6–9 on T2-weighted imaging, suggestive of an extensive acute transverse myelitis (Fig. 2a–c). Additionally, serum AQP4 (aquaporin) IgG levels were greatly increased and the diagnosis of NMO was established. The patient was treated with high-dose corticosteroids exhibiting gradual improvement of neurologic deficits and resolution of pulmonary infiltrates within a three-month period. He is still on tapering course of steroids with a schedule of rituximab initiation as maintenance therapy.

It is widely recognized that NMO is mainly antibody-mediated with the principal role played by the humoral immune system targeting astrocytes. More specifically, a circulating IgG autoantibody against the water channel protein aquaporin-4 (AQP4) expressed by astrocytes has been established as the major key factor in the pathogenesis of this disorder. The positivity for IgG-AQP4 antibodies is a robust criterion for NMO diagnosis in conjunction with typical clinical and MRI features.[1] The created IgG-AQP4 complex downregulates the surface expression of AQP4 in the central nervous system cells causing increased blood-brain barrier permeability, activating the complement, promoting the accumulation of inflammatory cells and leading to astrocyte damage and death.[3]

OP is an inflammatory lung disease that is characterized by the presence of buds of granulation tissue in the lumen of the distal pulmonary airspaces as a repair process of the lung in response to preceding alveolar injury.[4] The coexistence of NMO and OP in the present case might not be coincidental. The authors allege that AQP4 plays a pivotal role in this relationship. There is a growing body of evidence from studies on lung diseases that AQPs are involved especially in those lung diseases that are caused or at least accompanied by perturbed airway surface liquid volume homeostasis like asthma, COPD and acute lung injury.[5] Furthermore, the recognized role of AQPs in inflammatory cell infiltration, cell proliferation and migration may account for their evolving role in lung inflammatory disorders and various lung cancers. In particular, downregulation of AQP4 in alveolar epithelium thus leading to lung inflammation (increased vascular permeability, cellular infiltration, cytokine release) has recently been demonstrated in lung models.[6]

There is a paucity of literature concerning pulmonary complications associated with NMO and especially interstitial lung diseases. Strictly speaking, 5 cases have hitherto been published dealing with NMO-related ILDs (sarcoidosis, cryptogenic organizing pneumonia, and unclassified interstitial pneumonia).[7–10] However, the diagnosis of OP in 3 out of 5 cases was based solely on clinical grounds without confirmation by using bronchoscopic procedures (BAL/transbronchial biopsy).

In summary, OP could be associated with NMO. Although a causal association cannot be explicitly ascertained from this descriptive study, we suggest that AQP4 downregulation in astrocytes may also orchestrate the inflammatory process in organizing pneumonia due to its expression in lung tissue. However, more data are necessary to clarify the relationship, bearing in mind the small number of patients reported with this combination of diseases.

Funding

None.

Conflicts of interest

The authors have no conflicts of interest to declare.

Authors' contribution

TR was responsible for patient management and prepared the manuscript. AA and NF helped to confirm optic neuromyelitis and drafted the manuscript. SK and KP critically revised the manuscript and approved the final version. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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LETTER TO THE EDITOR

Rituximab for the treatment of acute onset Interstitial Lung Disease in primary Sjogren's syndrome

To the Editor,

Treatment of interstitial lung disease (ILD) in primary Sjogren's Syndrome (pSS) is a clinical need which still needs to be defined.[1] Our aim in the following paragraphs is to report the case of a patient with pSS and acute onset ILD successfully treated with Rituximab (RTX).

On May 2020, a 49 years-old former smoker Caucasian male was hospitalized for recent-onset of dyspnea. On assessment, the patient did not present pyrexia and the only past medical history was arterial hypertension.

A negative nasopharyngeal-throat swab excluded the SARS-CoV2 infection. The erythro-sedimentation rate was high (64 mm), whereas the C-reactive protein, the procalcitonin, the total leukocyte count and the renal and hepatic function were normal. The first chest high resolution computed tomography (HRCT) showed diffuse and bilateral ground glass opacities with thickened interlobular septa all over the lungs, which were suggestive of an infectious disease. For this reason, we started an empiric antibiotic therapy with amoxicillin/clavulanic acid and subsequently with levofloxacin, in association with oxygen supplementation (Fig. 1). No positivity was revealed on gargled samples for bacteria, viruses or other germs.

The patient presented a rapid worsening of respiratory failure needing support with high flow nasal oxygen (HFNO). Pneumocystis jirovecii was isolated in bronchoalveolar lavage (BAL) with a low replication load, so we increased the antibiotic therapy with trimethoprim/sulfamethoxazole. Because of disease severity vancomycin was also added to cover nosocomial pathogens. The BAL cellular analysis resulted nonspecific: it revealed mostly foamy macrophages.

Nevertheless, the patient's clinical and radiological features continued to deteriorate. The patient was transferred to the Intensive Care Unit where non-invasive mechanical ventilation was added to HFNO due to clinical deterioration with associated respiratory failure and also radiological worsening with finding of increased ground glass opacities in the chest HRCT scans.

Although a partial resolution of the diffuse basal thickening could be noticed on the chest HRCT, respiratory failure persisted. Therefore, the patient was transferred to our Respiratory Disease Unit, where other diagnostic investigations were performed.

Autoimmunity tests resulted in a marked positivity of anti-SSA/Ro-52 kDA, whereas rheumatoid factor, anti-citrullinated peptides antibodies were negative, and C3 and C4 fractions of complement were normal. Transbronchial biopsies performed earlier found foci of organizing pneumonia (OP).

A minor salivary glands biopsy was performed for the differential diagnosis of a mild sicca syndrome, documenting a salivary focus score >1.

In light of these results and after a multi-disciplinary discussion including pulmonologists and rheumatologists, the patient was diagnosed with pSS and prescribed a treatment with intravenous RTX (375 mg/m^2 once a week for four weeks) and prednisolone (1 mg/kg/daily).

After a month, a new chest HRCT showed a significant improvement in the lung parenchymal involvement and the respiratory failure was resolved (Fig. 2). Finally, mycophenolate mofetil (MMF) was added to the treatment as steroid-sparing and maintenance drug.

PSS is a chronic inflammatory autoimmune disease characterized by lymphocytic infiltration of exocrine glands, mainly salivary and lachrymal glands, leading to progressive loss of glandular secretory function, resulting in eye and mouth dryness (sicca syndrome).[2]

In Europe, the annual incidence of pSS is estimated between 3.9 and 5.3 individuals per 100.000 people. There is a female to male ratio of 9:1 and a peak incidence in the fourth and fifth decades of life.[3]

Many extra-glandular organs and systems can be involved in pSS, including the lungs, the kidneys, small vasculature and the central nervous system.[2] The prevalence of pulmonary involvement in pSS has been reported to be 9—70%, depending on the detection method and classification used. PSS-ILD is the most frequent form of pulmonary involvement and it has been observed in 3—11% of patients with pSS. Moreover, pSS related ILD is associated with a reduced quality of life and it is responsible for premature mortality.[3]

Our patient showed an OP pattern, which is the second most frequent ILD histological pattern in pSS after nonspecific interstitial pneumonia. Other less common patterns are

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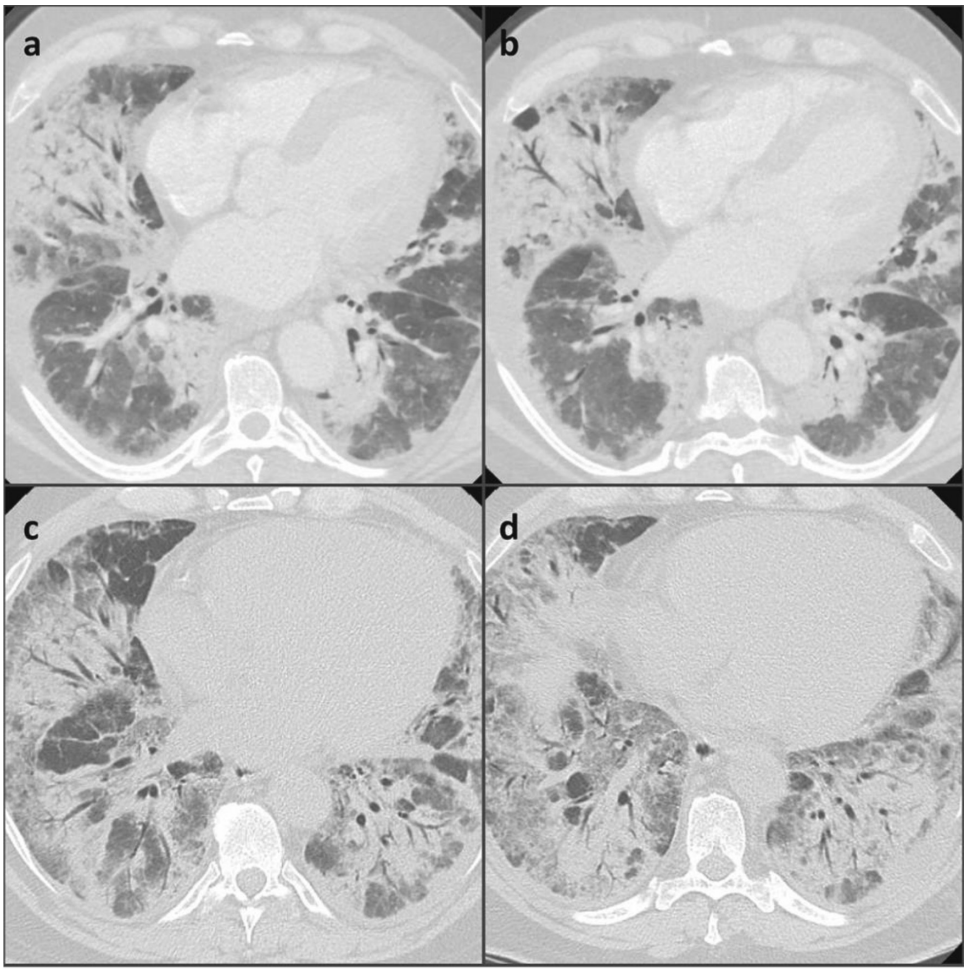

Fig. 1 Axial CT images before rituximab treatment and after the first line of antibiotic therapy (amoxicillin/clavulanic acid and levofloxacin).

usual interstitial pneumonia and lymphocytic interstitial pneumonia. Diagnosis of ILD is usually made late in the disease's clinical history (with a reported prevalence of 47% after 15 years of pSS onset[4]); however, more recently, many authors described ILD as a possible early complication of pSS, sometimes preceding the onset of the sicca syndrome. In this context, Roca et al. reported that 10—51% of patients developed ILD years before the onset and diagnosis of pSS, while in about 20% of patients the diagnoses of pSS and ILD are concurrent.[5]

Wang et al. reported that aging, cigarette smoking and ANA positivity may be potential risk factors associated with lung involvement in pSS. Previous studies involving systemic sclerosis, anti-synthetase syndrome and mixed connective tissue disease showed that anti-SSA/Ro antibodies are associated with ILD.[6] Burvy et al. reported that anti-Ro52 antibodies are an independent risk factor for ILD in pSS as well.[7]

In patients with acute onset-ILD, anti-Ro52 antibodies may represent the only sign suggesting an underlying pSS.[4]

Up to now, immunosuppressive treatment has been the main strategy in ILD associated to connective tissue diseases (CTD). Due to the well-known involvement of B cells in pSS pathogenesis, we decided to treat our patient with RTX, while MMF was proposed as maintenance therapy. The latest European League Against Rheumatism (EULAR) recommendations[8] do not advise the use of one immunosuppressive treatment over another, and, due to the lack of evidence, management for pSS-ILD remains empiric and dependent on the medical team's experience.[3] Nevertheless, previous studies have demonstrated that RTX is a safe and useful drug in both proposed regimens.[9] In particular, a French study on 78 pSS patients,[10] treated the systemic involvement with 1 g every other week for two infusions in 86% of patients, while administering four infusions, once a week, of 375 mg/m^2 in 14% of cases. In the AutoImmune and RTX registry, six of the eight pSS patients with ILD treated with RTX reported an improvement of pulmonary involvement.[10] In 2016, Roca et at. reported a good response to RTX in one pSS patient with steroid refractory ILD.[5] Furthermore, Chen et al. retrospectively investigated the effects of RTX in 10 pSS-ILD patients, showing improvement in DLCO and in symptoms after 6 months, with the stability of the HRCT score.[11] Moreover, a small case series suggests the effectiveness and safety of MMF in many connective tissue diseases, including pSS, ensuring stability or improvement of lung function, especially as a maintenance drug after treatment with RTX.[12]

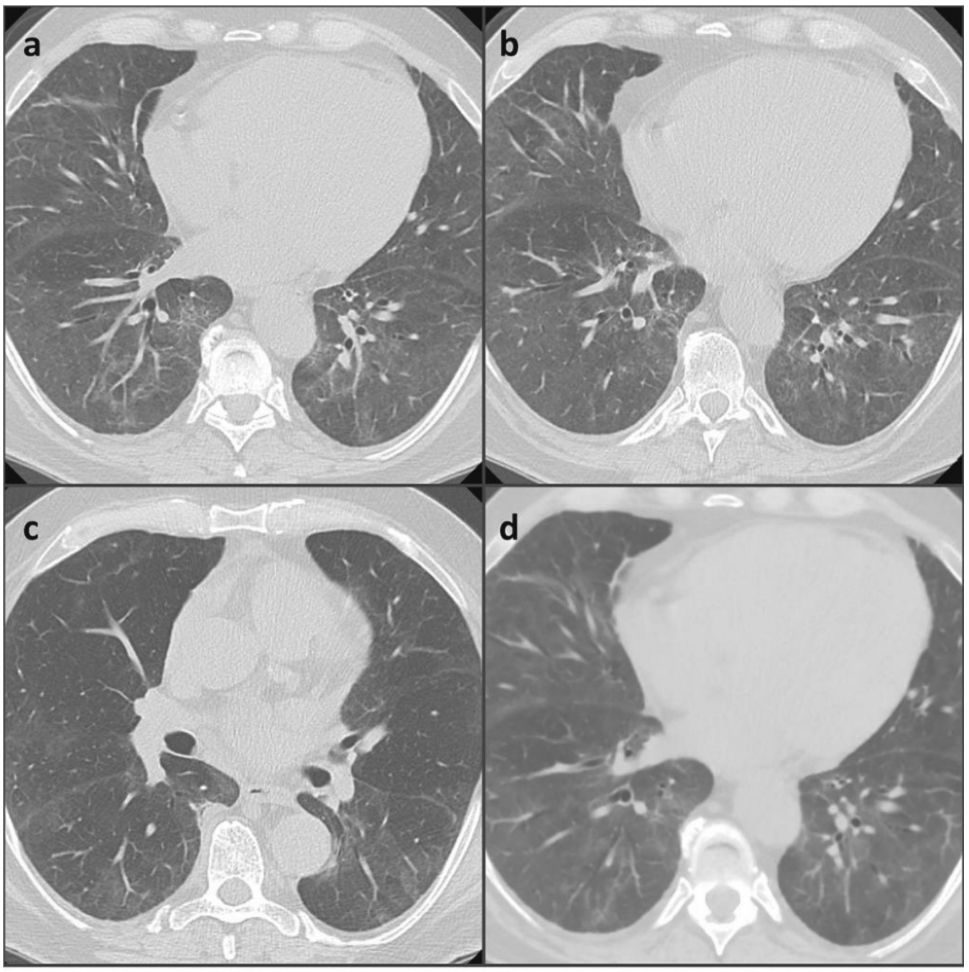

Fig. 2 Axial computed tomography image after rituximab treatment.

In this case, considering the severity of the clinical manifestations at disease onset, we decided to introduce immunosuppressive therapy with MMF to reduce the risk of relapse, saving RTX as possible rescue-therapy.

The number of reports of the early appearance of ILD in patients with misdiagnosed connective tissue diseases, including pSS, is increasing.[5] For this reason, we would like to underline the importance of a systematic screening for sicca syndrome as well as other specific symptoms of pSS in patients with newly diagnosed ILD.

Until now, treatment of CTD related acute ILD remains not well defined and often empiric. According to the current evidence, our experience confirms that Rituximab could be a safe and useful treatment for this life-threatening condition.

Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Mepolizumab for severe eosinophilic asthma − A one-year real life Portuguese study

To the editor

Mepolizumab, a monoclonal antibody anti-IL-5, has been marketed in Portugal since 2017. We aimed to assess its effectiveness and safety in Portuguese severe eosinophilic asthmatic patients.

We conducted a single-center, observational, retrospective study, involving severe asthmatic patients under mepolizumab 100 mg subcutaneous, every 4 weeks for ≥12 months, from July 2017 to August 2020. Eligibility for treatment included a blood eosinophil count (BEC) ≥150/mm^3 at baseline or ≥300/mm^3 during the previous year. Demographic and clinical data were collected from the Portuguese Severe Asthma Registry (RAG) database. A written informed consent was obtained. BEC, Forced Expiratory Volume in one second (FEV1), exacerbation rate and oral corticosteroid (OCS) intake, as well as patient-reported outcomes (PROs) Asthma Control Test (ACT), Control of Allergic Rhinitis and Asthma Test (CARAT) and Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) were accessed. Adverse events were documented. For statistical analyses (IBM-SPSS software, v25.0), t-independent and Mann-Whitney tests were used to compare parametric and non-parametric independent samples, respectively, while paired-t and Wilcoxon tests were employed to evaluate differences between intervals within the same variable, as appropriate. *P*-values <0.05 were considered statistically significant.

A total of 20 patients were enrolled in the study, mean age 54.0 ± 17.0 years [16−77 years], 13 were female (65%). Asthma diagnosis had been made, on average, 20 years before and severe asthma 10 years before. Mean BMI was 27.3 ± 5.4 Kg/m^2 [19.5−38.3 Kg/m^2], with six patients (30%) obese (BMI≥30 Kg/m^2). Total serum IgE (median 274 kU/L, IQR 417.5 kU/L) was ≥100 kU/L in 16 patients (80%), with 10 patients (50%) showing positive skin prick testing (SPT). Rhinitis (*N* = 15, 75%), rhinosinusitis (*N* = 8, 40%) and nasal polyposis (NP) (*N* = 8, 40%) were the most common comorbidities (Table 1).

Table 1 Baseline demographic and clinical characterization.

Baseline characteristic	
Total number of patients	20
Age, years	54.0 ± 17.0 [16−77]
Sex, male/female	7(35)/13(65)
BMI, Kg/m^2	27.3 ± 5.4 [19.5−38.3]
Smoking status	
− Non-smoker	18(90)
− Ex-smoker	2(10)
− Current smoker	0(0)
Age of Asthma onset, years	32.0 ± 16.0 [6−62]
Age of Severe Asthma diagnosis, years	44.0 ± 15.0 [13−70]
Total serum IgE, kU/L	274 (417.5) [8−1359]
FEV1, L	2.1 ± 0.9 [0.9−3.6]
Positive skin prick test	10(50)
− House dust mite	9
− Pollens	2
− Poly-sensitized	1
Comorbidities:	
− Rhinitis	15(75)
− Rhinosinusitis	8(40)
− Nasal Polyposis	8(40)
− NSAID hypersensitivity	5(25)
− GERD	2(10)
− Bronchiectasis	1(5)
Chronic therapy:	
− ICS+LABA	20(100)
− LAMA	20(100)
− LTRA	20(100)
− Methylxanthines	5(25)
− OCS	6 (30)
Previous Omalizumab	5(25)

Data presented as n(%), mean±SD and median(IQR) as appropriate. BMI, body mass index; FEV1, forced expiratory volume in one second; GERD, gastroesophageal reflux disease; ICS+LABA, inhaled corticosteroid + long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; NSAID, non-steroidal anti-inflammatory drugs; OCS, oral corticosteroids.

Regarding mepolizumab's efficacy (Fig. 1A), BEC significantly decreased from a mean of 753.2 ± 429/mm^3 to 101.7 ± 102/mm^3 (−86.5%, $p < 0.001$), as well as annual exacerbation rate (mean reduction 2.5/year, $p < 0.001$) and daily OCS intake with only two patients remaining under OCS after 12 months of mepolizumab (prednisolone 5 mg at alternate days, mean reduction 9.17 mg/day). There were no

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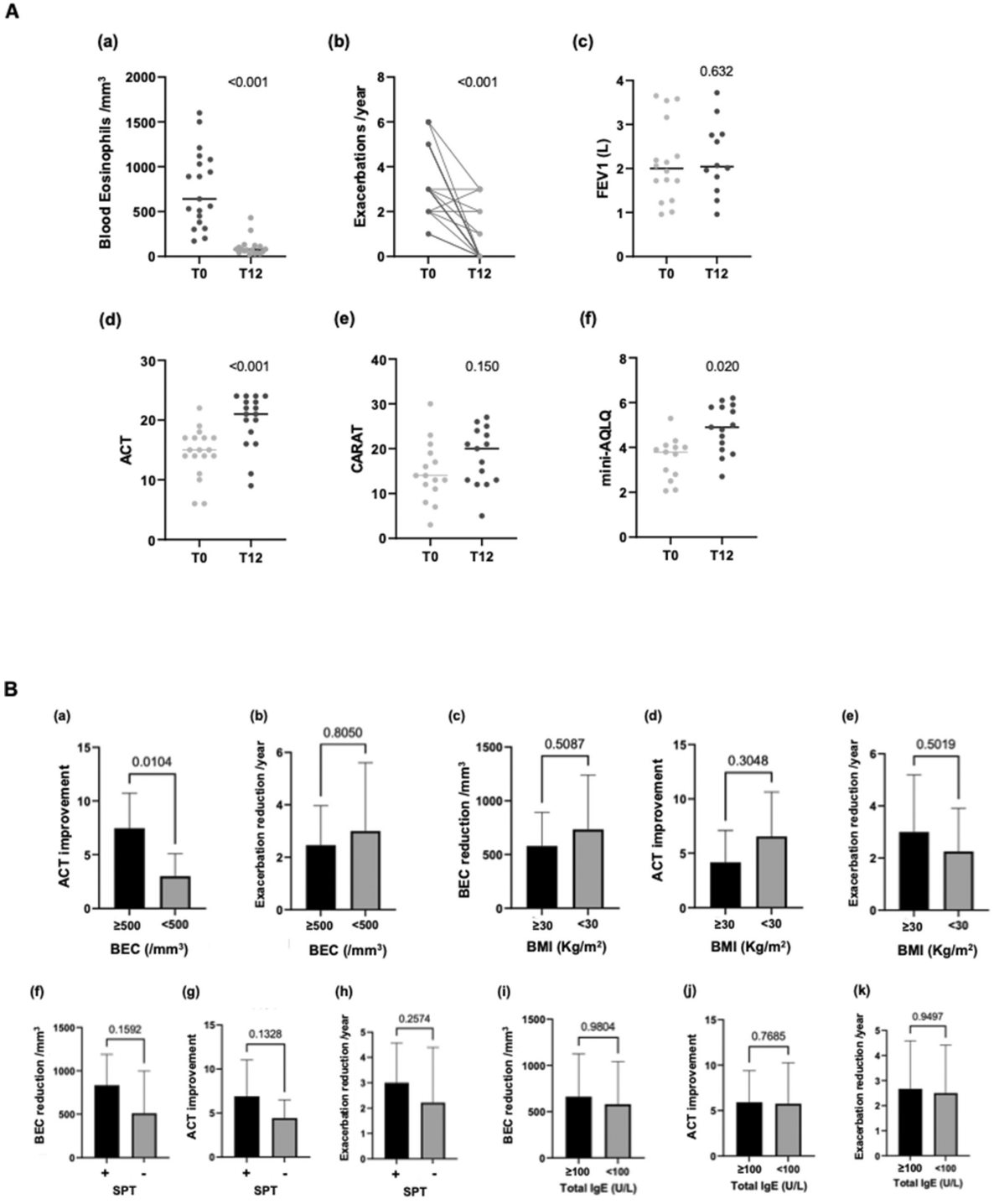

Figure 1 **A:** Changes in blood eosinophil count (a), exacerbation rate (b), FEV1 (Forced Expiratory Volume in one second) (c), ACT (Asthma Control Test) score (d), CARAT (Control of Allergic Rhinitis and Asthma Test) score (e) and mini-AQLQ (Mini Asthma Quality of Life Questionnaire) score (f) after 12 months of mepolizumab. **B:** Comparison of BEC (blood eosinophil count) reduction, ACT improvement and exacerbation rate reduction after 12 months of mepolizumab between different groups (baseline BEC$\geq$500/mm^3 vs $<$500/mm^3, BMI (Body Mass Index) $\geq$30 Kg/m^2 vs $<$30 Kg/m^2, positive vs negative SPT (Skin Prick Testing), total serum IgE$\geq$100 kU/L vs $<$100 kU/L).

hospitalizations. Considering FEV1, only a slight improvement was observed (mean baseline of 2.1 ± 0.9 L to 2.2 ± 0.8 L, $p > 0.05$).

Concerning PROs (Fig. 1A), statistically significant changes were observed in ACT (mean Δ-ACT 5.4 points, $p < 0.001$), with 16 patients (80%) presenting $\geq$20 points

after 12 months of treatment, and mini-AQLQ (mean Δ-mini-AQLQ 1.3 points, p 0.02), while CARAT improvement did not reach statistical significance. Worth noting, 12-month mean upper airways score was lower compared with mean lower airways score (6/12 vs 12/18 points). NP was not monitored, although we did not find significant differences in ACT or exacerbations in these patients ($p > 0.05$).

A sub-analysis was attempted comparing changes in BEC, ACT and exacerbation rate after 12 months of treatment in patients with baseline BEC$\geq$500/mm^3 vs $<$500/mm^3, BMI$\geq$30 Kg/m^2 vs $<$30 Kg/m^2, positive vs negative SPT, total serum IgE$\geq$100 kU/L vs $<$100 kU/L (Fig. 1B). There was a statistically significant difference ($p < 0.05$) between the groups of BEC$\geq$500/mm^3 vs $<$500/mm^3 regarding changes in ACT.

Mepolizumab was well tolerated. Adverse events reported included myalgias in three patients, reverted with administration of magnesium, and persistent abdominal pain in one patient whose biological therapy was switched to another anti-IL-5.

Our study confirms mepolizumab's efficacy and safety, being the first study in a Portuguese cohort with severe eosinophilic asthma. These effects were similar in allergic and non-allergic patients, irrespective of total IgE serum concentrations. Patients with higher baseline BEC reported better symptom control, although annual exacerbation rate did not differ significantly.

We report a 76% improvement in annual exacerbation rate and a 92% reduction in daily OCS intake, which is higher than the reports of MENSA and SIRIUS clinical trials,[1,2] but in line with other real-life studies.[3−5] Similarly, a significant improvement in ACT score was documented, reaching not only statistical but clinical significance with Δ-ACT $\geq$3 points and 80% of patients adequately controlled (ACT$\geq$20), as well as in quality of life. CARAT score did not reach statistical significance probably due to a less expressive improvement in nasal symptoms.

Despite real-life studies[3,6] generally showing better results in FEV1 changes, ours failed to show significant improvement, probably due to the lack of reversibility in some patients. On the other hand, mepolizumab significantly reduced BEC in our cohort, suggesting a decrease in inflammation, with better results in patients with higher baseline values. However, larger real-life studies did not find statistically significant results.[3,6,7]

Regarding positivity in SPT or baseline total IgE, our results are in line with others previously reported,[6] suggesting mepolizumab is effective in both allergic and non-allergic patients. Moreover, obese patients did not present significant differences in response to mepolizumab treatment compared to non-obese.

The limitations of our study include the reduced sample, limiting extrapolation of results, and its retrospective design, which could weaken our findings. However, it is the authors' opinion that it has an important added value in providing the first real world evidence about the effect of mepolizumab in a cohort of Portuguese severe eosinophilic asthmatic patients.

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Declaration of competing interest

The authors report no conflicts of interest.

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LETTER TO THE EDITOR

Encephalitis in non-small-cell lung cancer

Dear Editor,

Nivolumab is an immune checkpoint inhibitor (ICI) agent that targets programmed death receptor-1 (PD-1).[1] Immune-related adverse events (irAEs) under treatment with anti-PD-1/anti-PD-L1 antibodies are frequent (relative frequency — 70%).[1] For nivolumab, any treatment-related adverse events was documented in 74%—85% of patients, with 12%—20% being grade 3 and 4.[2] Encephalitis is an extremely rare and potentially fatal immune-mediated neurological adverse event (nAE).[1]

A 70-year-old Caucasian male presented a 4-day history of fever, somnolence and vomiting. Past medical history was significant for squamous cell carcinoma of the lung (diagnosed in 2018), initially staged as cT4N0M0—IIB (with chest wall invasion and left pulmonary artery involvement), with PD-L1 value of 0%, and proposed for chemotherapy followed by radical radiotherapy. After four cycles of carboplatin and oral vinorelbine with stable disease, radical radiotherapy was started but not completed due to recurrent infections of the pulmonary mass which resulted in mass enlargement and cavitation. Eastern Cooperative Oncology Group (ECOG) performance status was 1 and second line Nivolumab was started in March 2019, achieving stable disease as best response. At admission, the patient had received a total of 22 doses of Nivolumab (240 mg, every 2 weeks); denied other symptoms and no seizure activity or movement disorders were observed. Patient had no previous history of neurological disorders. Physical examination revealed fever, fluctuation in levels of consciousness, global aphasia and paratonia. Later, predominantly axial rigidity developed. Two days earlier to this admission he had been observed due to behavior alteration, confusion and a fall. A brain CT was performed showing no significant findings.

Initial workup revealed only mild anemia and hyponatremia. A brain magnetic resonance imaging (MRI) was performed with and without gadolinium, showing mild meningeal enhancement but no parenchymal alterations suggesting autoimmune or infectious cause (Fig. 1). Analysis of the cerebrospinal fluid (CSF) revealed normal glucose, mild pleocytosis (22/microL) with mononuclear cell predominance and elevated protein levels (113 mg/dL).

Empiric acyclovir and ampicillin were started until exclusion of infectious cause. Given the high suspicion of autoimmune encephalitis, high-dose intravenous methylprednisolone

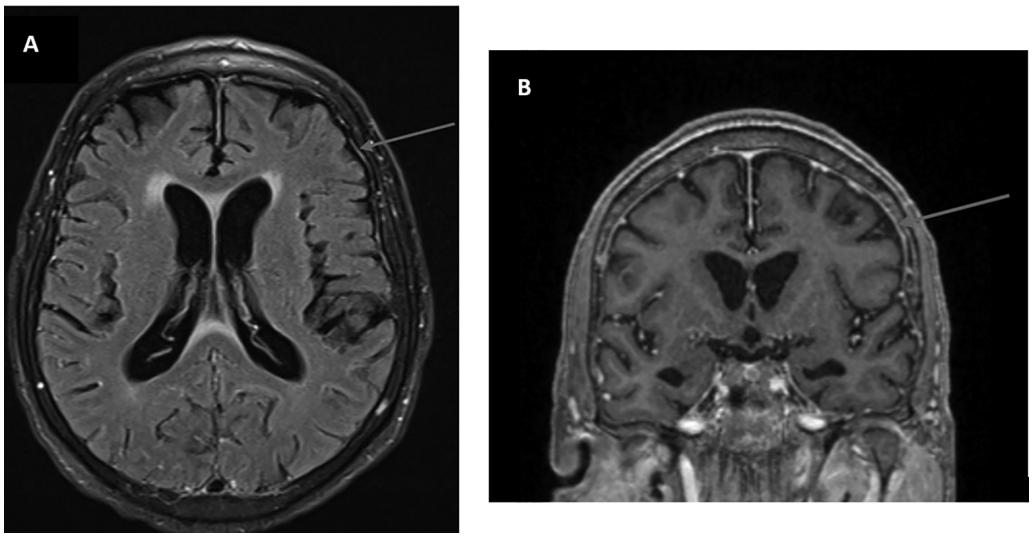

Figure 1 Brain MRI. **A** Axial FLAIR with gadolinium; **B** Coronal T1 with gadolinium — both show meningeal enhancement.

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1 g/d was started and maintained for 5 days, followed by intravenous immunoglobulin therapy 0.4 g/kg/daily for 5 additional days.

After day 1 of methylprednisolone, a major symptomatic improvement was observed, with partial cognitive recovery and apyrexia.

Pending tests from CSF analysis were negative for infectious agents and cytology showed no malignant cells. Cell-surface and intracellular anti-neuronal antibodies were also negative.

During hospitalization, tapering of corticosteroids was performed with continuous improvement in cognition and autonomy. Ultimately, patient was discharged after 16 days of hospitalization medicated with 20 mg of prednisolone. Steroids were tapered and stopped in the subsequent month, with no clinical worsening.

After exclusion of infection, metastatic etiology or other metabolic/endocrine etiologies, our report displays a rare and severe case of central nervous system (CNS) irAE, an immune-related Encephalitis (grade 4). Neurological toxicity occurs in 6.1% of patients receiving PD-1 inhibitors[2] and ICI-induced encephalitis was reported in 1% to 3% of cases.[3] Vogrig A. et al. characterized CNS complications of ICIs in three clinical phenotypes, limbic encephalitis, cerebellitis and meningoencephalitis, each with distinct immunological background, disease course and treatment response − our report presents a case of meningoencephalitis.[4]

To the best of our knowledge, only four case reports were found in literature describing association between PD-1 inhibitor nivolumab and autoimmune encephalitis in patients with NSCLC.[3,5,6]

These events are of concern with a high rate of residual symptoms and even fatal outcomes.[1] irEncephalitis mortality rate is as high as 19%.[7] Given the increasing use of ICI's, in monotherapy or as combination therapy, the prevalence of irEncephalitis is expected to increase.[7]

CNS irAEs are rare and knowledge on how to diagnose and treat them is limited.[4] Diagnosis is challenging, due to lack of specificity of CNS symptoms,[7] wide range of clinical features, lack of diagnostic biomarkers and the extensive list of differential diagnosis.

Brain MRI might be normal, reveal T2/FLAIR hyperintensities with no specific location, gadolinium enhanced or not, findings suggestive of an immune process, such as demyelinating lesions or limbic encephalitis. Our patient had no remarkable changes (Fig. 1).

CSF analysis can also present normal results.[7] Anti-Ma2 anti-bodies are usually associated with irEncephalitis,[7] and Epstein-Barr virus PCR was identified across multiple CSF samples, suggesting an association between viral infection and irEncephalitis.[4] These associations were not found in our case.

Average time of onset of nAEs is 6 weeks to 3 months.[4,5] In our case, nAEs appeared 11 months after starting Nivolumab, which stresses the need to remain alert at all phases of treatment with ICI, even after its discontinuation.[2]

Although causality cannot be proven in these cases, several features suggest that encephalitis was triggered by immune checkpoint blockade and is reversible after prompt cessation of immunotherapy and treatment with high doses of steroid with or without intravenous immunoglobulin therapy.[1]

Early recognition and successful management of irAEs are key to reducing its morbimortality; multidisciplinary discussion plays an essential role and more relevant cases should be collected and studied.

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REVIEW

Pulmonary vein stenosis mimicking interstitial lung disease

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Abstract Pulmonary vein stenosis (PVS) is a rare condition, often difficult to diagnose and associated with poor prognosis at advanced stages. Lung parenchymal abnormalities are indirect evidence of PVS and can manifest as multifocal opacities, nodular lesions, unilateral effusions, and interstitial septal thickening. These can lead to erroneous diagnoses of airway disease, pneumonia, malignancies or interstitial lung disease. This review summarizes the current literature about the approach to, evaluation and management of these patients. Our case report demonstrates that PVS is an under-recognized complication of cardiovascular surgery and should be considered in all patients presenting with respiratory symptoms after a cardiac procedure.

Introduction

Pulmonary vein stenosis (PVS) is an uncommon occurrence in adults, but one that carries significant morbidity and mortality. This entity can be secondary to neoplastic or non-neoplastic infiltration, extrinsic compression or iatrogenic intervention.[1,2]

PVS is characterized by progressive lumen size reduction of one or more pulmonary veins which, when significant, can raise lobar capillary pressure, leading to signs and symptoms such as shortness of breath, cough, and hemoptysis.[3] Therefore, PVS can be initially diagnosed as pneumonia, malignancy or other parenchymal lung diseases, leading to delay of care and unnecessary invasive diagnostic tests.[4,5] It is essential to consider the possibility of the disease in patients at-risk to guarantee early detection and treatment.

This article aims to describe a case of PVS that was primarily misdiagnosed as interstitial lung disease, and to review the literature that addresses the etiology, assessment, and management of this entity.

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Methods

The literature review was performed using four electronic databases (Pubmed, Cochrane, Scopus, and ISI-WOS) from inception until November 2019, involving the terms: ''pulmonary vein stenosis'', ''pulmonary venous infarction'', ''interstitial lung disease'', ''respiratory symptoms''. Further references from the case reports were considered. Exclusion criteria included commentaries and non-English language articles. Titles and abstracts were first examined to determine their relevance to the review. Duplicate articles between databases were initially identified and appropriately excluded.

Results

The identification results yielded 67 articles. After a careful analysis of the title and abstract, we included 23 articles. This information was summarized in a narrative review. We identified 4 case reports about PVS first diagnosed as primary lung disease (Table 1).

Case report

A 56-year-old man presented with progressive dyspnea on exertion and nonproductive cough for 3 months. He was a former smoker and had successfully undergone mitral valve reconstruction surgery due to ruptured chordae tendineae 4 months earlier. The computed tomography (CT) of the chest performed before surgery was normal, whereas six months later it revealed ground-glass opacities and patchy consolidations in the right upper and middle lobes (Fig. 1A).

Bronchoalveolar lavage fluid showed a normal cell count without pathogens or neoplastic cells. After antibiotic and diuretic treatment, he underwent another CT scan that revealed migratory pulmonary infiltrates, but still confined to the right upper and middle lobes. Respiratory function tests, including diffusing capacity for carbon monoxide, were normal. A transbronchial lung biopsy was then performed and the pathological analysis of the specimens identified thickening of the alveolar septa with no evidence of vasculitis or organizing pneumonia, suggesting nonspecific interstitial pneumonia (NSIP) (Fig. 1B). Despite lacking any systemic symptoms of connective tissue disease, he was started on steroids based on a tissue diagnosis of NSIP. After 2 months of steroid treatment, no symptomatic improvement was reported. The CT scan was then repeated and continued to reveal ground-glass opacities in the right upper and middle lobes. Because of the temporal relation between the symptoms and cardiac surgery, lack of improvement despite steroid therapy and negative auto-immune laboratory testing, we further expanded our search for an alternative diagnosis.

A chest angiography was performed and revealed stenosis of the right superior pulmonary vein, which would later be confirmed with a CT angiogram of the heart (Fig. 1C and D). The previous transbronchial lung biopsy was carefully reviewed and showed signs of severe congestion including thickening of the alveolar septa with rare lymphocytes and accumulation of hemosiderin macrophages in the alveoli. Transthoracic echocardiography excluded pulmonary hypertension or other major abnormalities. The case was then discussed in a multidisciplinary meeting and the diagnosis of PVS was established. Clinical and imaging monitoring was maintained every 3–6 months. In the last follow-up visit, the patient reported no symptoms and showed radiological improvement.

Discussion

Etiology

Congenital

Congenital PVS is an exceptional abnormality (0.4% of congenital heart diseases) consequence of a failed incorporation of the common right and/or left pulmonary vein into the left atrium during the embryologic development of the vessel that leads to partial or complete obliteration of the pulmonary veins on one or both sides.[2,3]

Acquired

Currently, radiofrequency ablation for atrial fibrillation (AF) has become the main cause of PVS. Incidence derived from recent studies reaches a mean and median of 2% and 3.1%, respectively.[3] However, there are other clinical conditions predisposing to the obstruction of the central pulmonary veins, like mediastinal masses, such as solid neoplasms or bulky lymphoma, fibrosing mediastinitis and mediastinal granulomatous diseases.[9,10] In addition, lung transplantation[11,12] and lobectomy[13] may result in PVS.

Symptoms

When acquired after radiofrequency ablation or heart surgery, clinical manifestations usually appear 3–6 months after the procedure and are related to the number of pulmonary veins affected.[3] Signs and symptoms include progressive exertional dyspnea, cough, chest pain fatigue, flu-like malaise, and hemoptysis.

In the largest published series, 33% of patients with PVS were initially diagnosed with bronchitis, pneumonia, or malignancy, leading to delayed care and unnecessary invasive diagnostic testing.[4,5]

Diagnosis

Lung parenchymal abnormalities are indirect evidence of PVS and can manifest as multifocal opacities, nodular lesions, unilateral effusions, and interstitial septal thickening.[6] Image techniques are essential to reach a final diagnosis and decide on an appropriate therapy.

Echocardiography

Transesophageal echocardiography (TEE) is a useful tool for PVS investigation. The transthoracic echo window is seldom satisfactory for the evaluation of the pulmonary venous flow in adults. PVS is suspected if peak flow velocity exceeds $1.0\,ms^{-1}$ and/or if pulmonary vein diameter is <5 mm.[9]

Table 1 Articles reported in the literature about adult patients with PVS first diagnosed as primary lung disease (infection, malignancy and interstitial lung disease).

Study, year, nr. Patients	Past medical history	Symptoms	High-resolution chest CT	Diagnostic approach	Treatment
Karthika R. Linga[6] 2015 Case Report 1 patient	Catheter ablation for AF 1 month before the onset of symptoms	Progressive dyspnea on exertion; dry cough	Bilateral ground-glass opacities; diffuse septal thickening; patchy consolidations in the left lung	(1) *Video-assisted thoracoscopic surgery*: severe congestion, including thickening of the interlobular and alveolar septa and accumulation of hemosiderin-laden macrophages in the alveoli (2) *Transthoracic echocardiogram*: normal mPAP (23 mmHg) with a severely elevated right upper pulmonary vein velocity of >103 cm/s (3) *CT angiography of the heart*: severe stenosis of all four pulmonary veins	Initial treatment with no improvement: (1) Antibiotics (2) Diuretics (3) High-dose steroids *Successful treatment*: Balloon angioplasty with pulmonary vein stenting
Erin Fender[5] 2017 Case Report 1 patient	Catheter ablation for AF 7 months before the onset of symptoms	Dry cough; fatigue; hemoptysis	Right upper lobe consolidations with interlobular septal thickening	(1) *Bronchoscopy and CT-guided needle biopsy*: no evidence of infection or malignancy (2) *CT pulmonary angiography*: critical stenosis of the right superior pulmonary vein with associated intraparenchymal lung hemorrhage and infarction (3) *Ventilation/perfusion scan*: severe perfusion defect in the right upper and middle lobes	Itraconazole for presumed fungal pneumonia *Successful* stenting of the right superior pulmonary vein
Fernández-Navarro[7] 2015 Case Report 1 patient	Catheter ablation for AF 4 months before the onset of symptoms	Dyspnea; sudden onset of intense left pleuritic pain	Peripheral alveolar consolidation in the left upper lobe and lingula, associated with pleural effusion	(1) *Chest CT angiography*: total occlusion of the left superior pulmonary vein (2) *Cardiac catheterization*: occlusion of the left superior pulmonary vein and critical stenosis of the left inferior pulmonary vein at the level of the ostium	Balloon angioplasty, followed by stent implantation

Table 1 (*Continued*)

Study, year, nr. Patients	Past medical history	Symptoms	High-resolution chest CT	Diagnostic approach	Treatment
Tatsuyuki Kawahara[8] 2019 Case Report 1 patient	Catheter ablation for AF 5 months before the onset of symptoms	Chest pain; low-grade fever; hemoptysis	Migratory consolidations in the left upper lobe	(1) *Transbronchial lung biopsy*: fibrous thickening of the interlobular septa and oedematous thickening of the alveolar wall, congestive capillary proliferation (capillary haemangiomatosis) (2) *Three-dimensional CT angiography and lung perfusion scintigraphy*: total perfusion deficit of the left lung	Initial treatment with no improvement: (1) Antibiotics (2) High-dose steroids *Successful* pericardial patch, venoplasty of the left pulmonary veins

AF, atrial fibrillation; CT, computed tomography; mPAP, mean pulmonary arterial pressure.

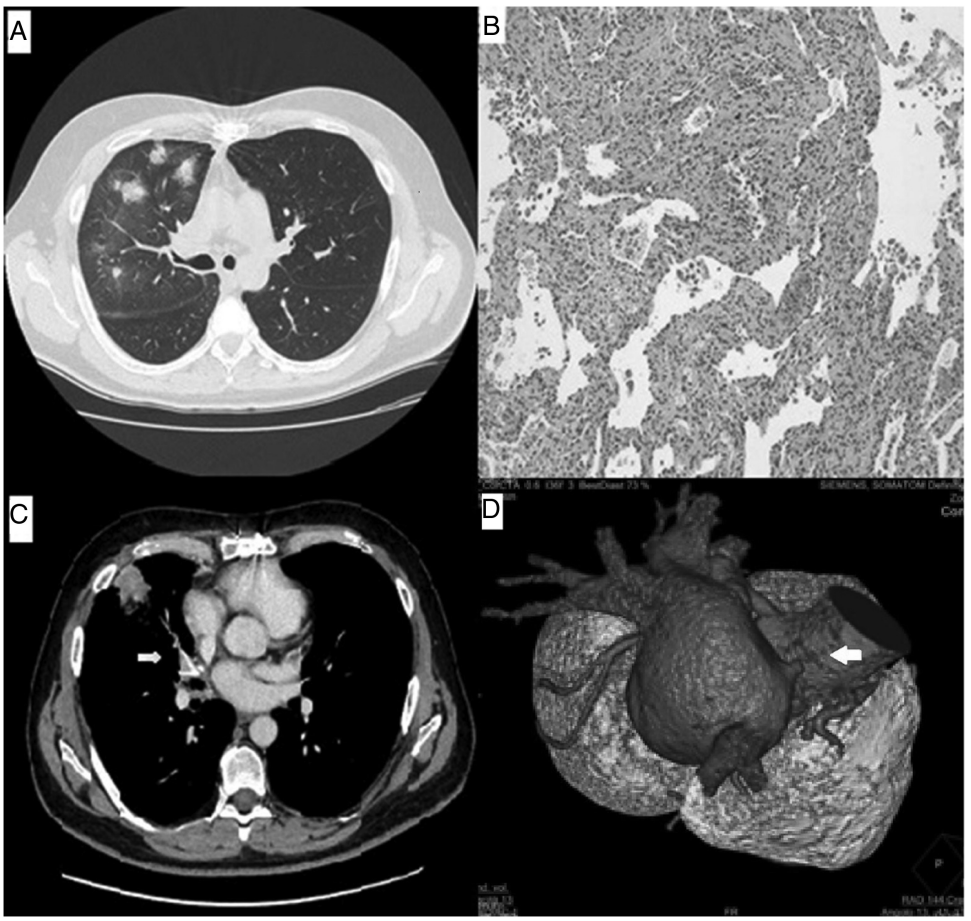

Figure 1 (A) CT of the chest revealed ground-glass opacities and patchy consolidations in the right upper and middle lobes. (B) Histologically, the transbronchial lung biopsy material revealed thickening of the alveolar septa with rare lymphocytes and accumulation of hemosiderin macrophages in the alveoli. (C) Chest angiography showed stenosis of the right superior pulmonary vein (arrow). (D) A 3-dimensional computed tomographic reconstruction demonstrated severe stenosis of the right superior pulmonary vein with subtotal occlusion (arrow).

Contrast-enhanced chest CT

Chest CT allows for assessment of the extension of mediastinal neoplastic and non-tumoral diseases infiltrating or compressing the pulmonary veins and enables the diagnosis of PVS after radiofrequency ablation by directly depicting vessel diameter (significant stenosis >50%).[3]

The main benefits of CT are short examination time, multiplanar views, high spatial resolution, and providing a three-dimensional (3D) data set, whereas disadvantages include patient exposition to ionizing radiation and need of intravenous iodine contrast agents that might impair renal function in vulnerable individuals.[3,9]

Magnetic resonance imaging (MRI)

MRI can be used to image the pulmonary veins.[14,15] Many different techniques have been used, including traditional contrast-enhanced MRI and, more recently, time-resolved magnetic resonance venography.[1] MRI, like CT, can provide a 3D data set but has the advantage of not using ionizing radiation. However, its spatial resolution is slightly inferior to that of CT, it requires a longer scanning time, and it may be contraindicated in patients with metal implants.

Ventilation/perfusion scan

The ventilation/perfusion scan is usually performed for the detection of pulmonary embolism but is also reported to serve as an effective screening tool for the detection of hemodynamically relevant PVS.[16,17] This exam, however, is not valuable for the etiological diagnosis of PVS and may be altered in other pathologies that decreased lobar perfusion (*i.e.*, pulmonary thromboembolism). It is not suitable for detection of <50% stenosis and may be inaccurate if significant compensating ipsilateral pulmonary vein flow is present.[3,1]

Management and follow up

Any patient with a history of radiofrequency ablation for AF or other cardiac surgery presenting with new-onset cough, chest pain, fatigue, or hemoptysis should be considered to have PVS until proven otherwise. The radiologist also needs to be made aware of the ablation history so the study is planned appropriately for pulmonary vein assessment.[5]

Mild and asymptomatic PVS may not need intervention. However, clinical and image surveillance every 3–6 months is advised, as the disease can evolve over time. Some authors recommend clinical and imaging monitoring in patients with 50%-85% stenosis, while others promote angioplasty if a single stenosis or a cumulative stenosis index (average stenosis of the pulmonary veins of one site) >75%.[3,18–21]

Surgery or transcatheter therapy are the preferred approaches in most congenital or acquired significant symptomatic PVS. However, evidence of treatment of PVS due to extrinsic compression, infiltration or cardiac surgery is restricted to case reports and the therapeutic decision is usually made subject to individual aspect.[22]

Early recognition of PVS is essential because stenosis can progress rapidly to complete occlusion. Late diagnosis can result in worsening of the underlying inflammation and progressive loss of the lumen.[20] Lung infarction is another possible consequence. As the vein narrows, it becomes more difficult to deploy a large stent and the risk for restenosis increases. In completely occluded veins, the rate of successful angioplasty or stenting is substantially reduced.[5]

Conclusions

PVS should be considered in all patients presenting with respiratory symptoms after cardiac surgery or radiofrequency ablation. Imaging techniques, such as CT angiography, play a fundamental role in the diagnosis and management of PVS, thanks to their good anatomical resolution, rapid results, and widespread availability.

Conflicts of interest

The authors have no conflicts of interest to declare.

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PHOTO

Crustacean renmants as a bronchial foreign body

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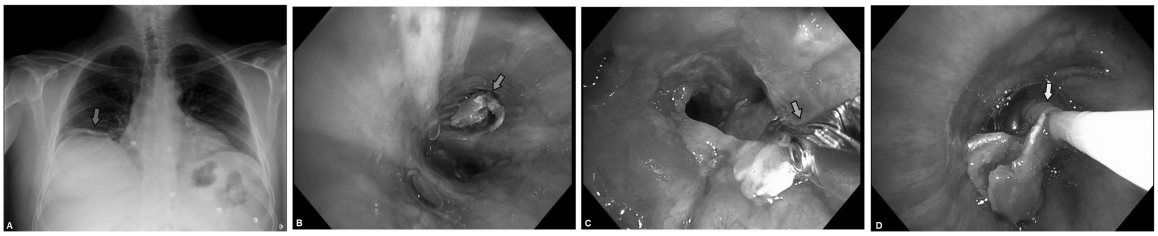

Figure 1 A Subsegmental atelectasis in the right lower lobe (red arrow). B. Crustacean remains (blue arrow) at the bronchial entrance B8-B10 and adjacent mucosal erythema. C-D. Extraction of crustacean remains using EndoJawFB-231D Olympus® forceps (green arrow) and Fogarty® catheter (yellow arrow).

Foreign body (FB) aspiration is uncommon in adults, with an estimated incidence around 0.2%.[1] FB can either be organic (e.g., peanuts, peas, etc.) or inorganic (e.g., pins, screws, nails, etc.). Identification of FB aspiration requires clinical suspicion, especially in those presenting with no history of aspiration. Occasionally, a forgotten FB may be detected during bronchoscopy or on a chest radiograph obtained for unrelated reasons. During bronchoscopy, a FB can be directly visualized. Granulation tissue, endobronchial stenosis, or edema—all features of tissue reaction to an aspirated FB—may also be present. In children, rigid bronchoscopy is the procedure of choice for FB removal due to its ability to secure the airway, whereas flexible bronchoscopy can be employed to confirm adult diagnoses and remove the FB. Furthermore, in children, FBs lodge in the proximal tracheobronchial tree, which can be easily accessed using a rigid bronchoscope. In adults, foreign bodies lodge in the distal tracheobronchial tree.[2]

A 57-year-old male with no medical history was referred for evaluation of cough and dyspnea grade II / IV mMRC for 3 months' duration after choking while eating, without improvement of vilanterol and inhaled fluticasone furoate. Physical examination revealed normal expiratory wheezing in the right hemithorax in complementary tests, except elevation of the right hemidiaphragm with subsegmental atelectasis in the right lower lobe (Fig. 1A).

Flexible bronchoscopy was performed, revealing a circumferentially hard consistency, dotted irregular surface, and brown coloration FB was proximal to the entrance to bronchi B8-B10 and adjacent erythematous mucosa, with abundant whitish secretions. Complete removal was performed using EndoJawFB-231D Olympus® forceps, flexible ERBE® cryotherapy probe (2.4 mm diameter) and Fogarty® catheter (Image 1B-D). The pathological anatomy was compatible with crustacean remains. Oral treatment with methylprednisolone was prescribed, along with subsequent

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endoscopic and radiological revision without alterations. The patient reported cessation of symptoms after intervention.

In the face of chronic cough, a correct anamnesis and physical examination informed by the possible etiology should be carried out.[3] FB aspiration has variable symptoms: cough, dyspnea, expectoration, wheezing or asphyxia. Symptoms may also be absent. When FB is suspected, chest radiography should be the initial test, after which a bronchoscopy should be performed for extraction.[1]

Conflicts of interest

The authors have no conflicts of interest to declare.

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