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EDITORIAL

Two years of COVID-19: Trends in rehabilitation

Rehabilitation is an important therapeutic strategy for patients who are exposed to COVID-19-related complications and particularly for those at risk of prolonged hospitalisation. Two years ago we had a paucity of information on dealing with such an unprecedented situation except for general recommendations.[1] Among these, in April 2020 an Italian position paper considering different phases of the disease and organisational issues, has furnished detailed recommendations that have substantially contributed to the development of safe and appropriate rehabilitative interventions particularly for the provision of respiratory physiotherapy.[2] The information released in that document is still valid and consistent after two years. As already pointed out, from the COVID-19 pandemic we have learned that physiotherapists already substantially contributed to implementing appropriate procedures and treatments at the beginning of the SARS-CoV-2 outbreak.[3] However, at the time of writing, we have now more data available, and we can infer additional details about rehabilitation for patients with COVID-19 at different stages of the disease.

COVID-19 has several extrapulmonary manifestations of rehabilitative interest, including neurological, physical, and functional limitations[4-7] which can last even months after the acute illness phase.[8,9] Over time, an increasing number of studies have been published reporting data about rehabilitative therapies adopted and implemented in COVID-19 settings. Observational studies are confirmed to be particularly helpful during this COVID-19 pandemic since they allow researchers to understand better different characteristics of the disease and related rehabilitative treatments to be implemented accordingly.[10]

During the first pandemic wave, one of the most worrying concerns was represented by hypercoagulability, a relevant factor in the pathogenesis of COVID-19 complications, with potential repercussions on the rehabilitative treatment.[11]

The surge in cases around the globe has stimulated easing administrative procedures to transfer hospitalised COVID-19 patients from acute COVID-19 hospitals to inpatient rehabilitation facilities producing positive effects on availability of beds.[12] In addition, rehabilitation has played a crucial role in facilitating patients' activity and mobility, a timely discharge, and the possibility of being discharged home or to "Covid hotels" from acute hospitals.[13] Several studies of acute inpatient rehabilitation conducted during the first pandemic wave, have demonstrated that an early rehabilitative approach was effective at improving outcomes and facilitating discharge to home.[14-18] Nevertheless, the same efficacy was not confirmed when considering mortality; while in some studies rehabilitation was associated with reduced mortality,[19] in others patients had a longer duration of invasive mechanical ventilation, a longer ICU stay, a more extended hospital stay and higher mortality rates.[20] It could be speculated that such differences are probably correlated to pre-existing comorbidities and patient selection.

From data available in the literature, the rehabilitative treatment provided in acute and subacute hospital settings seems to commence within the first 3-10 days after hospital admission, to be constituted by 15/30-minute sessions having heterogeneous frequencies ranging from twice a week to a daily schedule.[14-21]

Another aspect emerging from different clinical experiences is the use of assisted techniques implemented with rehabilitation such as muscle electrical stimulation and in-bed ergometry, showing they are feasible and contribute to reducing personnel exposure and saving personal protective equipment (PPE).[15,22] Indeed, the availability of PPE was a primary concern during the first pandemic wave. Although at the time of writing it seems there are no critical limitations to obtaining sufficient quantities of PPE, their uninterrupted use during the personnel shifts continues to be a cause of fatigue and attention, particularly regarding undressing and correct usage procedures.[23] In addition, high-risk interventions such as patient pronation, oxygen therapy, noninvasive ventilation, and chest physiotherapy, continue to be a matter of attention regarding personnel exposure. At the same time, manufacturers have been encouraged to develop a new generation of respiratory devices taking into consideration safety issues related to ventilation in critical settings dedicated to patients with respiratory viruses.[24] To reduce personnel exposure and save

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medical resources, other authors have implemented a belt-type muscle electrical stimulation protocol consisting of three 50-minute daily sessions to counteract muscle loss and the onset of ICU-acquired weakness in patients subjected to intensive organ support.[15]

There are no doubts about the challenges the COVID-19 pandemic has posed in managing an unparalleled volume of hospital admissions because of severe complications caused by the disease. However, the most critical concern has been and still is —at the time of writing— avoiding pressure on health care systems worldwide. In doing this, it is evident that expediting patient flow from acute to step-down units is a solution to making more beds available for those needing care. Such an approach might be facilitated by treating patients as soon as they are hospitalised, sharing a culture of mobility within the care settings. In this context, acute inpatient rehabilitation is a valuable means of accomplishing the mission to have patients participate in motor activities as much as possible and be able to execute respiratory exercises, even under challenging clinical conditions.[25]

The principal barriers to developing these abilities are often represented by the lack of human resources and the absence of a mobility culture within the teams. Nevertheless, these concerns can be addressed and observed from three perspectives: patient, organisational structure, and professionals. For the patient, pre-existing daily autonomy, care complexity and comorbidities are predictors of compliance with the therapeutic measures and clinical outcomes. It is well known that appropriate staffing, skill mix, training strategies, and turnover of human resources can influence the determination of the time reserved for patient assistance and the quality of multidisciplinary integration and communicative strategies between hospital settings. Furthermore, the effective management of the patients' clinical information contributes to enhancing the continuity of care from acute to step-down units as well as from hospitals to territorial rehabilitative facilities.

Eventually, from the professional's point of view, sharing common schemes for preserving motor, respiratory, swallowing functions should be implemented within the teams because they will influence the patients' journey to home or post-acute rehabilitative structures and expected outcomes. Patients who do not require further hospitalisation in out-patient settings, but are still in need of care, can be discharged home and continue to follow a specific rehabilitative protocol via telerehabilitation. The COVID-19 pandemic has contributed to the development of telemedicine strategies that are proving of crucial importance for reducing the risk of infection and responding to the need of care for patients who, during the first pandemic wave, had no access due to the contraction of healthcare services. Initial experiences of telerehabilitation have demonstrated that it is feasible and produces positive effects on functional capacity, exercise tolerance and dyspnoea.[26]

However, one of the most positive aspects of the rehabilitative pathway within critical settings is the capacity of sharing different tasks among health care professionals, involving various rehabilitation disciplines. In addition, COVID-19 has highlighted the ability of team members to cooperate, producing a virtuous circle of multidisciplinarity.[27,28] Last, but not least the published studies did not on average report a high level of contamination among the rehabilitative staff, even in those exposed to aerosol-generating procedures.[29] Indeed, a comprehensive and multidisciplinary approach is crucial to reducing the burden of care for families and caregivers, expediting patients' return to social and working contexts, thus mitigating costs.

After two years of COVID-19, we are observing that rehabilitation has several components that are fit to address different phases of the disease. An early rehabilitative approach in ICUs and sub-intensive settings has been demonstrated to be safe and feasible; to the same extent, patients developing long-COVID syndrome have found a prompt response which is further implemented by telerehabilitation.

Wave after wave, the COVID-19 pandemic demonstrates that health care systems are facing the same problems and difficulties worldwide. Nevertheless, rehabilitation professionals providing care in different settings contribute to establishing a rehabilitative regimen for patients with COVID-19, paving the way for further advancements.

Consent to publish data

Not applicable.

Conflicts of interest

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COMMENT

Improving non-small-cell lung cancer survival through molecular characterization: Perspective of a multidisciplinary expert panel

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Perspective of an expert panel on current challenges in the molecular characterization of non-small-cell lung cancer: What can be improved towards better treatment outcomes?

Substantial progress has been made over the last years in understanding critical molecular and cellular mechanisms driving tumor initiation and progression, with more than 50% of lung adenocarcinomas — the main subtype of non-small-cell lung cancer (NSCLC) — harboring oncogenic drivers.[1—3] These findings led to the development of several novel drugs and treatment strategies and shifted the treatment paradigm of advanced NSCLC from a morphology-based to a predictive biomarker-driven approach based on tumor molecular genotyping.

Targeted therapies are the first treatment option for patients with advanced or metastatic disease with tumors harboring oncogenic mutations. In the absence of targetable

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oncogenic drivers, immunotherapy, either in monotherapy or combination, is the treatment of choice. Molecular alterations with approved therapies in NSCLC are depicted in Table 1.

Given the established efficacy of targeted therapies in tumors harboring oncogenic drivers, the European and American guidelines recommend molecular testing for all advanced NSCLCs of non-squamous histology, particularly those with probable or definite adenocarcinoma, as in patients with non-adenocarcinoma histology, with low tobacco exposure, young age, or small specimen biopsy regardless of the performance status, to retrieve the most complete information to define the first-line treatment.[4–9]

Despite the recognition of the relevance of molecular characterization in the management of NSCLC, several challenges still need to be addressed and overcome in the clinical practice to ensure a complete and fast molecular assessment. An expert panel of pulmonologists and oncologists dedicated to thoracic Oncology convened to debate the molecular characterization of NSCLC at diagnosis and progression and identify key aspects to improve patient outcomes, highlighting the current evidence on NSCLC molecular profiling and discussing its benefits and challenges.

The following aspects were identified as most relevant for standardizing and optimizing the molecular diagnostic process considering both the laboratory and clinical approach:

- Reflex testing has the advantage of optimizing sample management. It reduces the time until treatment initiation and should be performed by the pathologist after histological assessment.[5]
- Molecular analysis should include a comprehensive gene panel, ideally a targeted multiplex next-generation sequencing (NGS) panel including point mutations, deletions, and rearrangements. Given the increasing number of mutations with potential clinical impact, NGS allows to optimize sample processing and simultaneously screen for several genes, with high throughput and sensitivity and low cost per test.[10–13] Although NGS is a costly technique for most centres, it will predictably become more accessible in the future, as demonstrated in studies exploring the cost-effectiveness of the method.[10]
- Biomarkers assessed should target genomic drivers with approved therapies, including the epidermal growth factor receptor (*EGFR*), the anaplastic lymphoma kinase *(ALK)*, the C-ros oncogene 1 (*ROS1*), the rearranged during transfection (*RET*), and the B-Raf proto-oncogene (*BRAF*). In addition, given the fast pace of therapeutic progress, molecular alterations with targeted therapies in advanced stages of development or likely to become therapeutic targets in the short term should also be assessed, specifically those in the human epidermal growth factor 2 (*HER2*), neurotrophic tyrosine receptor kinase *(NTRK)*, mesenchymal-epithelial transition (*MET)*, and Kirsten rat sarcoma viral oncogene homologue (*KRAS)*. This approach is in accordance with the European Society for Medical Oncology (ESMO) recommendations for the use of NGS in the clinical practice,[10] and allows the treatment in routine clinical practice as well as access to ongoing clinical trials and early access programs.[5,6]
- In specific cases of very symptomatic patients with aggressive disease and urgent need for treatment, rapid tests can be considered to define the first-line treatment, namely polymerase chain reaction (PCR) to detect *EGFR* mutations and immunohistochemistry or FISH to detect *ALK* and *ROS1* rearrangements, while maintaining NGS ongoing.
- In patients without sufficient tumor tissue to undergo molecular testing who are ineligible for rebiopsy, liquid biopsy can be considered to identify therapeutic targets. Liquid biopsy has several advantages, like avoiding the potential complications of tissue biopsy and allowing serial monitoring. In addition, it can provide a complete and real-time molecular profile, with information about clonal evolution and dynamic modifications within the tumor.[14] The clinical use of liquid biopsy in detecting *EGFR* mutations in plasma from advanced NSCLC patients has been validated[6,13,15–21] and is currently being assessed for other oncogenic drivers, as *ALK*, *BRAF, ROS1*, *MEK*, and *HER2*.[13,22–25]
- Despite the significant improvements in patient outcomes achieved with *EGFR*-tyrosine kinase inhibitors (TKI), most patients acquire resistance and develop progressive

Table 1 Molecular alterations with approved therapies in non-small-cell lung cancer

Gene/protein alteration	Approved therapy
EGFR exon 19 deletion or exon 21 L858R mutations	Afatinib*, dacomitinib*, erlotinib*, gefitinib*, osimertinib*
EGFR S678I, L861Q, G719X mutations	Afatinib*
EGFR exon 20 insertions	Avimantanab**, mobocertinib**
BRAF V600E mutation	Dabrafenib*, trametinib*
ALK rearrangement	Alectinib*, brigatinib*, ceritinib*, crizotinib*, lorlatinib*
ROS1 rearrangement	Crizotinib*, entrectinib*
RET rearrangement	Pralsetinib*, selpercatinib*
NTRK rearrangements	Entrectinib*, larotrectinib*
MET exon 14 skipping mutation	Capmatinib**, crizotinib*, tepotinib**
KRAS G12C mutation	Sotorasib**

* FDA- and EMA-approved
** only FDA-approved
ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor 2; KRAS, kirsten rat sarcoma viral oncogene homologue; MET, mesenchymal-epithelial transition; NRG1, neuregulin-1; NTRK, neurotrophic tyrosine receptor kinase 1; RET, rearranged during transfection; ROS1, C-ros oncogene 1

disease within 10–12 months of treatment, limiting its long-term efficacy. This is particularly true when considering first- and second-generation TKIs.[26] The most commonly acquired resistance mutation to first- and second-generation *EGFR*-TKIs is the T790M mutation in *EGFR* exon 20, identified in around 50–60% of cases.[27–29] Other acquired resistance mechanisms to these inhibitors include alternative pathway activation through c-Met amplification, *HER2* activation, and *PIK3CA* and *BRAF* mutations and histological transformation.[30] T790M confers resistance to gefitinib, erlotinib, and afatinib, and its detection allows the use of the third-generation *EGFR*-TKI osimertinib in second line.[24] At disease progression, rebiopsy should be considered to look for targetable resistance mechanisms. In the setting of *EGFR*-mutated disease, liquid biopsy can be the first step, as it is more accessible and less invasive than other methods. In cases of progression to third-generation TKIs, NGS is preferred to single-detection testing.[8] Tissue biopsy should be considered in cases of negative or inconclusive liquid biopsy, progression to third-generation TKIs, and rapidly progressive disease, to investigate histological transformation.[8]
- The average time between histological diagnosis and getting the molecular test result is heterogeneous among institutions, but ideally should not exceed two weeks.[6] Minimizing bureaucratic issues and adopting reflex testing can reduce this time. Irrespective of the test being performed in-house or in an external laboratory, timely retrieval of results should be ensured.
- The molecular study report should be presented in a simplified and systematic way and include the molecular test results (gene panel used and genomic changes identified and respective allele frequencies), their clinical interpretation given the available evidence, therapeutic options, and ongoing clinical trials (which should be regularly updated).[31]
- Molecular study results should always be discussed within a multidisciplinary context, to allow complete and thorough data analysis. Defining a molecular tumor board is a recommended best practice that all centers should adopt.[8]

The management of NSCLC remains challenging, and the integration of data from predictive biomarkers in routine clinical practice can contribute to an optimal, individualized patient approach, particularly given the rapid emergence of effective targeted therapies. When considering molecular biomarker testing, the choice of the biomarker panel, target population, testing approach, and turnaround time are key issues that, when properly addressed, can improve the survival outcomes of NSCLC patients.

Declaration of Competing Interest

MGF declares having received honoraria from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, MSD, Pfizer, Roche.

FE declares having received honoraria from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Janssen-Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi.

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JML declares having received honoraria from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Roche.

SA declares having received honoraria from Boehringer Ingelheim, Novartis, MSD, Pfizer, and Roche.

TS received consultancy honoraria from Boehringer-Ingelheim.

FB received speaker's fees and honoraria from AstraZeneca, Boeringher Ingelheim, Bristol Myers Squibb, MSD Oncology, Pfizer, Roche and Takeda.

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ORIGINAL ARTICLE

High efficiency particulate air filters and heat & moisture exchanger filters increase positive end-expiratory pressure in helmet continuous positive airway pressure: A bench-top study

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KEYWORDS
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Abstract

Background: Helmet continuous positive airway pressure (CPAP) has been widely used during the COVID-19 pandemic. Specific filters (i.e. High Efficiency Particulate Air filter: HEPA; Heat & Moisture Exchanger Filter: HMEF) were used to prevent Sars-CoV2 environmental dispersion and were connected to the CPAP helmet. However, HEPA and HMEF filters may act as resistors to expiratory gas flow and increase the levels of pressure within the hood.

Methods: In a bench-top study, we investigated the levels of airway pressure generated by different HEPA and HMEF filters connected to the CPAP helmet in the absence of a Positive End Expiratory Pressure (PEEP) valve and with two levels of PEEP (5 and 10 cmH_2O). All steps were performed using 3 increasing levels of gas flow (60, 80, 100 L/min).

Results: The use of 8 different commercially available filters significantly increased the pressure within the hood of the CPAP helmet with or without the use of PEEP valves. On average, the

Abbreviations: CPAP, Continuous Positive Airway Pressure; HEPA, High Efficiency Particulate Air Filter; HMEF, Heat and Moisture Exchange Filter; ICU, Intensive Care Unit; NIV, Non-Invasive Ventilation; PEEP, Positive End Expiratory Pressure; ZEEP, Zero End Expiratory Pressure.
The present study was performed at the General Intensive Care Unit, Emergency Department and Intensive Care, San Gerardo Hospital — ASST Monza, Via Pergolesi 33 — Monza (MB), Milan-Bicocca University — Italy.

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increase of pressure above the set PEEP ranged from 3 cmH_2O to 10 cmH_2O across gas flow rates of 60 to 100 L/min. The measure of airway pressure was highly correlated between the laboratory pressure transducer and the Helmet manometer. Bias with 95% Confidence Interval of Bias between the devices was 0.7 (-2.06; 0.66) cmH_2O.

Conclusions: The use of HEPA and HMEF filters placed before the PEEP valve at the expiratory port of the CPAP helmet significantly increase the levels of airway pressure compared to the set level of PEEP. The manometer can detect accurately the airway pressure in the presence of HEPA and HMEF filters in the helmet CPAP and its use should considered.

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Introduction

Helmet continuous positive airway pressure (CPAP) was considered a useful and effective treatment in COVID-19 hypoxemic respiratory failure outside the Intensive Care Unit (ICU).[1] The use of non-invasive ventilation (NIV) helped to avoid intubation by reducing complications associated with invasive mechanical ventilation.[2-5] Ideally, COVID-19 patients should be admitted to hospital in a negative pressure room in order to prevent the contamination coming from the outside environment.[6-8] In this context, Helmet CPAP would reduce the environmental spread of Sars-CoV2.[9,10] Helmet CPAP is composed of a flexible plastic hood attached to a stiff plastic ring surrounding a soft plastic collar. The continuous gas flow of CPAP is guaranteed by a flow generator that blends together a gas mixture composed of ambient air (Air) and pure oxygen. In order to prevent CO_2 rebreathing and to maintain a stable level of PEEP throughout the entire respiratory cycle, the gas flow should be at >50 L/min.[11,12] PEEP is obtained by the use of expiratory valves that serve as gas flow resistors.[13] Helmet CPAP decreases significantly the air leaks compared to the total face-mask[14] and expired gas flow can be purified thanks to specific filters at the outlet of the helmet (i.e. High Efficiency Particulate Air filter − HEPA; and Heat & Moisture Exchanger Filter - HMEF). HEPA and HMEF filters have a hydrophobic membrane composed of glass fibers and confer a high antiviral and anti-bacterial efficiency (i.e. 99.999%).[15] By using these filters, helmet CPAP is superior compared to other non-invasive respiratory devices in decreasing the virus dispersion.[8,9,16] Unfortunately, the gas flow delivered through the helmet CPAP is rarely measured. The pressure within the hood may be considerably under estimated despite the level of pressure set on the PEEP valve.[17] This phenomenon may be amplified in the presence of HEPA and HMEF filters placed before the PEEP valve.

We hypothesized that HEPA and HMEF filters - used before the PEEP valve for environmental protection against Sars-CoV2 dispersion, may act as a resistor and may greatly increase the airway pressure. The primary aim of the current study is to assess whether different HEPA and HMEF commercial filters may increase the airway pressure in the helmet CPAP above set levels of PEEP. This aim was tested using increasing levels of fresh gas flow. The secondary aim was to test the reliability of the reading system of airway pressure attached to the helmet CPAP (i.e. manometer) by comparing it with a calibrated pressure transducer.

Materials and methods

The hood of a commercially used helmet CPAP (DIMAR S.r.l. Via Galilei 6, 41036 Medolla Italy − mod. DimAir 500/9666) was placed on a mock manikin head and connected to a flow generator (EasyMIX by flow-meter Made in Italy − SN 00GMCZ), by a tubing connector (MALLINCKRODT DAR S.r.l., via G. Bove, 41037 Mirandola Modena - mod. 285/5063). The exit line of the hood was configured by using 2 different mechanical PEEP valves (DEAS valve - Deaflux Respiratory Production - NS 03986 [*PEEP valve 1*]; DIMAR Valve - DimAir mod. 700/6336 [*PEEP valve 2*]) and 8 different commercially available mechanical filters, 2 of them were HEPA and 6 of them were HMEF (Table 1). A calibrated pneumotachograph (ADINSTRUMENTS PowerLab 16/30 − Model: ML141 Serial 141-0990) was used to measure gas flow (Liter/sec). A pre-calibrated pressure transducer to atmospheric pressure was used to measure the pressure within the hood of the helmet CPAP (i.e. airway pressure) (EDWARDS LIFESCIENCE - Irvine, CA 92614 − Truwave PX260). The pressure transducer was placed at the exit line of the hood and connected to the acquisition system. At the same time, the levels of airway pressure were recorded by the manometer of the hood and reported in cmH2O (DIMAR S.r.l. − DimAir manometer mod. 700/6355) included in the helmet kit box. (Fig. 1). The pressure and flow tracings were recorded by a dedicated software and stored for off line analysis ("LABCHART" (ADINSTRUMENTS LabChart®7 v 7.2 Copyright ©1994-2010). We investigated the levels of airway pressure generated by different HEPA and HMEF filters in the absence of a PEEP valve (PEEP=0 cmH_2O, zero PEEP, ZEEP) or in the presence of two levels of PEEP (i.e. 5 and 10 cmH_2O) by using two commercially available mechanical PEEP valves, and 3 increasing levels of gas flow were tested (i.e. 60, 80 and 100 L/min). As first, we evaluated the airway pressure by using all studied HEPA and HMEF filters without the presence of a PEEP valve in order to assess whether the airway pressure could change by increasing the fresh gas flow. Subsequently, we explored the change in airway pressure levels by increasing fresh gas flow in the presence of 2 levels of PEEP (i.e. 5 and 10 cmH_2O) and by using two different mechanical PEEP valves. For each step, we investigated the

Table 1 Technical specifics of HEPA and HMEF filters.

Filter Model	HEPA versus HMEF	Suggested tidal volume	Average resistance to flow $cmH_2O(mbar)/L/min$
F1 DAR COVIDIEN 351/5878	HMEF	200 – 1500 ml	0.8 cmH_2O at 30 L/min 1.9 cmH_2O at 60 L/min 3.2 cmH_2O at 90 L/min
F2 DRAGER MP01790	HEPA	300 – 1500 ml	1.3 mbar at 30 L/min 2.9 mbar at 60 L/min 4.6 mbar at 90 L/min
F3 INTERSURGICAL 1545000	HEPA	> 225 ml	0.8 cmH_2O at 30 L/min 2.1 cmH_2O at 60 L/min
F4 PALL ULTIPOR BB100PS	HMEF	/	2 cmH_2O at 60 L/min
F5 DAR COVIDIEN 354/5876	HMEF	300 – 1500 ml	1.1 cmH_2O at 30 L/min 2.5 cmH_2O at 60 L/min 4.2 cmH_2O at 90 L/min
F6 TELEFLEX ISO GARD 28001/02	HMEF	300 – 1200 ml	2 cmH_2O at 60 L/min
F7 DRAGER MP01801	HMEF	300 – 1500 ml	1.3 mbar at 30 L/min 2,7 mbar at 60 L/min 4.3 mbar at 90 L/min
F8 TELEFLEX HUMID-VENT 19401	HMEF	150 – 1000 ml	1.8 cmH_2O at 60 L/min

Data source: DAR COVIDIEN 351/5878 - https://www.medtronic.com/content/dam/covidien/library/ca/en/product/acute-care-ventilation/CA-PMR-0401-E-DAR-Filter-Catalog.pdf
DRAGER MP01790 - https://www.draeger.com/Products/Content/TwinStar-brochure-9066151-en-master_AFO.pdf
INTERSURGICAL 1545000 - https://www.intersurgical.com/products/airway-management/clearguard-range-medium-efficiency
PALL ULTIPOR BB100PS - https://shop.pall.com/us/en/products/zidBB100A
DAR COVIDIEN 354/5876 - https://www.medtronic.com/content/dam/covidien/library/ca/en/product/acute-care-ventilation/CA-PMR-0401-E-DAR-Filter-Catalog.pdf
TELEFLEX ISO GARD 28001/02 - https://www.teleflex.com/usa/en/product-areas/anesthesia/airway-management/passive-humidification-and-filtration/gibeck-iso-gard-filters/index.html
DRAGER MP01801 - https://www.draeger.com/Products/Content/TwinStar-brochure-9066151-en-master_AFO.pdf
TELEFLEX HUMID-VENT 19401 - https://www.teleflex.com/usa/en/product-areas/anesthesia/airway-management/passive-humidification-and-filtration/gibeck-hmefs/index.html

association between airway pressure levels measured by using the pressure transducers placed in the hood and the pressure manometer of the helmet CPAP.

Statistical analysis

Continuous variables were expressed as median with interquartile range (25^{th}-75^{th} percentile). Normality of distribution was assessed by using the Shapiro-Wilk test. Given the design of the bench study, differences in continuous variables across increasing levels of fresh gas flow (i.e. 60, 80 e 100 L/min) were tested by using the non-parametric test for repeated measurements Friedman's test. Post-hoc comparison across different flow rates was assessed by using the Benjamini, Krieger e Yekuteli test. The correlation between the levels of pressure measured by using the pressure transducer and the manometer of the helmet CPAP was evaluated by a linear regression using the Pearson's correlation coefficient. Analysis of agreement between the manometer placed on the helmet CPAP and the gold standard used to measure the pressure by using a pressure transducer was performed by using the Bland-Altman analysis. Bias with 95% confidence interval (CI) was reported. Statistical significance was set at a two-tailed p-value<0.05. Statistical analyses were performed using STATA/MP 17.0 for Mac (StataCorp, College Station, TX 77845, USA) and GraphPad Prism 9 for MacOs (Version 9.3.1, GraphPad, GraphPad Software, Inc.).

Results

HEPA and HMEF filters gradually increase airway pressure at zero PEEP (ZEEP)

We evaluated the change of airway pressure within the hood of the helmet CPAP with and without HEPA and HMEF filters in the absence of PEEP (i.e., ZEEP). As compared to atmospheric pressure, as expected the absence of HEPA and HMEF filters resulted in 0 ΔZEEP. In contrast, the use of HEPA and HMEF filters led to a gradual increase in ΔZEEP across increasing levels of gas flow, specifically ranging between 1.9-3.3 cmH_2O, 2.9-5.9 cmH_2O, to 3.6-7.6 cmH_2O, at 60, 80 and 100 L/min of fresh gas flow, respectively (Fig. 2). We further evaluated the average effect on airway pressure of all HEPA/HMEF filters – as aggregate data in the absence of a PEEP valve - across increasing gas flow rates. Median increase ranged from 2.2 to 5.3 cmH_2O (Table 2 and Supplemental Figure 1).

HEPA and HMEF filters gradually increase airway pressure in the presence of a mechanical PEEP valve set at 5 cmH_2O

We evaluated the change of airway pressure within the hood of the helmet CPAP with and without HEPA and HMEF filters in the presence of PEEP=5 cmH_2O with 2 different mechanical

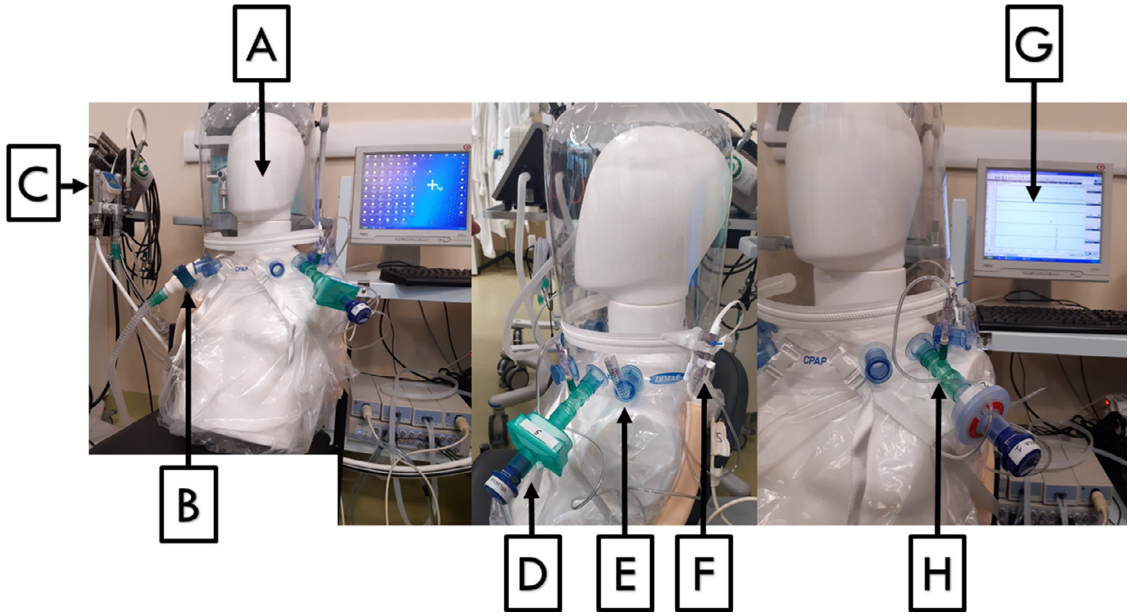

Fig. 1 Helmet CPAP in vitro configuration. A) Helmet CPAP; B) Pneumotachograph place at the inlet of the helmet; C) Gas flow generator; D) Mechanical PEEP valve with HEPA/HMEF filter; E) Manometer; F) Pressure transducer; G) Acquisition system and pressure and flow tracings; H) airway pressure reading point.

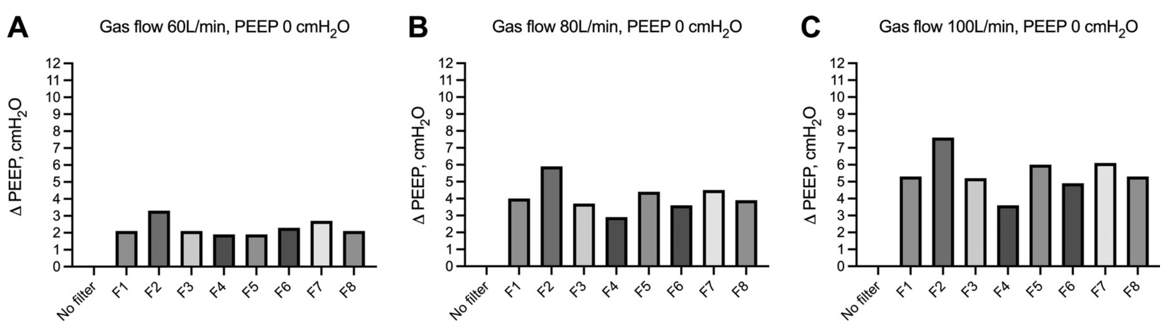

Fig. 2 Change in airway pressure within the hood of the helmet CPAP (ΔZEEP) without and with different HEPA and HMEF filters across increasing gas flows and in the absence of a mechanical PEEP valve. Increasing flow rates are reported ~~in~~ from panel A — 60 L/min; to panel B — 80 L/min; to panel C, 100 L/min. Description of HEPA and HMEF (i.e. from F1 to F8) filters are reported in Table 1. Histobars summarize median and interquartile range.

PEEP valves (i.e. valve 1 and valve 2). Using valve 1, as compared to set airway pressure at 5 cmH_2O, the absence of HEPA and HMEF filters resulted in a ΔPEEP ranging from 0 to 1.5 cmH_2O at increasing flow rates. The use of HEPA and HMEF filters led to a gradual increase in ΔPEEP across increasing levels of gas flow ranging between 1.9-4.3 cmH_2O, 3.9-6.4 cmH_2O, to 5.4-8.8 cmH_2O, at 60, 80 and 100 L/min of fresh gas flow, respectively (Fig. 3**a**). We observed a similar effect

Table 2 Change in airway pressure (ΔPressure, cmH_2O) over increasing gas flows and without using any PEEP valve and by using 2 different commercially available PEEP valves (PEEP valve 1 and 2).

Tested condition	Gas flow 60 L/min	Gas flow 80 L/min	Gas flow 100 L/min	p-value
No PEEP valve	2.2 (1.9-2.6)	3.9 (3.6-4.5)*	5.3 (5.0-6.1)*#	<0.001
PEEP valve 1				
• **Set at 5 cmH_2O**	2.8 (2.2-3.8)	4.9 (4.4-5.4)*	6.7 (5.9-7.1)*#	<0.001
• **Set at 10 cmH_2O**	3.0 (2.4-3.4)	4.5 (3.9-5.4)*	6.3 (6.0-6.7)*#	<0.001
PEEP valve 2				
• **Set at 5 cmH_2O**	5.2 (4.5-6.1)	7.5 (6.9-8.0)*	9.8 (9.0-10.3)*#	<0.001
• **Set at 10 cmH_2O**	5.7 (5.6-6.3)	7.7 (7.3-8.7)*	10.1 (9.2-10.8)*#	<0.001

ΔPressure are reported in cmH_2O as median and interquartile range. p-value of the Friedman's test. * $p < 0.05$ versus 60 L/min. # $p < 0.05$ versus 80 L/min.

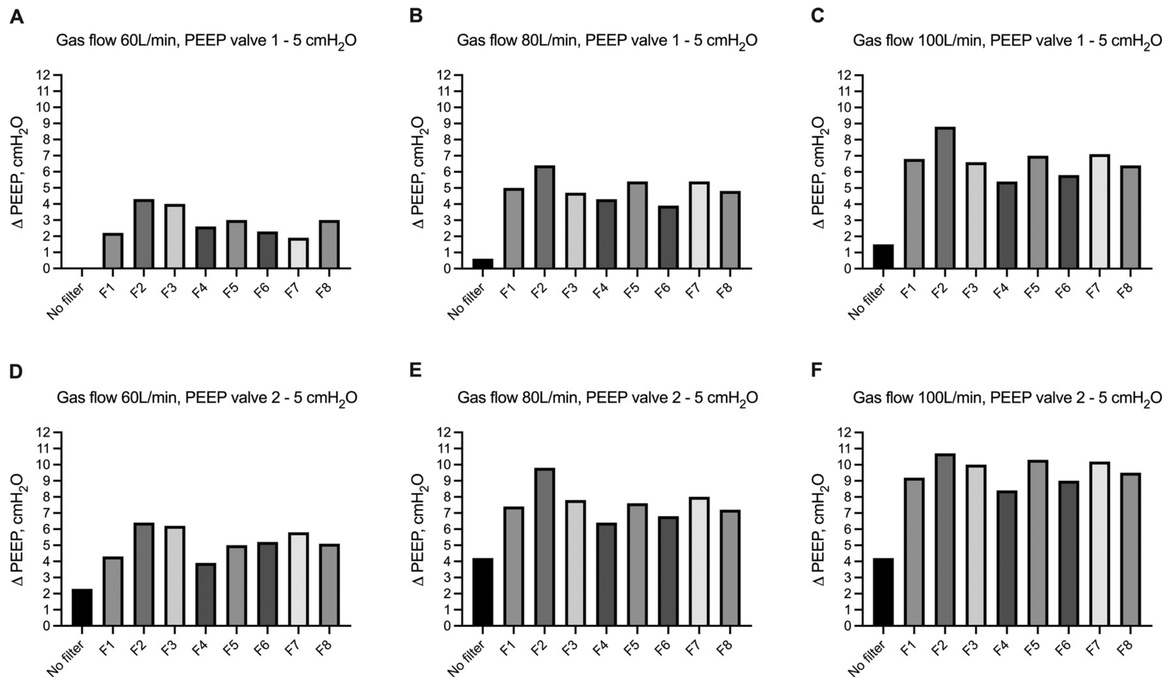

Fig. 3 Change in airway pressure within the hood of the helmet CPAP (ΔPEEP) without and with different HEPA and HMEF filters in presence of mechanical PEEP set at 5 cmH_2O. Increasing flow rates – from 60 L/min to 100 L/min - are reported ~~in~~ from panel A to panel C by using ~~a)~~ PEEP valve 1, and from Panel D to panel F by using PEEP valve 2. Description of HEPA and HMEF (i.e. from F1 to F8) filters are reported in Table 1. Histobars summarize median and interquartile range.

using a different mechanical PEEP valve (i.e. valve 2). In the absence of HEPA and HMEF filters, ΔPEEP ranged from 2.3 to 4.2 cmH_2O at increasing flow rates. The use of HEPA and HMEF filters led to a gradual increase in ΔPEEP across increasing levels of gas flow ranging between 3.9-6.4 cmH_2O, 6.4-9.8 cmH_2O, to 8.4-10.7 cmH_2O, at 60, 80 and 100 L/min of fresh gas flow, respectively (Fig. 3**b**). We further evaluated the average effect on airway pressure of all HEPA/HMEF filters – as aggregate data in the presence of PEEP valve set at 5 cmH_2O using both types of valves (i.e. valve 1 and vale 2) - across increasing gas flow rates. Average increase in ΔPEEP ranged from 2.8 to 6.7 cmH_2O and from 5.2 to 9.8 cmH_2O using PEEP valve 1 and PEEP valve 2, respectively (Table 2 and Supplemental Figure 2).

HEPA and HMEF filters gradually increase airway pressure in the presence of a mechanical PEEP valve set at 10 cmH_2O

We evaluated the change of airway pressure within the hood of the helmet CPAP with and without HEPA and HMEF filters in the presence of PEEP=10 cmH_2O with 2 different mechanical PEEP valves (i.e. valve 1 and valve 2). Using valve 1, as compared to set airway pressure at 10 cmH_2O, the absence of HEPA and HMEF filters resulted in a ΔPEEP ranging from 0 to 1.3 cmH_2O at increasing flow rates. The use of HEPA and HMEF filters led to a gradual increase in ΔPEEP across increasing levels of gas flow ranging between 2.1-4.6 cmH_2O, 2.9-5.8 cmH_2O, to 4.9-8.8 cmH_2O, at 60, 80 and 100 L/min of fresh gas flow, respectively (Fig. 4**a**). We observed a similar effect using a different mechanical PEEP valve (i.e. valve 2). In the absence of HEPA and HMEF filters, ΔPEEP ranged from 3.3 to 4.4 cmH_2O at increasing flow rates. The use of HEPA and HMEF filters led to a gradual increase in ΔPEEP across increasing levels of gas flow ranging between 5.4-7.2 cmH_2O, 6.8-10.0 cmH_2O, to 9.2-12.7 cmH_2O, at 60, 80 and 100 L/min of fresh gas flow, respectively (Fig. 4**b**). We further evaluated the average effect on airway pressure of all HEPA/HMEF filters – as aggregate data in the presence of PEEP valve set at 10 cmH_2O using both types of valve (i.e. valve 1 and vale 2) - across increasing gas flow rates. Average increase in ΔPEEP ranged from 3.0 to 6.3 cmH_2O and from 5.7 to 10.1 cmH_2O using PEEP valve 1 and PEEP valve 2, respectively (Table 2 and Supplemental Figure 3).

Correlation and agreement between airway pressure measured by gold standard versus helmet manometer

We tested the association between the airway pressure with the pressure transducer on within the hood and the manometer placed on the helmet CPAP across all the steps performed at different gas flow rates (60, 80 and 100 L/min) and with different HEPA/HMEF filters and in the absence of PEEP (i.e. ZEEP) or at PEEP of 5 and 10 cmH_2O. The correlation between the 2 measurements was very robust ($r = 0.993$, $p < 0.001$) (Fig. 5, **panel A**). Agreement between the 2 devices was good with a bias less than 1 cmH_2O and a 95% CI within 3 cmH_2O (Fig. 5, **panel B**).

Discussion

In this bench-top study, we investigated whether HEPA and HMEF filters placed at the expiratory port of the helmet

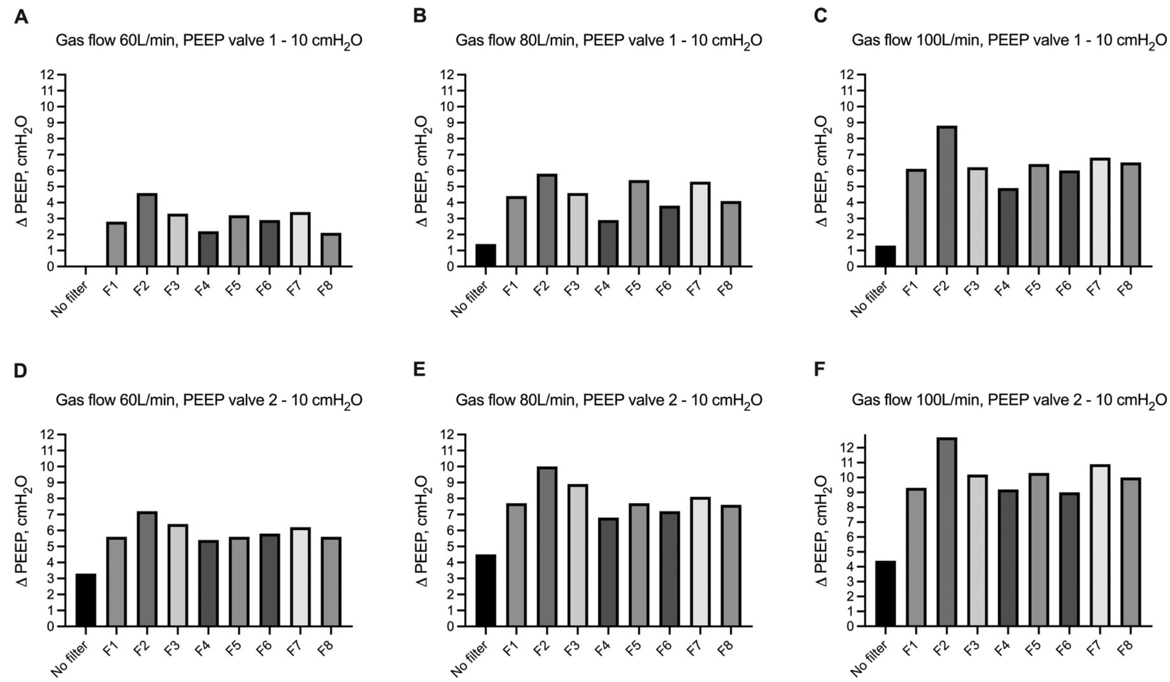

Fig. 4 Change in airway pressure within the hood of the helmet CPAP (ΔPEEP) without and with different HEPA and HMEF filters in presence of mechanical PEEP set at 10 cmH_2O. Increasing flow rates – from 60 L/min to 100 L/min - are reported ~~in~~ from panel A to panel C by using PEEP valve 1, and from Panel D to panel F by using PEEP valve 2. Description of HEPA and HMEF (i.e from F1 to F8) filters are reported in Table 1. Histobars summarize median and interquartile range.

CPAP may play a role in changing airway pressure within the hood in the presence of a set level of PEEP.

The primary findings of this study were that HEPA and HMEF filters – aimed at preventing microorganism dispersion – increase airway pressure in the helmet CPAP. The increment in airway pressure increases with the gas flow rate. This finding confirms that HEPA and HMEF filters act as resistors to fresh gas flow and significantly increase the airway pressure. This finding is concerning as it suggests that without a strict monitoring of the airway pressure in the helmet CPAP, the set level of PEEP may be unreliable. Furthermore, – as observed in this study – HEPA and HMEF filters may greatly underestimate the real pressure developed in the helmet CPAP. We reported that in the presence of high flow rates of fresh gas delivered through the helmet, we may easily double the set level of PEEP. This may lead to a dramatic increase in the risk of barotrauma which may further worsen the outcome of patients with respiratory failure.[18] In a recent case series published in 2020, the authors reported that COVID-19 patients – more often male – may be inclined to develop spontaneous pneumomediastinum or pneumothorax.[19,20] In other reports, the development of barotrauma has been reported in COVID-19 patients in all modalities of ventilation such as spontaneous breathing,[21,22] NIV[23] or in controlled mechanical ventilation.[24,25] In this context, the potential increase of airway pressure determined by HEPA/HMEF filters may promote barotrauma.

Our study demonstrated that all studied HEPA/HMEF filters generated additive levels of pressure to the set levels of PEEP. This may make their use unpredictable and unsafe with the risk of inappropriate airway pressure delivery in the absence of an accurate pressure monitoring system. This was observed even at the lowest tested flow rate of 60 L/min. The increase of pressure determined by the HEPA and HMEF filters across increasing levels of flow, suggested that the increase of pressure within the helmet is determined by both HEPA/HMEF filters on one hand, and - on the other hand - by the type of PEEP valve used in the CPAP system.[18]

The second finding of the study is that the manometer used with the CPAP helmet is accurate and provides reliable measurements of the airway pressure within the CPAP helmet as compared to the gold standard (i.e. calibrated pressure transducer) in the presence of HEPA/HMEF filters. Furthermore, agreement between the two technique was good and clinically acceptable (i.e., Bias less than 1 cmH_2O). This was reported with and without mechanical PEEP valve. This is a clinically relevant result that suggests that using the manometer on the CPAP helmet in daily clinical practice can reliably provide immediate information on the real airway pressure developed within the CPAP helmet at the end of expiration. Furthermore, this may suggest whether the modality of ventilation (i.e., gas flow, level of PEEP) should be changed and / or optimized.

Study limitation

This study has some limitations that should be acknowledged. First, this is a bench top study and the findings were not validated in the humans. Second, we evaluated 8 HEPA/HMEF filters commercially available, 2 different mechanical PEEP valve and one type of helmet CPAP on the market. We should then consider that our findings cannot be representative of all the types of filters, PEEP valves and helmets available on the market. This study it aims at raising awareness about the potential risk of barotrauma during the ventilation of patients

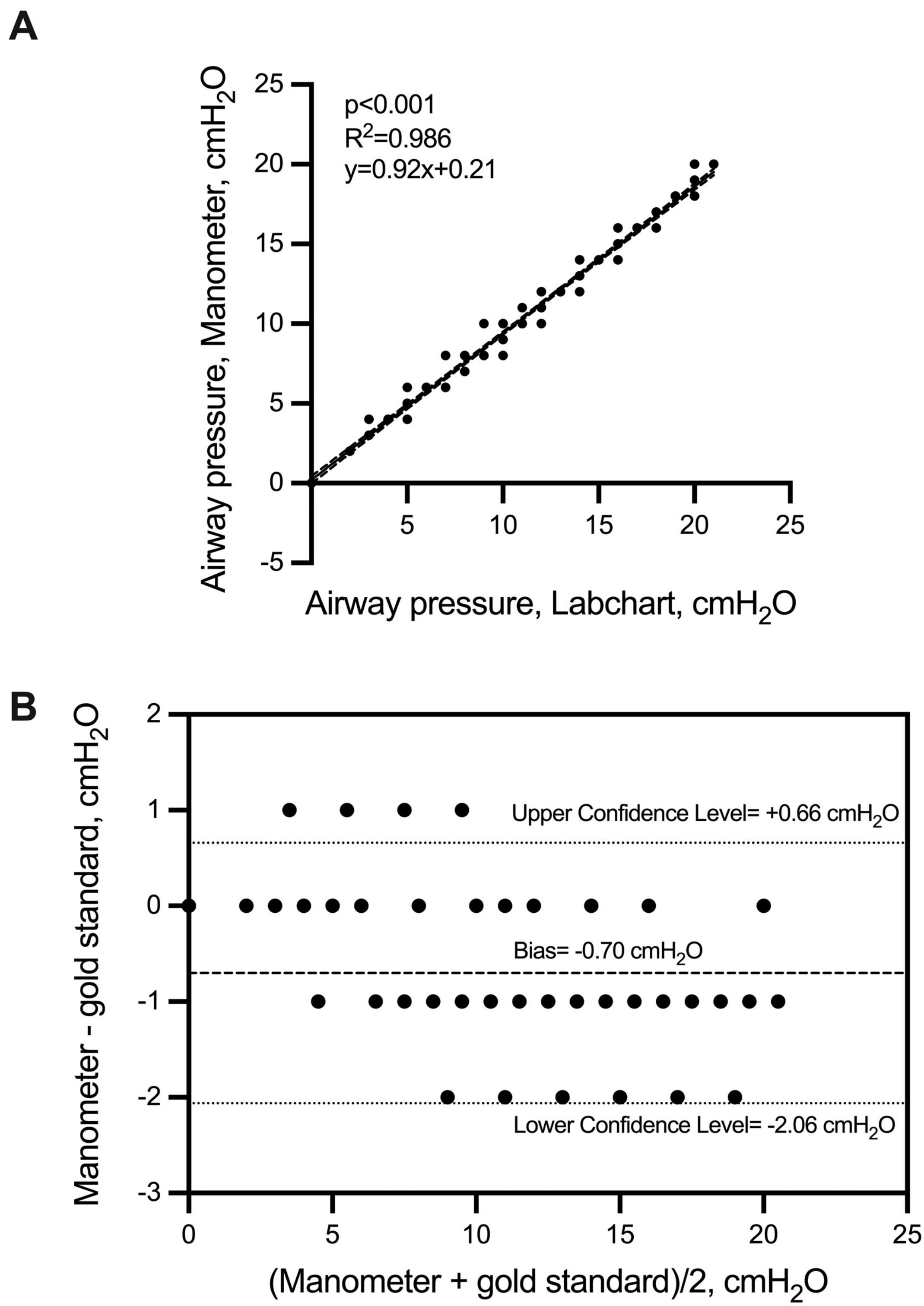

Fig. 5 Correlation (**panel A**) and agreement (**panel B**) between pressure levels measured by using a pre-calibrated pressure transducer and Helmet manometer. **Panel A.** Linear correlation (continuous line) with 95% CI (dotted line) between pressure levels measured by using a pre-calibrated pressure transducer (i.e. gold standard) and a manometer positioned on the helmet CPAP. Two-sided p-value, R^2, and the equation of the fitted linear regression are reported; n=134. **Panel B.** Bland Altman plot with Bias and 95% Confidence Interval representing agreement between the 2 techniques performed to measure airway pressure within the helmet CPAP (i.e. Upper and Lower Confidence Level).

with helmet CPAP that may have a role on their outcome. Furthermore, as this is an in vitro study - with the aim of providing precision and reproducibility of the results - it further aims at evaluating differences in the levels of airway pressure using a continuous flow. However, cyclic changes of flow were not part of this investigation.

Conclusions

In this bench study, the use of HEPA and HMEF filters on the expiratory port of the helmet CPAP can increase the resistance to the continuous airflow with the consequent increase of the airway pressure within the hood. The use of a manometer applied to the helmet CPAP can provides accurate and reliable measurements of the airway pressure within the helmet CPAP as compared to a calibrated pressure transducer. Airway pressure generated within the helmet should be closely monitored in order to confirm that its levels matched with the targeted level of PEEP.

Authors' contribution

ER, AL, RF, GB and GF: Conceptualization and Methodology, writing original draft. ER, GC, AG, LD, GPG and AL: data curation and validation. ER, GB and AL: formal analysis. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.05.003.

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ORIGINAL ARTICLE

Comparison of different field tests to assess the physical capacity of post-COVID-19 patients

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KEYWORDS
COVID-19;
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Dyspnoea

Abstract
Background: In coronavirus disease (COVID-19), physical capacity is one of the most impaired sequelae. Due to their simplicity and low cost, field tests such as the six-minute walk test (6MWT) are widely used However, in many places it is difficult to perform them and alternatives can be used such as the 1 min sit-to-stand test (1min-STST) or the Chester step test (CST). Therefore, our objective was to compare the 6MWT, 1min-STST and the CST in post-COVID-19 patients.
Methods: We conducted a cross-sectional analysis in post-COVID-19 patients, compared with matched controls (CG). Demographic characteristics and comorbidities were collected. We analysed oxygen saturation (SpO_2), heart rate (HR), and the modified Borg scale in the 6MWT, 1min-STST, and CST. Additionally, the correlations between tests were analysed.
Results: We recruited 27 post-COVID-19 patients and 27 matched controls. The median age was 48 (IQR 43-59) years old (44% female). The median distance walked in 6MWT was 461 (IQR 415-506) m in post-COVID-patients and 517 (IQR 461-560) m in CG (p = 0.001). In 1min-STST, the repetitions were 21.9 ± 6.7 and 28.3 ± 7.1 in the post-COVID-19 group and CG, respectively (p = 0.001). In the CST, the post-COVID-19 group performed 150 (86-204) steps vs the CG with 250 (250-250) steps ($p < 0.001$). We found correlations between the 6MWT with the 1min-STST in COVID-19 patients (r = 0.681, $p < 0.001$) and CG (r = 0.668, $p < 0.001$), and between the 6MWT and the CST in COVID-19 patients (r = 0.692, $p < 0.001$).

Abbreviation: 1min-STST, 1-minute sit-to-stand test; 6MWT, Six-minute walk test; COVID-19, Coronavirus disease 2019; CST, Chester step test; EID, Exercise-induced desaturation; HR, Heart rate; SpO_2, Oxygen saturation; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology guidelines.

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Conclusion: The 1min-STST and the CST correlated significantly with the 6MWT in patients post-COVID-19 being alternatives if the 6MWT cannot be performed.
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Introduction

The coronavirus disease (COVID-19) pandemic has been a challenge for health systems, affecting more than 500 million people, with more than 6 million deaths as of June 2022.[1] Although the vast majority of people infected by the SARS-CoV-2 virus develop mild or asymptomatic disease, about 20% develop severe disease requiring hospitalisation, and about 6% require critical care in an intensive care unit.[2]

Albeit the disease is primarily respiratory, it affects multiple systems such as cardiovascular or neurological, leaving a broad spectrum of sequelae that affect COVID-19 survivors in the short, medium and long term.[3–6] Among the most commonly reported sequelae are fatigue, dyspnoea, headache and impairment of physical capacity.[4,7] Undoubtedly, the appearance of sequelae affects the quality of life and the return to work in the active population.[4]

Due to the sequelae, the different health systems have had to generate follow-up programmes that focus primarily on imaging, lung function, symptoms, and physical capacity.[8,9] One of the pillars of the follow-up is the evaluation of physical capacity, which can be assessed with laboratory tests or field tests, such as the six-minute walk test (6MWT), the 1 min sit-to-stand test (1min-STST) or the Chester step test (CST).[10–14]

These tests can be performed in low-resource contexts and have widely demonstrated their usefulness in evaluating physical capacity in different respiratory, metabolic, cardiological or neurological diseases.[10] However, to provide specific information, functional or exercise capacity, a test must be chosen according to the characteristics of each subject, the setting and the physiological expected answer. For example, the 6MWT is a widely used test; however, it has shown a low execution rate in some COVID-19 patients at hospital discharge.[15] In addition, the execution of the 6MWT requires a 20-to-30-metre corridor that is often unavailable in hospitals or rehabilitation centres[16] and even less so at home.

There are modifications of the 6MWT in the length of the corridor, the space limitations being the main reason for using a shorter than recommended walkway.[17] A recent study compared the 10-metre and 30-metre circuits, finding that patients with chronic non-communicable diseases walk about 70 m less on the 10-metre circuit, which also exceeds the minimally clinically important difference.[18] This effect may be exacerbated in patients with post-COVID-19 with prolonged bed rest and older age, which can affect balance and gait patterns and/or strategies.[19]

Field tests are widely used in intervention programmes such as rehabilitation, and because of that and the need to find simple, reliable and effective measures, it is essential to look at alternatives to the 6MWT to assess COVID-19 patients during the follow-up and rehabilitation.[13,20,21] Therefore, our objective was to compare the 6MWT, 1min-STST and the CST in post-COVID-19 patients.

Methods

Design and participants

We conducted a cross-sectional analysis in patients recovering from COVID-19 pneumonia admitted to the follow-up programme in the Hospital Virgen de la Torre (Madrid, Spain) between March 2021 and May 2021. Ethics committee approval was obtained, and all patients signed the informed consent. This study follows the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology guidelines (STROBE).[22]

Inclusion criteria were as follows: patients older than 18 years, diagnostic of COVID-19 by positive PCR assay findings for nasal and pharyngeal swab specimens, patients with dyspnoea and/or persistent fatigue, with mild/moderate physical activity previous to infection, oxygen supply equal to or less than 4 litres per minute. Exclusion criteria were as follows: the presence of locomotor or cognitive impairment before the infection, refusal to participate, and any pre-existing condition such as orthopaedic or neurological comorbidities limiting the ability to perform the standard field test.

The control group participants, without infection by COVID-19, without symptoms such as fatigue or dyspnoea, with mild/moderate physical activity, were recruited by inviting medical staff and their relatives. These participants were matched to the treatment group based on gender and age.

Sample size calculation

For the sample size, we used the study of Karloh et al., which compared different field tests in COPD patients.[20] Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 23 subjects are necessary for each group to recognise as statistically significant a difference greater than or equal to 1 unit. The expected standard deviation is assumed to be 1.1. A drop-out rate of 15% has been anticipated.

Measurements

At the time of admission, demographic characteristics, medical history, exposure history and underlying comorbidities were collected. The main outcome measures were physical capacity, assessed through 6MWT, 1min-STST, and CST. All tests were conducted in the same room, with only the presence of the researcher and the patient to avoid distractions. The order of application of each test was randomised. Adequate rest was provided between the tests, which allowedg SpO_2 and heart rate to return to pre-exercise values with a minimum of 30 min between tests.

6MWT: The 6MWT was performed indoors, along a flat, straight, 30 m walking course, according to international guidelines.[10] Subjects were instructed to walk the circuit from one end to the other covering as much distance as possible in the assigned six-minute period.[10] We used the reference values based on the healthy adult population reported by Enright and Sherrill.[23]

1min-STST: The test was performed with a chair of standard height (46 cm) without armrests positioned against a wall. Participants were not allowed to use their hands/arms to push the seat of the chair or their body. Participants were instructed to complete as many sit-and-stand cycles as possible in 60 s at self-paced speed.[24] We used the reference values based on the healthy adult population previously reported by Strassmann et al.[24]

Chester step test: The CST consists of going up and down a step up to 30 cm in height at a pace set by a signal sound, which progressively increases in speed up to five levels. We used a step of 16 cm. In the first minute, patients go up and down the step 15 times, increasing every two minutes. The maximum test time is 10 min.[20]

The modified Borg scale (0−10) measured dyspnoea and fatigue immediately before and after all tests.[25] A finger oximeter was used to record oxygen saturation (SpO_2) and heart rate (HR). A desaturation level of $\geq$4% was considered clinically significant.[26] The evaluator had previous experience in this test. All tests were performed two times due to the learning effect described in some field tests.[27]

Statistical analyses

The SPSS software version 25.0 (IBM SPSS Statistics, Armonk, NY, USA) was used for all the statistical analyses. The Shapiro-Wilk normality test will be applied to the recorded data, and, depending on the nature of the variables, the corresponding parametric or non-parametric test will be applied. The t-test for independent samples or the Mann-Whitney U test will be used for pre-post comparisons. Mann-Whitney U test, the analysis of variance (ANOVA) or the Kruskal-Wallis test with Tukey's post-hoc test will be used to compare HR, SpO_2, dyspnoea and leg fatigue pre-post.

The variation in cardiorespiratory variables between test levels will be compared by means of a two-way ANOVA or the corresponding non-parametric test, with a test, with a post-hoc paired t-test or a Wilcoxon test. The association between the variables will be verified by means of Pearson's or Spearman's correlation coefficient. Data are presented as the mean $\pm$ standard deviation. Statistical significance was set at 5% ($p < 0.05$).

Results

We recruited 27 patients with COVID-19 diagnosis who were compared with 27 healthy matched controls. The median age was 48 (IQR 43−59) years (12 females, 44%). The mean time between hospitalisation and the field tests evaluation was 5.8 $\pm$ 0.5 months. The baseline patient characteristics are presented in Table 1. Fourteen patients were hospitalised with a mean of 28.1 $\pm$ 34.0 days of the length of stay. Only four required ICU admission. The mean mMRC score was 1.35 $\pm$ 0.5.

Regarding the physical capacity, the median distance walked in 6MWD was 461 m (IQR 415−506) in post-COVID-patients and 517 m (IQR 461−560) in the CG (p = 0.001). The final SpO_2, HR baseline, final dyspnoea and final leg fatigue significantly differed between groups. For the 1min-STST, the number of repetitions was 21.9 $\pm$ 6.7 and 28.3 $\pm$ 7.1 in post-COVID-19 and control groups, respectively (p = 0.001). The SpO_2 baseline, final SpO_2, final HR, final dyspnoea and final leg fatigue differed significantly. Regarding the CST, we found differences between the number of steps; the COVID-19 group performed a median (IQR) of 150 (86−204) versus the control group with 250 (250−250). The SpO_2 at baseline, final SpO_2, final HR, final dyspnoea and final leg fatigue showed a significant difference. At the end of the 6MWT and 1min-STST, 22% of the patients showed exercise-induced desaturations (EID) (Table 2).

Finally, we also found correlations between 6MWT and 1min-STST in COVID-19 patients (r = 0.681, $p < 0.001$) and in control group (r = 0.668, $p < 0.001$), and between 6MWT and CST only in COVID-19 patients (r = 0.692, $p < 0.001$) (Fig. 1).

Discussion

This research showed that the 1min-STST and the CST correlated significantly with the 6MWT in patients post-COVID-19.

The reference test to assess physical capacity in respiratory, cardiovascular or metabolic diseases is the 6MWT.[10,28] However, the pandemic has shown us that it is not always easy to perform the 6MWT since it requires certain special conditions for its development, such as a 30 metres corridor (or at least 20 m).[10] Our results show, referencingthe obtained data, that there is an important correlation between the CST and the 1min-STST with the 6MWT. This correlation is in line with similar studies but in different populations such as lung transplant candidates, interstitial lung diseases, or chronic obstructive pulmonary disease.[20,29−31] Therefore, when there are limitations to performing the 6MWT in COVID-19 patients, the 1min-STST and CST could be alternatives.

We compared the physiological exercise response between the three tests in the COVID-19 group and the CG. For the CG, we did not observe significant differences in physiologicalvariables, although there was a tendency to increase perceived symptoms at the end of CST. A possible explanation of those results is because the CST is an incremental test that tries to achieve the maximal subject exercise capacity. Furthermore, step climbing is a heavy exercise that supposes a technical gesture, going up and down, that involves a much greater muscle mass and energy expenditure, by having to lift the whole body weight, than walking on a flat corridor as in the 6MWT or lifting the body weight from a chair.[32]

However, in COVID-19 patients, we found a significant increase in the symptoms at the end of CST, but not a parallel increase with similar magnitude on the HR. Probably it can be attributed to the fact that COVID-19 patients have a cardiorespiratory impairment that limits the maximal exercise capacity and forces patients to decrease performance.[21,33]

Regarding EID, our data showed that 22% of patients had EID. These results are similar to those found previously.[34,35] Previous reports state that the low intensity and short duration of the STS might have underestimated the severity of exercise-induced desaturations as compared with standard exercise tests such as the 6-min walking test or

Table 1 Descriptive statistics of the included patients.

Variable	Control group (*n* = 27)	COVID-19 group (*n* = 27)	*p*
Age (years)	48 (43–59)	48 (43–59)	1
Gender			
Male (n,%)	15 (56%)	15 (56%)	
Female (n,%)	12 (44%)	12 (44%)	
Weight (Kg)	80.0 ± 15.0	84.2 ± 20.1	0.386
Height (cm)	168 ± 8.6	168 ± 8.5	0.671
BMI (m/Kg^2)	27.3 (23.2–32.3)	28.8 (25.0–35.0)	0.382
Comorbidities			
Obesity (n,%)	8 (29.6)	9 (33.3)	0.77
Arterial hypertension (n,%)	0 (0)	3 (11.1)	0.075
Cardiac disease (n,%)	0 (0)	2 (7.4)	0.15
Diabetes (n,%)	0 (0)	1 (3.7)	0.313
CCI	0 (0–1)	1 (0–1)	0.381
Hospitalized (yes/no)	NA	13/14	NA
Length of stay (days)	NA	22.5 ± 29.2	NA
ICU admission (yes/no)	NA	22-Apr	NA
mMRC	NA	1.3 ± 0.5	NA
6MWT			
Distance (m)	517 (461–560)	461 (415–506)	0.001
Distance (%pred)	90.3 ± 10.0	79.1 ± 16.9	0.005
SpO_2 baseline (%)	97.7 ± 1.0	96.6 ± 1.6	0.05
SpO_2 final (%)	97.3 ± 1.2	94.7 ± 3.8	0.001
HR baseline (bpm)	79.4 ± 7.6	84.6 ± 11.4	0.04
HR final (bpm)	106.7 ± 15.8	104.6 ± 18.3	0.811
Dyspnoea baseline	0 (0-0)	0 (0–1)	0.013
Dyspnoea final	2 (0–2)	4 (3–5)	<0.001
Leg fatigue baseline	0 (0–0)	0 (0–1)	0.002
Leg fatigue final	2 (0–2)	3 (2–5)	<0.001
1min-STST			
Repetitions (n)	28.3 ± 7.1	21.9 ± 6.7	0.001
Repetitions (%pred)	68.6 ± 15.9	53.1 ± 15.0	0.001
SpO_2 baseline (%)	97.5 ± 0.8	96.7 ± 1.3	0.006
SpO_2 final (%)	97.4 ± 1.1	94.9 ± 2.2	<0.001
HR baseline (bpm)	85.1 ± 6.8	83.4 ± 12.2	0.52
HR final (bpm)	116.7 ± 13.3	105.5 ± 18.4	0.013
Dyspnoea baseline	0 (0-0)	0 (0–2)	0.013
Dyspnoea final	2 (1–3)	4 (3–5)	<0.001
Leg fatigue baseline	0 (0-0)	0 (0–2)	0.023
Leg fatigue final	2 (1–3)	4 (3.8–5)	<0.001
CST			
Steps	250 (250–250)	150 (86–204)	<0.001
SpO_2 baseline (%)	97.6 ± 0.7	96.3 ± 1.5	<0.001
SpO_2 final (%)	96.8 ± 1.6	93.3 ± 4.1	<0.001
HR baseline (bpm)	81.8 ± 6.5	82.4 ± 11.1	0.824
HR final (bpm)	138.0 ± 14.5	117.4 ± 29.1	0.002
Dyspnoea baseline	0 (0-0)	0 (0–2)	0.04
Dyspnoea final	4 (2–4)	5 (4–6)	<0.001
Leg fatigue baseline	0 (0-0)	0 (0–2)	0.228
Leg fatigue final	3 (2–3)	5 (3–7)	0.003

Abbreviations: BMI: Body mass index; CCI: Charlson comorbidities index; ICU: Intensive care unit; mMRC: Modified medical research council; 6MWT: Six-minute walk test; SpO_2: Oxygen saturation; HR: Heart rate; bpm: beats per minute; 1min-STST: 1-minute sit-to-stand test; CST: Chester step test. Values are expressed as the mean ± SD if data are normally distributed or as the median (P25–P75) if data distribution is skewed.

cardiopulmonary exercise tests.[34] Our data coincide with these findings given that both groups had the same number of desaturators, however EID during the 6MWT was greater than 6% in 5/6 patients (one even decreased 13%), whereas in the 1min-STST, only 1 of the 6 patients desaturated more than 5%.

Although the three tests achieved similar results, it is crucial to consider that a more significant lower extremities effort is

Table 2 Comparison between exercise physiological response between different tests.

Variable	Control group (*n* = 20)				COVID-19 group (*n* = 20)			
	6MWT	1min-STST	CST	p	6MWT	1min-STST	CST	p
SpO_2 baseline	97.7 ± 1.0	97.5 ± 0.8	97.6 ± 0.7	0.422	96.6 ± 1.6	96.7 ± 1.3	96.3 ± 1.5	0.404
SpO_2 final	97.3 ± 1.2	97.4 ± 1.1	96.8 ± 1.6	0.055	94.7 ± 3.8	94.9 ± 2.2	93.3 ± 4.1	0.020
HR baseline	79.4 ± 7.6	85.1 ± 6.8	81.8 ± 6.5	0.006	84.6 ± 11.4	83.4 ± 12.2	82.4 ± 11.1	0.505
HR final	106.7 ± 15.8	116.7 ± 13.3	138.0 ± 14.5	<0.001	104.6 ± 18.3	105.5 ± 18.4	117.4 ± 29.1	0.002
Dyspnoea baseline	0 (0-0)	0 (0-0)	0 (0-0)	0.244	0 (0−1)	0 (0−2)	0 (0−2)	0.273
Dyspnoea final	2 (0−2)	2 (1−3)	4 (2−4)	<0.001	4 (3−5)	4 (3−5)	5 (4−6)	0.001
Leg fatigue baseline	0 (0-0)	0 (0-0)	0 (0-0)	0.039	0 (0−1)	0 (0−2)	0 (0−2)	0.375
Leg fatigue final	2 (0−2)	2 (1−3)	3 (2−3)	0.001	3 (2−5)	4 (3.8−5)	5 (3−7)	0.017

Abbreviations: 6MWT: Six-minute walk test; 1min-STST: 1-minute sit-to-stand test; CST: Chester step test; SpO_2: Oxygen saturation; HR: Heart rate.

required to execute the CST or the 1min-STST.[20,24,36] This result was confirmed by the reported perception of lower extremity fatigue compared to 6MWT. Therefore, not doing these testst should be considered nwhen extreme lower extremity fatigue is reported before the assessments. Although in some patients the 6MWT can behave as a maximal test, it is considered a sub-maximal test, so our results should be analysed with caution since they are tests aimed at different objectives. On the other hand, the CST is an incremental maximum capacity test and should be used with caution in a remote setting, especially in patients with a probability of desaturation.

There are at least three different versions of the STST.[36] We decided only to study the one-minute version, given that, in other pathologies, such as COPD, the literature has shown that 1min-STST has the best correlation with the 6MWT.[37] Although the technical movement of the 5-STST or the 30 s STST is the same because the test expended time, the 1min-STST stress lower extremities significantly, but it does not employ the cardiorespiratory reserves in the same way.[37] For this reason, these shorter exercise tests are typically used to predict falls in older adults or assess the strength of the lower extremities in those populations.[38,39]

Given the moderate correlation observed between both tests with the 6MWT, because of its simplicity, their use could be considered face-to-face or in remote evaluations.[40,41] Furthermore, the literature has shown and recommended using the 1min-STST for rehabilitation and telerehabilitation programmes.[13,36,42] This fact is a critical point in the current pandemic since many services have had to generate remote monitoring and rehabilitation programmes due to the operational problems of rehabilitation services.[43] Our results show that 1min-STST and CST can be used as an alternative in remote programmes.

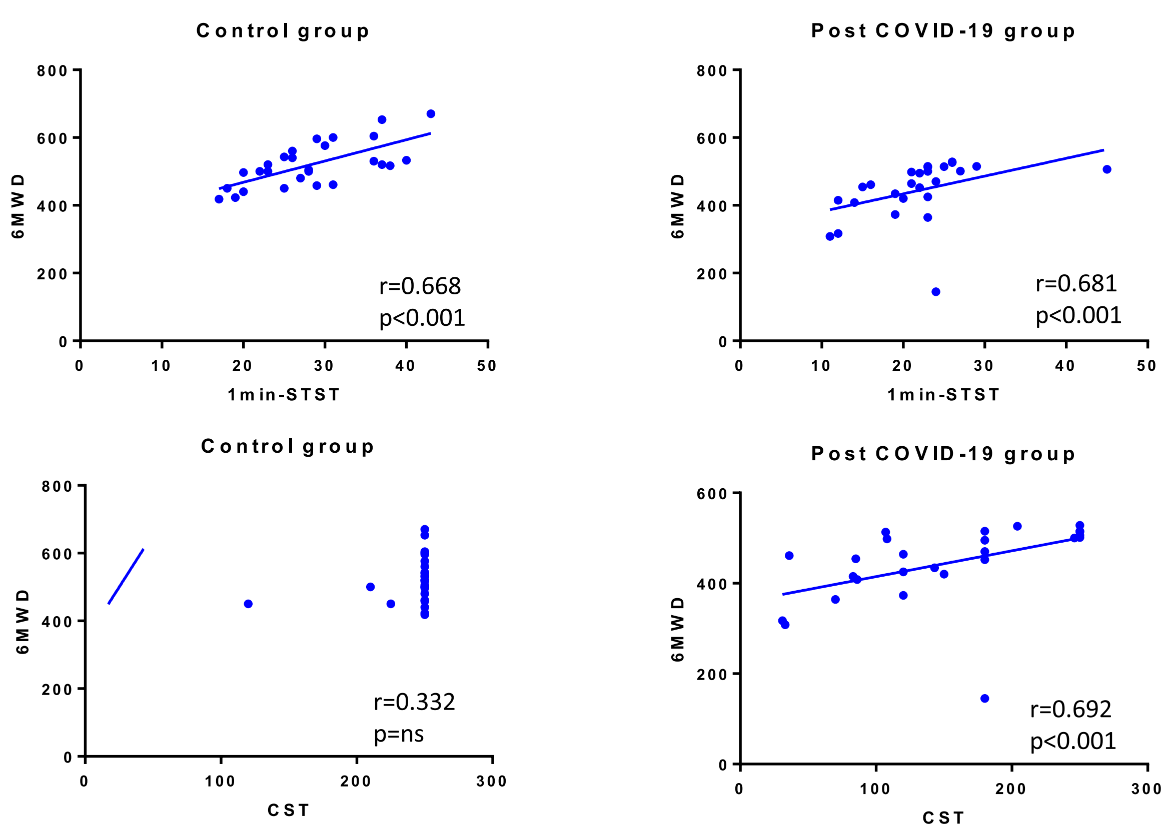

Fig. 1 Correlation graphs between the different field tests.

The present study has some limitations. The sample size is small; however, the calculated sample size was 23 subjects per group for a power of 80%. At the end of the study, the calculated power was 93%, so the sample size was sufficient. On the other hand, our study did not evaluate the oxygen consumption response. It requires sophisticated equipment and specialist professionals not commonly available in the clinical setting. However, our objective was to show field tests that can be carried out in different contexts, from primary care to the hospital. Additionally, our population was young, so they had few comorbidities and it was not possible to determine if this could have had an effect on the performance of the tests. Finally, it was not possible to blind the evaluator since she was the professional who worked in the pulmonary rehabilitation programme.

Conclusion

This research showed that the 1min-STST and the CST correlated significantly with the 6MWT in patients post-COVID-19. The 1min-STST and the CST can be an alternative to evaluate functional capacity when the 6MWT cannot be performed. Future studies should evaluate whether these field tests are sensitive to alterations such as rehabilitation or recovery from COVID-19 over the months.

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Conflicts of interest

The authors declare to have no conflict of interest.

CRediT authorship contribution statement

R. Peroy-Badal: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **A. Sevillano-Castaño:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **R. Torres-Castro:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **P. García-Fernández:** Methodology, Writing – original draft, Writing – review & editing. **J.L. Maté-Muñoz:** Formal analysis, Methodology, Writing – review & editing. **C. Dumitrana:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **E. Sánchez Rodriguez:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **M.J. de Frutos Lobo:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **J. Vilaró:** Formal analysis, Writing – original draft, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.07.011.

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ORIGINAL ARTICLE

Baseline dependent minimally important differences for clinical outcomes of pulmonary rehabilitation in people with COPD

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KEYWORDS
Minimally important differences;
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Abstract
Introduction: Minimally important differences (MIDs) for common outcomes of pulmonary rehabilitation are well documented for people with chronic obstructive pulmonary disease (COPD). It is not known whether MIDs differ based on COPD disease characteristics. This study aimed to estimate MIDs for clinical outcomes of pulmonary rehabilitation dependent upon baseline characteristics.
Methods: A database containing 2791 people with COPD was split into derivation (n=2245; age 66±9 years; 50% males; FEV_1 47±20% predicted) and comparator (n=546; age 66±9 years; 47% males; FEV_1 46±21% predicted) cohorts. MIDs were estimated using 0.5 x SD (symmetrically distributed) or 0.5 x IQR (non-symmetrically distributed) for: 6-minute walk test (6MWT), constant work rate test (CWRT), COPD assessment test (CAT), St. George's respiratory questionnaire (SGRQ), hospital anxiety and depression scale (HADS), and fat-free mass index (FFMI). MIDs were estimated based on baseline outcome scores, lung function, modified medical research council (mMRC) grade and FFMI.
Results: MID estimates were comparable to previously reported values. MIDs for SGRQ domains (Symptom=8.7 points, Activity=7.1 points, Impact=8.1 points) and FFMI were produced (0.36kg/m^2). There was greater variation of change in 6MWT, SGRQ-activity, SGRQ-impact, HADS and FFMI on which the MIDs were determined when categorising for baseline values (all, $p<0.05$). Greater variation of change in 6MWT on which the MIDs were determined was evident with COPD

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disease severity grouping ($p<0.05$). The magnitude of change in 6MWT, CAT, CWRT, SGRQ-activity, and FFMI with baseline mMRC score categorisation resulted in greater variation on which the MIDs were determined (all, $p<0.05$). Baseline stratification for FFMI resulted in greater variation of change in CWRT ($p<0.001$) and HADS-depression ($p = 0.043$) on which MIDs were determined.
Discussion: Findings suggest that baseline presentation should be considered for people with COPD when assessing the efficacy of pulmonary rehabilitation. However, clinical significance of the variation underpinning MIDs is yet to be determined.
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Introduction

Pulmonary rehabilitation is considered a cornerstone treatment in the management of Chronic Obstructive Pulmonary Disease (COPD) for inducing improvements in exercise capacity and health-related quality of life.[1] People with COPD undergoing pulmonary rehabilitation present with a diverse range of health care needs as defined by variability in disease severity, functional exercise capacity and psychological well-being.[2] The effectiveness of pulmonary rehabilitation programmes is commonly determined by changes in exercise capacity (e.g., 6-minute walk test (6MWT), constant work rate test (CWRT)), health-related quality of life measures (e.g., COPD Assessment Tool (CAT), St. Georges Respiratory Questionnaire (SGRQ)), mental health (e.g., Hospital Anxiety & Depression Scale (HADS)), and body composition (fat free mass index (FFMI)).[3] However, statistical analysis of changes in clinical outcome measures can often be misleading and may not be clinically relevant to patients and/or healthcare professionals.[4]

The minimally important difference (MID) was defined to address misleading statistics by calculating the smallest difference in a measured clinical parameter that is assumed to reflect a clinically meaningful impact in a patient's condition, for better or worse, as perceived by the patient, clinician, or investigator.[5] MIDs can be determined using different approaches; anchor-based, distribution-based, and Delphi methods.[4] The MIDs developed in respiratory research thus far have been highlighted with differing thresholds and/or ranges defined using either anchor-based or distribution-based methods.[6] Distribution-based methods have been suggested to have an advantage of being simpler to use as they do not require an external criterion as observed with the anchor-based method.[7]

There is established evidence, especially in the field of medical statistics, stating that baseline differences could be key to the variety in the magnitude of effect seen with intervention.[8] This has recently been demonstrated to be the case with pulmonary rehabilitation,[9-11] whereby people with COPD presenting with poorer exercise capacity and higher symptom burden pre-rehabilitation stand to achieve greater benefits with pulmonary rehabilitation. Several MIDs used in practice are based on distribution-based approaches covering the COPD population as a whole, whereby the variation in response to pulmonary rehabilitation is used to determine MIDs. It is important to reassess the current state of MIDs to evaluate programme efficacy accounting for baseline differences. Currently available MIDs are disease specific and not patient specific. These MIDs may lack specificity leading to the potential over- or under-estimation of effects seen with pulmonary rehabilitation depending on patient presentation. Therefore, it is important to begin to build on the development of MIDs in the context of pulmonary rehabilitation to offer more personalised and contextualised MIDs for common clinical outcomes.

This study aimed to develop new MIDs for clinical outcomes (6MWT, CWRT, HADS, CAT & SGRQ, FFMI) of pulmonary rehabilitation in people with COPD based on stratification for baseline values and disease characteristics (disease severity according to GOLD grade, modified Medical Research Council dyspnea scale (mMRC) grade, body composition according to FFMI) using the distribution-based approach.

Methods

This study was conducted using the Ciro clinical pulmonary rehabilitation database for which patients had not objected to the storing of data for research purposes. Ethical approval for this study was waived by the medical ethics committee of the University Hospital Maastricht and Maastricht University (METC azM/UM) because the Medical Research Involving Human Subjects Act (WMO) does not apply to this study (METC 2020-1542).

Population

Data were extracted from the electronic patient files consisting of 2791 people with a clinical diagnosis of COPD (International Classification of Diseases and Related Health Problems (ICD-10) J43 or J44, mMRC >0, post-bronchodilator FEV_1/FVC <0.70 according to GOLD guidelines[12]). Patients were evaluated at initial assessment of a comprehensive pulmonary rehabilitation programme at Ciro, a tertiary care centre for people with complex chronic respiratory diseases in Horn (The Netherlands) which they completed between July 2013 and August 2020.

Intervention

The pulmonary rehabilitation programme delivered by Ciro for people with COPD is comprehensive and multidisciplinary in nature. Performed in line with the American Thoracic Society & European Respiratory Society guidance,[13] the programme consists of supervised exercise training, education, psychosocial counselling, nutritional counselling, COPD exacerbation management, and occupational therapy.[10]

Ciro offers pulmonary rehabilitation in both the inpatient (8 weeks, 5 sessions per week; 40 sessions in total) and outpatient (8 weeks, 3 sessions per week, followed by 8 weeks, 2 sessions per week; total of 40 sessions) setting.[10] Exercise training was performed at a moderate-high intensity to achieve an overload stimulus. Intensity was increased during rehabilitation based on dyspnoea and fatigue symptom scores. The exercise programme comprised of flexibility exercises, general physical exercise for lower and upper extremities, and daily supervised 30-min outdoor walks. The most dyspneic and frail inpatients were offered neuromuscular electrical stimulation of lower-limb muscles instead of the exercise training, as described before.[14] A detailed psychosocial and physical assessment of each patient was undertaken during the initial and final assessments for pulmonary rehabilitation.

Measurements

Demographics, body mass index (BMI), body composition (FFMI: determined by dual-energy x-ray absorptiometry), and degree of breathlessness (mMRC grade) were assessed pre- and post-pulmonary rehabilitation. Post-bronchodilator spirometry was performed to confirm COPD diagnosis (FEV_1/FVC $<$0.70) and divide patients into GOLD stages of disease severity; mild, moderate, severe, and very severe.[12] Health status was assessed using the CAT[15] (score range: 0-40 points) and Dutch version of the COPD-specific SGRQ[16] (score range: 0-100 points). Symptoms of anxiety and depression were assessed using the HADS scale[17] (score range: 0-21 points). Functional exercise capacity was assessed using the 6MWT, performed in accordance with ERS/ATS standards,[18] and the CWRT, set at 75% of the determined peak work rate derived from a maximal incremental cycle test.[19]

MID calculation

Distribution-based MIDs were calculated for each clinical outcome using 0.5 x standard deviation (SD) of change from pre- to post-rehabilitation for symmetrically distributed outcomes. Where outcomes were non-symmetrically distributed, 0.5 x interquartile range (IQR) was used. To calculate personalised MIDs for CWRT, SGRQ-S, SGRQ-A, and SGRQ-I, data were split into tertiles for each outcome using baseline outcome scores (T1 = low, T2 = moderate, T3 = high). For 6MWT ($<$350m vs $\geq$350m),[20] CAT ($<$18 vs $\geq$18 points),[21] SGRQ-T ($<$46 vs $\geq$46 points),[22] HADS-A ($<$8 vs $\geq$8 points),[22] HADS-D ($<$8 vs $\geq$8 points),[22] and FFMI ('abnormal' $<$15kg/m^2 for females and $<$17kg/m^2 for males vs 'normal' $\geq$15kg/m^2 for females and $\geq$17kg/m^2 for males)[23] patients were split into 'abnormal' or 'normal' baseline outcome values using clinically relevant cut-offs. Further subset MIDs for these outcomes were calculated based on disease characteristics at baseline (mild, moderate, severe, very severe COPD; mMRC 1, 2, 3, 4; 'abnormal' FFMI vs 'normal' FFMI (*in line with the criteria above*)).

Statistical analysis

Statistical analyses were performed using SPSS (v25.00; SPSS Inc., Chicago, IL, USA). Data was randomly partitioned with an 80/20 ratio, as is commonly used and recommended in large datasets,[24] into two groups to provide a derivation (n = 2245) and comparator (n = 546) cohort for the calculating of MIDs. All statistical analyses were undertaken primarily using the derivation cohort, with estimated MIDs compared with the comparator cohort. Baseline demographics and outcomes of the derivation cohort are presented as mean and SD for symmetrically distributed outcomes, and as median and IQR for non-symmetrically distributed outcomes. All data were tested for symmetry by assessing skewness scores with values lower than -0.5 or above 0.5 considered as non-symmetrically distributed. If one MID was not normally distributed, all MIDs for the outcome were assessed using 0.5 x IQR. To assess differences in the MIDs between groups in both cohorts (low (T1) vs moderate (T2) vs high (T3); abnormal vs normal; mild vs moderate vs severe vs very severe; mMRC 1 vs 2 vs 3 vs 4; abnormal FFMI vs normal FFMI), the homogeneity of variances was tested with Levene's test to assess whether the variances were equal between groups. Statistical significance was accepted at $p < 0.05$. If the assumption of Levene's was violated when including $>$2 groups, post-hoc Levene's independent t-test was used to further explore differences between subgroups. An adjustment for multiple testing was made with a Bonferroni correction. Statistical significance following correction was accepted at $p < 0.0167$.

Results

The demographics of the derivation and comparator cohorts who completed a pre-rehabilitation assessment are presented in Table 1.

MIDs for whole population

There were no significant differences between the derivation and comparator cohorts in terms of MIDs for each outcome (all, $p > 0.05$) (Table 2).

MIDs stratified for baseline values

Variation of change on which MIDs were based for CWRT were not significantly different across tertiles for the derivation cohort (p = 0.281) but were for the comparator cohort ($p < 0.001$). Post-hoc analyses in the comparator cohort showed greater variation of change on which the MID was determined for CWRT in the high (T3) group compared to the moderate (T2) (p = 0.001) and low (T1) ($p < 0.001$) groups. No significant differences were observed between low (T1) and moderate (T2) groups (p = 0.225).

Variation of change across tertiles on which MIDs were determined for SGRQ-A was evident in both cohorts ($p < 0.05$). Post-hoc analyses showed greater variation of change on which the MID was determined for SGRQ-A in the low (T1) compared to the high group (T3) (derivation, p = 0.014; comparator, p = 0.016). In the comparator cohort only, the variation of change was greater for determining the MID for SGRQ-A in the moderate (T2) compared to the high (T3) group (p = 0.008). All other tertile comparisons were found to not be statistically significant in the post-hoc analysis ($p > 0.0167$). Variation of change across tertiles on which MIDs were determined for SGRQ-I was evident in both cohorts ($p < 0.05$). Post-hoc analyses showed greater

Table 1 Baseline population characteristics.

Characteristic	Derivation cohort	Comparator cohort
Age (years)	65.7 ± 8.7	65.6 ± 8.5
Male, n (%)	1132 (50.4%)	259 (47.4%)
FEV_1 % predicted	43.6 [31.4,60.2]	42.7 [29.8,59.3]
Mild COPD, n (%)	167 (7.5%)	36 (6.6%)
Moderate COPD, n (%)	688 (31.1%)	171 (31.4%)
Severe COPD, n (%)	862 (38.9%)	200 (36.8%)
Very Severe COPD, n (%)	498 (22.5%)	137 (25.2%)
GOLD[a]		
A, n (%)	114 (5.2%)	28 (5.2%)
B, n (%)	506 (23.2%)	139 (25.8%)
C, n (%)	142 (6.5%)	29 (5.4%)
D, n (%)	1423 (65.1%)	342 (63.6%)
mMRC		
mMRC 1, n (%)	259 (11.7%)	58 (10.7%)
mMRC 2, n (%)	871 (39.3%)	206 (37.9%)
mMRC 3, n (%)	574 (25.9%)	154 (28.4%)
mMRC 4, n (%)	513 (23.1%)	125 (23.0%)
6MWT (m)	380 ± 120	381 ± 117
CWRT (secs)	213 [160,302]	215 [163,308]
CAT (points)	21.7 ± 6.5	21.6 ± 6.6
SGRQ-Total (points)	59.4 ± 14.4	59.9 ± 16.5
SGRQ-Symptom (points)	62.9 ± 17.7	63.0 ± 20.2
SGRQ-Activity (points)	80.3 [67.7,86.9]	79.9 [66.7,94]
SGRQ-Impact (points)	47.3 ± 17.7	48.0 ± 19.8
HADS-A (points)	7.7 ± 4.2	7.6 ± 4.5
HADS-D (points)	7.5 ± 4.0	7.6 ± 4.1
FFMI (kg/m^2)	16.6 ± 2.5	16.6 ± 2.5

Data presented as mean ± SD, % of population or median [IQR].

[a] GOLD grade based on mMRC grade. 6MWT, six-minute walk test; CAT, COPD assessment tool; COPD, chronic obstructive pulmonary disease; CWRT, constant work rate test; FEV_1, forced expiratory volume in one second; FFMI, fat-free mass index; GOLD, global initiative for chronic obstructive lung disease; HADS, hospital anxiety and depression scale; mMRC, modified medical research council dyspnoea scale; SGRQ- St. George's Respiratory Questionnaire.

variation of change for determining the MID for SGRQ-I in the high (T3) compared to low (T1) (derivation, $p < 0.001$; comparator, $p = 0.003$) group. All other tertile comparisons were found to not be statistically significant in the post-hoc analysis ($p > 0.0167$). No significant differences between tertiles were seen for SGRQ-S in both cohorts ($p > 0.05$).

Variation of change on which MIDs were determined was evident in people categorised as abnormal according to clinical cut-offs for the outcomes of 6MWT (derivation, $p < 0.001$; comparator, $p = 0.001$), HADS-A (both, $p < 0.001$) and HADS-D (both, $p < 0.001$) when compared to people categorised as normal in both cohorts. Greater variation of change on which MIDs were determined was seen in people categorised as normal for the outcome of FFMI when compared to people categorised as abnormal in both cohorts (derivation, $p = 0.006$; comparator, $p = 0.014$). No significant differences between abnormal and normal baseline scores were seen for CAT and SGRQ-T in either cohort (all, $p > 0.05$) (Table 3).

MIDs stratified for lung function

Variation of change on which MIDs were determined across disease severities for the outcome of 6MWT was evident in the derivation cohort only ($p = 0.024$). Post-hoc analyses showed greater variation of change on which to determine the MID for 6MWT in very-severe COPD when compared to moderate COPD ($p = 0.008$). No other significant differences were observed between disease severities ($p > 0.0167$). No significant differences between disease severities were observed in the comparator cohort ($p = 0.807$).

No significant differences between disease severity groups were seen for CWRT, CAT, SGRQ-T, SGRQ-S, SGRQ-A, SGRQ-I, HADS-A, HADS-D, and FFMI (Table 4).

MIDs stratified for mMRC grade

Variation of change on which the MIDs were determined was evident across mMRC scores for 6MWT in the derivation cohort ($p < 0.001$). Post-hoc analyses showed greater variation of change on which the MID was determined in people with an mMRC of 4 for 6MWT when compared to people with an mMRC of 1 ($p < 0.001$), mMRC of 2 ($p < 0.001$), and mMRC of 3 ($p = 0.013$). Greater variation of change on which the MID was based was also evident in people with an mMRC score of 3 for 6MWT when compared to people with an mMRC of 1 ($p = 0.002$). No other significant differences were observed between mMRC scores ($p > 0.0167$). No significant differences between mMRC scores were observed in the comparator cohort.

Table 2 MIDs for outcomes following pulmonary rehabilitation.

Variable	Derivation cohort	Comparator cohort	p-values
6MWT (m)	32	27	0.178
CWRT (secs)	170*	146*	0.091
CAT (points)	3.1	3.1	0.862
SGRQ-T (points)	6.4	6.0	0.523
SGRQ-S (points)	8.7	8.6	0.907
SGRQ-A (points)	7.1*	7.2*	0.590
SGRQ-I (points)	8.1	7.4	0.266
HADS-A (points)	1.5*	2.0*	0.811
HADS-D (points)	2.0*	2.0*	0.964
FFMI (kg/m^2)	0.36*	0.37*	0.610

* Due to non-symmetrical distribution, MIDs presented as 0.5 x IQR. 6MWT, six-minute walk test; CAT, COPD assessment tool; CWRT, constant work rate test; FFMI, fat-free mass index; HADS, hospital anxiety (A) and depression (D) scale; SGRQ, St. George's Respiratory Questionnaire. CAT (Total, *n* = 1879; Derivation, *n* = 1507; Comparator, *n* = 372), SGRQ (Total, Symptom, Activity, Impact domains: Total, *n* = 716; Derivation, *n* = 566; Comparator, *n* = 150), HADS (Total, *n* = 1833; Derivation, *n* = 1469; Comparator, *n* = 364), 6MWT (Total, *n* = 2018; Derivation, *n* = 1613; Comparator, *n* = 405), CWRT (Total, *n* = 1797; Derivation, *n* = 1431; Comparator, *n* = 366), and FFMI (Total, *n* = 2079; Derivation, *n* = 1654; Comparator, *n* = 425).

Table 3 MIDs following stratification for baseline outcome values.

Variable		Low (T1)	Moderate (T2)	High (T3)	p-values
CWRT (secs)	Derivation	110*	142*	275*	0.281
	Comparator	85*	103*	270*	<0.001
	Tertile cut-off	≤178.00	178.01-270.67	≥270.68	-
SGRQ-S (points)	Derivation	9.8*	8.6*	11.7*	0.173
	Comparator	12.5*	8.3*	11.8*	0.180
	Tertile cut-off	≤55.50	55.51-70.90	≥70.91	-
SGRQ-A (points)	Derivation	7.3*	7.2*	7.2*	0.040
	Comparator	7.4*	7.5*	7.2*	0.018
	Tertile cut-off	≤73.00	73.01-86.80	≥86.81	-
SGRQ-I (points)	Derivation	7.8*	10.0*	11.9*	<0.001
	Comparator	8.2*	9.3*	12.6*	0.010
	Tertile cut-off	≤37.60	37.61-54.03	≥54.04	-

		Abnormal	Normal	p-values
6MWT (m)	Derivation	39*	27*	<0.001
	Comparator	41*	28*	0.001
	Clinical cut-off	<350	≥350	-
SGRQ-T (points)	Derivation	8.5*	7.0*	0.188
	Comparator	7.8*	10.3*	0.993
	Clinical cut-off	<46	≥46	-
CAT (points)	Derivation	4.0*	3.5*	0.196
	Comparator	3.5*	3.5*	0.750
	Clinical cut-off	<18	≥18	-
HADS-A (points)	Derivation	2.0*	1.5*	<0.001
	Comparator	2.5*	1.5*	<0.001
	Clinical cut-off	<8	≥8	-
HADS-D (points)	Derivation	1.8	1.3	<0.001
	Comparator	1.9	1.2	<0.001
	Clinical cut-off	<8	≥8	-
FFMI (kg/m^2)	Derivation	0.34*	0.38*	0.006
	Comparator	0.32*	0.40*	0.014
	Clinical cut-off	<15 (female) <17 (male)	≥15 (female) ≥17 (male)	-

* Due to non-symmetrical distribution, MIDs presented as 0.5 x IQR. 6MWT, six-minute walk test; CAT, COPD assessment tool; CWRT, constant work rate test; FFMI, fat-free mass index; HADS, hospital anxiety (A) and depression (D) scale; SGRQ, St. George's Respiratory Questionnaire.

Table 4 MIDs following stratification for GOLD severity.

Variable		Mild	Moderate	Severe	Very Severe	p-values
6MWT (m)	Derivation	26*	28*	30*	36*	0.024
	Comparator	27*	29*	30*	35*	0.807
CWRT (secs)	Derivation	183*	177*	177*	123*	0.188
	Comparator	238*	184*	104*	155*	0.199
CAT (points)	Derivation	4.5*	4.0*	4.0*	3.5*	0.242
	Comparator	5.0*	5.0*	3.0*	3.0*	0.320
SGRQ-T (points)	Derivation	8.4*	9.0*	7.6*	8.3*	0.951
	Comparator	7.2*	9.5*	6.8*	8.3*	0.764
SGRQ-S (points)	Derivation	9.9	9.0	8.1	8.3	0.314
	Comparator	9.2	8.2	8.6	9.4	0.956
SGRQ-A (points)	Derivation	8.3*	8.7*	6.9*	6.7*	0.173
	Comparator	7.3**	10.3*	7.2*	7.2*	0.067
SGRQ-I (points)	Derivation	12.2*	10.4*	10.3*	10.3*	0.986
	Comparator	8.4*	10.6*	8.8*	12.0*	0.849
HADS-A (points)	Derivation	2.0*	2.0*	1.5*	2.0*	0.250
	Comparator	1.1*	2.0*	1.5*	2.5*	0.301
HADS-D (points)	Derivation	1.5*	2.0*	2.0*	2.0*	0.931
	Comparator	3.0*	2.0*	2.0*	2.0*	0.899
FFMI (kg/m^2)	Derivation	0.34*	0.36*	0.37*	0.38*	0.053
	Comparator	0.31*	0.38*	0.36*	0.42*	0.808

* Due to non-symmetrical distribution, MIDs presented as 0.5 x IQR. 6MWT, six-minute walk test; CAT, COPD assessment tool; CWRT, constant work rate test; FFMI, fat-free mass index; HADS, hospital anxiety (A) and depression (D) scale; SGRQ, St. George's Respiratory Questionnaire.

Variation of change on which the MIDs were determined was evident across mMRC scores for CWRT in the derivation cohort (p = 0.030). Post-hoc analyses showed greater variation of change on which the MID was determined in people with an mMRC of 1 for CWRT when compared to people with an mMRC of 3 (p = 0.013). No other significant differences were observed between mMRC scores ($p > 0.0167$). No significant differences between mMRC scores were observed in the comparator cohort.

Variation of change on which the MIDs were determined was evident across mMRC scores for CAT in the derivation cohort (p = 0.021). Post-hoc analyses showed greater variation of change on which the MID was determined in people with an mMRC of 1 for CAT when compared to people with an mMRC of 3 (p = 0.007) and mMRC of 2 (p = 0.015). No other significant differences were observed between mMRC scores ($p > 0.0167$). No significant differences between mMRC scores were observed in the comparator cohort.

Variation of change on which the MIDs were determined was evident across mMRC scores for CAT in both cohorts (derivation, p = 0.001; p = 0.005). Post-hoc analyses showed greater variation of change on which the MID was determined in people with an mMRC of 1 for SGRQ-A when compared to people with an mMRC of 2 (p = 0.011), mMRC of 3 ($p < 0.001$), and mMRC of 4 (p = 0.002) in the derivation cohort. In the comparator cohort, less variation of change on which the MID was determined was evident in people with an mMRC of 3 when compared to people with an mMRC of 2 (p = 0.010) and mMRC of 1 (p = 0.001). No other significant differences were observed between mMRC scores across derivation and comparator cohorts ($p > 0.0167$).

Variation of change on which the MIDs were determined was evident across mMRC scores for SGRQ-I in the comparator cohort (p = 0.039). Post-hoc analyses showed greater variation of change on which the MID was determined in people with an mMRC of 3 for SGRQ-I when compared to people with an mMRC of 2 (p = 0.004). No other significant differences were observed between mMRC scores ($p > 0.0167$). No significant differences between mMRC scores were observed in the derivation cohort.

Variation of change on which the MIDs were determined was evident across mMRC scores for FFMI in the derivation cohort ($p < 0.001$). Post-hoc analyses showed greater variation of change on which the MID was determined in people with an mMRC of 4 for FFMI when compared to people with an mMRC of 1 (p = 0.002) and mMRC of 2 ($p < 0.001$). No other significant differences were observed between mMRC scores ($p > 0.0167$). No significant differences between mMRC scores were observed in the comparator cohort.

No significant differences in MIDs between mMRC groups were seen for SGRQ-T, SGRQ-S, HADS-A, and HADS-D (Table 5).

MIDs stratified for baseline FFMI

There was greater variation of change on which the MID was determined in people categorised as having normal FFMI for the outcome of CWRT when compared to people categorised as having abnormal FFMI at baseline (derivation, $p < 0.001$; comparator, p = 0.001) in both cohorts. Greater variation of change on which the MID was determined was seen in people categorised as having abnormal FFMI for HADS-D when compared to people categorised as having normal FFMI at baseline in the derivation cohort (p = 0.043), but not the comparator cohort (p = 0.297). No significant differences between abnormal and normal baseline FFMI groups were seen for 6MWT, CAT, SGRQ-T, SGRQ-S, SGRQ-A, SGRQ-I, and HADS-A in either cohort (all, $p > 0.05$) (Table 6).

Table 5 MIDs following stratification for mMRC.

Variable		mMRC 1	mMRC 2	mMRC 3	mMRC 4	p-values
6MWT (m)	Derivation	26*	27*	31*	40*	<0.001
	Comparator	24*	31*	31*	39*	0.361
CWRT (secs)	Derivation	229*	172*	147*	178*	0.030
	Comparator	245*	165*	144*	89*	0.458
CAT (points)	Derivation	4.0*	4.0*	3.0*	4.0*	0.021
	Comparator	5.0*	4.1*	3.0*	3.6*	0.088
SGRQ-T (points)	Derivation	9.8*	7.4*	7.3*	8.6*	0.542
	Comparator	11.2*	6.8*	9.0*	9.4*	0.075
SGRQ-S (points)	Derivation	12.7*	10.3*	10.9*	11.6*	0.213
	Comparator	12.2*	11.2*	10.3*	11.9*	0.537
SGRQ-A (points)	Derivation	12.3*	9.4*	6.8*	6.9*	0.001
	Comparator	11.0*	7.5*	3.7*	7.2*	0.005
SGRQ-I (points)	Derivation	10.7*	9.2*	10.9*	12.5*	0.318
	Comparator	10.7*	8.8*	11.6*	9.6*	0.039
HADS-A (points)	Derivation	2.0*	2.0*	1.5*	2.0*	0.057
	Comparator	2.0*	2.0*	2.3*	2.5*	0.334
HADS-D (points)	Derivation	1.5*	2.0*	2.0*	2.0*	0.985
	Comparator	2.5*	1.5*	2.0*	2.5*	0.152
FFMI (kg/m^2)	Derivation	0.31*	0.36*	0.40*	0.40*	<0.001
	Comparator	0.32*	0.34*	0.38*	0.41*	0.167

[*] Due to non-symmetrical distribution, MIDs presented as 0.5 x IQR as opposed to 0.5 x SD. 6MWT, six-minute walk test; CAT, COPD assessment tool; CWRT, constant work rate test; FFMI, fat-free mass index; HADS, hospital anxiety (A) and depression (D) scale; mMRC, modified medical research council dyspnoea scale; SGRQ, St. George's Respiratory Questionnaire.

Discussion

To the best of our knowledge, this is the first study in the context of pulmonary rehabilitation in COPD to calculate MIDs for commonly used clinical outcomes based on baseline disease characteristics. Firstly, the present study corroborates previous MID estimates for 6MWT (32m vs 30m[18,25]), CAT (-3.1 points vs -3.0 to -2.0 points[26,27]), SGRQ-total (-6.4 points vs -7.43 to -4.0 points[6,26]), HADS-A (-1.5 points vs -1.8 to -1.3 points[27]), HADS-D (-2.0 points vs -1.7 to -1.5 points[27]), and CWRT (170s vs 100-200s[28]). New MIDs for pulmonary rehabilitation outcomes proposed because of this study include SGRQ-S (-8.7 points), SGRQ-A (-7.1 points), SGRQ-I (-8.1 points), and FFMI (0.36 kg/m^2). This is the first study to show that MID estimates differentiate statistically based upon baseline outcome values (6MWT, SGRQ-A, SGRQ-I, HADS-A, HADS-D, FFMI), GOLD disease severity (6MWT), mMRC dyspnoea score (6MWT, CAT, CWRT, SGRQ-A, FFMI),

Table 6 MIDs following stratification for FFMI.

		Abnormal	Normal	p-values
6MWT (m)	Derivation	32	31	0.464
	Comparator	26	27	0.439
CWRT (secs)	Derivation	126*	205*	<0.001
	Comparator	74*	199*	<0.001
CAT (points)	Derivation	3.0	3.1	0.517
	Comparator	3.0	3.1	0.136
SGRQ-T (points)	Derivation	7.4*	8.3*	0.412
	Comparator	8.4*	8.0*	0.696
SGRQ-S (points)	Derivation	8.2	8.9	0.255
	Comparator	9.1	8.3	0.285
SGRQ-A (points)	Derivation	7.0*	7.2*	0.322
	Comparator	7.0*	7.3*	0.540
SGRQ-I (points)	Derivation	7.7	8.3	0.573
	Comparator	6.7	7.7	0.429
HADS-A (points)	Derivation	1.5*	1.5*	0.214
	Comparator	2.5*	2.0*	0.620
HADS-D (points)	Derivation	2.0*	2.0*	0.043
	Comparator	2.0*	2.0*	0.297

[*] Due to non-symmetrical distribution, MIDs presented as 0.5 x IQR. 6MWT, six-minute walk test; CAT, COPD assessment tool; CWRT, constant work rate test; HADS, hospital anxiety (A) and depression (D) scale; SGRQ, St. George's Respiratory Questionnaire.

and baseline FFMI (CWRT, HADS-D). SGRQ-T and SGRQ-S MID estimates were not found to be statistically different in terms of variation dependent upon baseline characteristics.

Recently, there has been evidence emerging suggesting that baseline characteristics, in terms of disease, psychological and physical health, have an impact on the magnitude of response to pulmonary rehabilitation in terms of exercise-based and health-related quality of life outcomes.[9] It is not implausible to suggest that those with higher baseline exercise capacity and/or better self-reported health-related quality of life might experience a 'ceiling effect' in response to any intervention, let alone pulmonary rehabilitation, when such used constructs are restricted to a scoring limit which could lead to less variation in responses seen. Whilst the results reported in this study corroborate previously reported MIDs, this study is the first to demonstrate that MIDs can differ based on baseline characteristics of people with COPD presenting to pulmonary rehabilitation.

In terms of exercise capacity, 6MWT and CWRT did not follow a similar path. The MID for 6MWT was amenable to change dependent upon baseline values and lung function whereas the MID for CWRT was not. However, the MID for CWRT was amenable to change dependent upon baseline FFMI values whereas the MID for 6MWT was not. This study demonstrates for the first time that the MID for 6MWT is statistically higher for people with COPD with heightened disease burden (i.e., low exercise capacity, poorer lung function, heightened dyspnea). Given the MIDs used within this study have been determined by distribution-based methods (i.e., 0.5 x SD or 0.5 x IQR), the higher MID in those with heightened disease burden at baseline for pulmonary rehabilitation reflects greater variation in responses to pulmonary rehabilitation consequently resulting in a higher MID. It was interesting to report the relative stability of the MID for CWRT when accounting for differing disease characteristics, with FFMI and mMRC being the only factors to impact the MID for CWRT. The lack of concordance between 6MWT and CWRT may be attributed to the differing nature of the tests with the 6MWT being a self-paced test where stopping for rest is an option, whilst the CWRT is conducted at a set workload with the test stopped if effort at the set intensity cannot be maintained.

For quality-of-life measures, the MIDs for HADS, CAT and SGRQ domains of activity and impact were amenable to change based upon baseline values. However, this was not the case for SGRQ domains of total score and symptoms. This lack of concordance within the SGRQ suggests a need to examine the tool on both a domain basis, as well as total score. Interestingly, lung function nor mMRC appeared to impact the MIDs for SGRQ or HADS, apart from in the SGRQ-A domain which was impacted by mMRC as was CAT. All MIDs for health-related quality of outcomes remained stable when accounting for baseline FFMI. The lack of differences observed in the SGRQ domains of total and symptoms when accounting for all baseline factors suggests the MIDs for these outcomes are stable across the COPD disease spectrum. However, this was not the case for HADS, CAT and SGRQ domains of activity and impact which need to be assessed on a baseline characteristic dependent level. All in all, as seen with exercise capacity, the observed differences suggested that people with COPD with heightened disease burden (i.e., poorer self-reported quality of life and mood status) had statistically higher MIDs.

In terms of body composition, the MID for FFMI appeared to be amenable to change based on baseline values and dyspnea. The MID for FFMI was higher in those with an mMRC score of 4. In keeping with the other outcomes, people with COPD presenting with poorer health (i.e., lower FFMI) had heightened MIDs. However, people with COPD with higher baseline FFMI had a higher MID. This study for the first time has produced an MID for use with pulmonary rehabilitation for a body composition outcome based on a large dataset.

The most influential factor on MIDs in the context of people with COPD in pulmonary rehabilitation is the baseline values of clinical outcomes. Lung function and mMRC appeared to have a modest impact on the MIDs of certain clinical outcomes but were far less prominent than baseline values themselves. Body composition had little impact on the MIDs of clinical outcomes. Some outcomes, mainly SGRQ-total and symptom domain appeared to have robust MIDs which were not amenable to certain disease characteristics in this large cohort. The 6MWT seemed to be the most consistently amenable outcome to a change in MID based on disease characteristics.

When interpreting the findings of this study, it is important to consider the limitations. Firstly, as far as we are aware there is no comparative literature across diseases which has statistically analysed estimated MIDs dependent upon baseline disease characteristics using a distribution-based approach. We consulted and opted for the Levene's test to measure the variance between clinically relevant cut-offs/tertiles/disease characteristic groups as our MID was based on distribution. It is also worth noting that whilst statistical differences between certain MIDs were seen, it is not possible to determine the clinical relevance of such differences between groups. This combined with the use of a large dataset also increase the possibility of relatively small changes leading to statistically significant differences. However, it is important to note that this study has implications for clinical practice in that MIDs have been produced based on a wide range of disease characteristics allowing service providers to contextualize responses to pulmonary rehabilitation in people with COPD in a variety of different ways which are more relevant to individuals. In turn, these MIDs may also be used in the design of future trials involving pulmonary rehabilitation to assess interventional efficacy through more specified MIDs. This study was not able to include an anchor to weight the changes in outcomes against self-reported improvements. It is important to highlight that there is still ongoing debate as to the accuracy of using differing approaches for estimating the MID.[28-32] Due to the large nature of the dataset, there were outcomes which were found to be non-symmetrically distributed which posed challenges for determining the MID based on the standard deviation of data. Therefore, we opted to present a non-parametric equivalent in the form of 0.5 x IQR alongside 0.5 x SD for comparison purposes, and visually, MIDs appeared to be largely similar between approaches. It is important to note that some observations were not replicated in the comparator cohort, and vice versa meaning some results should be interpreted with caution.

In conclusion, this study further confirms the currently available MIDs for the COPD population, whilst also demonstrating that disease characteristics such as baseline outcome values, GOLD disease severity, mMRC score, and baseline FFMI can result in differing MIDs, but not necessarily for all outcomes.

The findings suggest a potential need to shift from umbrella MIDs for measuring intervention efficacy with pulmonary rehabilitation and move towards individually tailored MIDs.

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Conflicts of interest

The authors declare no conflicts of interest in relation to the production of this manuscript.

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ORIGINAL ARTICLE

Red cell distribution in critically ill patients with chronic obstructive pulmonary disease

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Abstract
Background: Red blood cell distribution width (RDW) is associated with increased mortality risk in patients with chronic obstructive pulmonary disease (COPD). However, limited data are available for critically ill patients with COPD.
Methods: Data from the Medical Information Mart for Intensive Care III V1.4 database were analyzed in this retrospective cohort research. The International Classification of Diseases codes were used to identify critically ill patients with COPD. The first value of RDW was extracted within the first 24 h after intensive care unit admission. The endpoint was 28-day all-cause mortality. Multivariable logistic regression analysis was performed to examine the relationship between RDW and 28-day mortality. Age, sex, ethnicity, anemia status, comorbidities, clinical therapy, and disease severity score were considered for subgroup analysis.
Results: A total of 2,344 patients were included with mean (standard deviation) age of 72.3 (11.3) years, in which 1,739 (53.6%) patients were men. The increase in RDW was correlated with an increased risk of 28-day mortality in the multivariate logistic regression model (odds ratio [OR] 1.15; 95% confidence interval [CI] 1.09—1.21). In comparison with the low-RDW group, the middle and high-RDW groups tended to have higher risks of 28-day all-cause mortality (OR [95% CI] 1.03 [0.78—1.34]; OR [95% CI] 1.70 [1.29—2.22]; P trend $<$ 0.0001). Subgroup analyses show no evidence of effect modifications on the correlation of RDW and 28-day all-cause mortality.
Conclusion: An increase in RDW was associated with an increased risk of 28-day all-cause mortality in critically ill patients with COPD. Further studies are required to investigate this association.

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Introduction

COPD is an irreversible, progressive airway inflammatory disease characterized by chronic respiratory symptoms and airflow limitation.[1] According to the Burden of Obstructive Lung Diseases and other large-scale epidemiological studies, patients with COPD increased to 384 million in 2010, with a global prevalence of 11.7% (95% confidence interval [CI] 8.4%–15.0%) in 2010 and 12.16% (95% CI 10.91–13.40%) in 2015.[2,3] Across the World Health Organization regions, the USA have recorded the highest prevalence of COPD (13.3% in 1990, 15.2% in 2010, and 14.53% in 2015).[2,3] Furthermore, COPD is the third leading cause of death globally according to the Global Burden of Disease.[4] Thus, COPD is a substantial clinical and financial burden with significant influence on patients' quality of life and healthcare expenditure. Red blood cell distribution width (RDW) is a quantitative measure of circulating erythrocyte volume variability, and it is measured as part of a complete blood count examination. Furthermore, RDW has significant associations with the risk of adverse clinical outcomes in patients with coronary artery disease,[5-17] heart failure,[18,19] stroke,[20,21] acute pulmonary embolism,[22-25] community-acquired pneumonia,[26-28] peripheral occlusive artery disease,[29] cancer,[30,31] sepsis,[32] and kidney disease.[33-35] Furthermore, an increase in RDW is associated with right ventricular dysfunction,[36,37] pulmonary arterial hypertension,[37] and mortality.[38-41]

However, previous studies employed small sample sizes and did not adjust for other potential confounders. In addition, limited studies have focused on the correlation between RDW and outcome in critically ill COPD patients.

Thus, the present study aimed to investigate the association between RDW and 28-day all-cause mortality in critically ill COPD patients by using the Medical Information Mart for Intensive Care III (MIMIC-III) database. We hypothesized that increasing RDW in critically ill COPD patients is related to increased risk of mortality.

Methods

Database introduction

MIMIC-III database (version 1.4) is open to the public and contains information on over 50,000 patients hospitalized to the Beth Israel Deaconess Medical Center's intensive care unit (ICU) between 2001 and 2012.[42] This database can be accessed at https://mimic.physionet.org/. Enqian Liu obtained access to the database (No. 35919439). The use of the data was approved by the Beth Israel Deaconess Medical Center (Boston, MA) and Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA).[43] The requirement for written informed consent was waived, because each patient information in the database was anonymized and de-identified.[43] The ethics committee of Lishui Municipal Central Hospital approved this study (no. 2021184).

Population selection criteria

Data from each patient's initial ICU admission were analyzed. Patients with COPD were selected using International Classification of Diseases, Ninth Revision (ICD-9) codes (491.20, 491.21, 491.22, and 496). We excluded patients aged $<$18 years, those admitted to the ICU for $<$24 h, those with survival times $<$0, and those with missing RDW data.

Data extraction

Data were extracted using PostgreSQL (version 9.6) and a structured query language. The following variable data were extracted: age, sex, ethnicity, weight, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, respiratory rate, percutaneous oxygen saturation (SpO_2), mean blood pressure (MBP), vasopressor use, renal replacement therapy (RRT), congestive heart failure, hypertension, diabetes, cardiac arrhythmias, sepsis, liver disease, acute kidney injury (AKI), renal failure, serum sodium, serum creatinine, serum potassium, blood urea nitrogen (BUN), serum hemoglobin, serum bicarbonate, serum glucose, serum hematocrit, anion gap, serum chloride, platelet, and white blood cell (WBC), Sequential Organ Failure Assessment (SOFA) score, and Simplified Acute Physiology Score II (SAPS II). The baseline data were obtained within the first 24 h after ICU admission. The initial value was considered for a variable that was measured multiple times within 24 h after ICU admission. Comorbidities, except AKI, were diagnosed according to ICD-9 codes. Severe sepsis was defined as the presence of either (a) a combination of ICD-9 codes for infection and one or more organ dysfunctions,[44] or (b) the ICD-9 code for severe sepsis (995.92) or septic shock (785.52).[45] According to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines, AKI was induced within the first 24 h of ICU admission and was identified based on serum creatinine and urine output.[46] Anemia was diagnosed as a hemoglobin level $<$12 g/dL in women and $<$13 g/dL in men according to the World Health Organization guidelines.[47] The clinical outcome was the 28-day all-cause mortality after ICU admission.

Statistical analysis

Participants were divided into tertiles based on RDW levels. Continuous data were expressed as mean (standard deviation) or median (interquartile range), while categorical variables were presented as percentages. The baseline characteristics of the different RDW tertile groups were analyzed using chi-square test for categorical variables, one-way analysis of variance test for normally distributed data, and Kruskal-Wallis H test for non-normally distributed data. The relationship between RDW and 28-day all-cause mortality was determined using multivariate logistic regression analysis. Values of the variation inflation factor (VIF) were used to assess multicollinearity. More than 10 VIFs showed multicollinearity. We constructed three models, namely, model 1 that was unadjusted, model 2 that was adjusted for age, sex, and ethnicity, and model 3 that was adjusted for age, sex, ethnicity, and other variables with $P < 0.1$ in univariate analysis or those with >10% change in effect estimates (weight, SBP, MBP, heart rate, respiratory rate, SpO_2, hematocrit level, platelet level, anion gap, creatinine level, bicarbonate, chloride, glucose, BUN, WBC, and potassium levels, SAPS II, SOFA, cardiac arrhythmias, hypertension, sepsis, liver disease, vasopressor use, ventilation, RRT, AKI, and anemia). To investigate the non-linearity further, we turned RDW into a categorical variable based on the tertiles, and then into a continuous variable by entering the tertiles' median values into the variable. For the sensitivity analysis, interaction and subgroup analyses were based on age (<75 and ≥75 years), sex, ethnicity, congestive heart failure, diabetes, renal failure, hypertension, cardiac arrhythmias, liver disease, sepsis, anemia, AKI, RRT, vasopressor use, ventilation, SAPS II (<37 and ≥37), and SOFA score (<4 and ≥4). Missing values were not found in the category variables. Missing values for continuous variables were imputed using the mean (normal data) or median (non-normal data). The statistical significance was considered at $p < 0.05$. Data analysis was performed using the R statistical software package (version 4.1.1).

Results

Baseline characteristics of the included participants

A total of 3,244 patients in the MIMIC-III database satisfied the inclusion criteria (Fig. 1). The baseline characteristics of the RDW tertile groupings are shown in Table 1. The mean patient age was 72.3 ± 11.3 years, and approximately 53.6% patients were men. RDW values at baseline varied from 11.50% to 28.20% (median 14.70%; mean 15.18%). No significant differences were observed between the different groups concerning sex, heart rate, platelet level, serum chloride, glucose, and serum sodium levels, hypertension, and vasopressor use (all $P > 0.05$). Patients in the highest RDW tertile group were likely to develop congestive heart failure, cardiac arrhythmias, diabetes, real failure, liver disease, sepsis, anemia, AKI, and RRT, and were less likely to require ventilation than patients in the lowest group. As the RDW increased, respiratory rate, weight, anion gap, potassium, creatinine, and BUN levels, SOFA score, and SAPS II increased, whereas SBP, DBP, MBP, temperature, SpO_2, and hematocrit, hemoglobin, WBC, and bicarbonate levels decreased.

Results of logistic regression

The independent effects of RDW on 28-day all-cause mortality in critically ill COPD patients were evaluated by constructing three different logistic regression models.

Logistic regression analysis for 28-day mortality (Table 2) show that RDW was positively related to the risk of 28-day all-cause mortality (unadjusted odds ratio [OR] 1.20; 95% CI 1.15–1.25). The crude ORs were 1.24 (95% CI 0.98–1.58) and 2.36 (95% CI 1.89–2.96) in the second and third tertile groups of RDW, respectively, with the first RDW tertile group as the reference. After adjusting for age, sex, and ethnicity, higher RDW values were correlated to higher risks of 28-day mortality (OR 1.21; 95% CI 1.16–1.27). In comparison with the first tertile group, the ORs were 1.18 (95% CI 0.93–1.51) and 2.37 (95% CI 1.89–2.98) in the second and third tertile groups, respectively. RDW was strongly correlated with 28-day all-cause mortality (OR 1.15; 95% CI 1.09–1.21) in Model 3. Furthermore, a higher RDW value was related to a greater risk of 28-day all-cause mortality in the second RDW tertile group (OR 1.03; 95% CI 0.78–1.34) and the third RDW tertile group (OR 1.70; 95% CI 1.29–2.22) after adjusting for age, sex, ethnicity, weight, SBP, MBP, heart rate, respiratory rate, SpO_2, hematocrit level, platelet level, anion gap; creatinine, bicarbonate, chloride, glucose, BUN, WBC, and potassium levels, SAPS II, SOFA score, cardiac arrhythmias, hypertension, sepsis, liver disease, vasopressor use, ventilation, RRT, AKI, and anemia. The linear trend tests for 28-day mortality yielded remarkable results in the three different models.

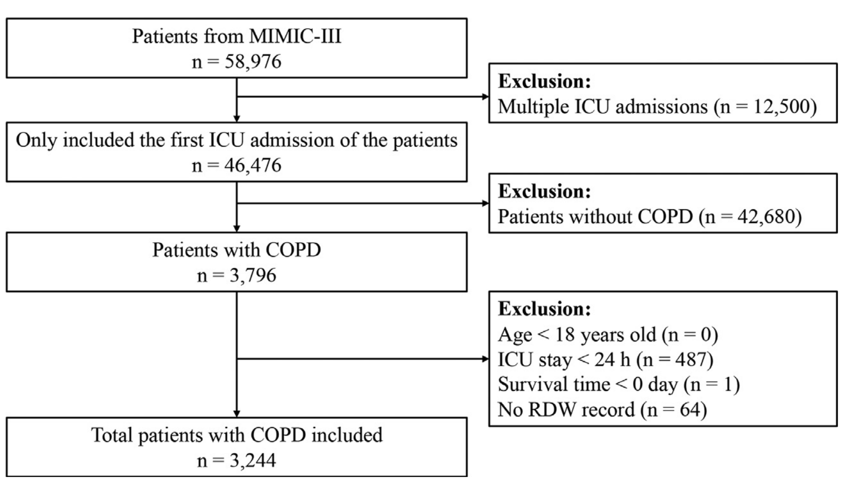

Fig. 1 Flow diagram of patient recruitment according to the cohort selection and exclusion criteria. MIMIC-III, multiparameter intelligent monitoring in intensive care III; COPD, chronic obstructive pulmonary disease; RDW, red blood cell distribution width

Table 1 Patient characteristics according to tertiles of red blood cell distribution width.

		RDW, %			P value
Characteristics	All patients	Tertile 1	Tertile 2	Tertile 3	
Number	3244	998	1105	1141	
Age, years	72.3 (11.3)	71.5 (11.3)	72.8 (11.5)	72.4 (11.0)	0.024
Sex, n (%)					0.309
Male	1,739 (53.6)	550 (55.1)	597 (54.0)	592 (51.9)	
Female	1,505 (46.4)	448 (44.9)	508 (46.0)	549 (48.1)	
Ethnicity, n (%)					0.033
White	2,480 (76.4)	769 (77.1)	853 (77.2)	858 (75.2)	
Non-white	286 (8.8)	76 (7.6)	85 (7.7)	125 (11.0)	
Unknown	478 (14.7)	153 (15.3)	167 (15.1)	158 (13.8)	
SBP, mmHg	123.6 (25.1)	125.0 (24.5)	125.0 (26.1)	121.1 (24.6)	<0.001
DBP, mmHg	62.4 (16.5)	63.5 (15.9)	63.1 (16.9)	60.7 (16.3)	<0.001
MBP, mmHg	81.0 (18.1)	83.0 (19.1)	81.8 (18.0)	78.3 (16.9)	<0.001
Heart rate, beats/min	89.1 (18.8)	89.0 (17.8)	89.4 (19.3)	89.0 (19.1)	0.84
Respiratory rate, beats/min	19.0 (6.0)	18.4 (5.9)	19.1 (6.0)	19.4 (6.0)	0.001
Temperature, °C	36.6 (0.9)	36.6 (0.8)	36.6 (0.9)	36.5 (0.9)	0.042
SpO_2, %	96.7 (4.5)	97.0 (3.9)	96.7 (5.2)	96.5 (4.3)	0.032
Weight, kg	80.1 (23.1)	78.1 (20.5)	80.5 (23.8)	81.4 (24.3)	0.003
Hematocrit, %	34.5 (6.3)	37.0 (5.7)	35.0 (6.1)	31.8 (5.9)	<0.001
Hemoglobin, g/dL	11.5 (2.1)	12.4 (1.9)	11.6 (2.0)	10.4 (1.9)	<0.001
Platelet, K/uL	222.0 [162. 0-298.2]	224.0 [174.0- 298.0]	222.0 [162.0- 294.0]	220.0 [149.0- 307.0]	0.085
WBC, K/uL	11.5 [8.3-15.8]	11.7 [8.5-15.8]	11.7 [8.6-16.0]	11.1 [7.6-15.5]	0.017
Anion gap, mEq/L	14.5 (4.1)	14.0 (3.9)	14.4 (4.1)	15.0 (4.3)	<0.001
Bicarbonate, mEq/L	25.5 (5.5)	25.9 (5.4)	25.6 (5.3)	25.1 (5.7)	0.002
Chloride, mEq/L	102.4 (6.5)	102.1 (6.5)	102.6 (6.1)	102.4 (6.9)	0.167
Glucose, mg/dL	149.2 (74.2)	148.7 (74.5)	150.7 (73.7)	148.3 (74.6)	0.708
Sodium, mEq/L	138.2 (5.1)	138.0 (5.1)	138.4 (4.6)	138.1 (5.5)	0.155
Potassium, mEq/L	4.3 (0.8)	4.3 (0.7)	4.3 (0.8)	4.4 (0.9)	0.002
Creatinine, mg/dL	1.0 [0.7-1.5]	0.9 [0.7-1.2]	1.0 [0.7-1.4]	1.2 [0.8-1.9]	<0.001
BUN, mg/dL	22.0 [15.0-35.0]	19.0 [14.0-28.0]	22.0 [15.0-33.0]	27.0 [18.0-45.0]	<0.001
SOFA	4.0 [2.0-6.0]	4.0 [2.0-5.0]	4.0 [2.0-6.0]	5.0 [3.0-7.0]	<0.001
SAPS II	39.2 (13.0)	36.6 (12.2)	39.2 (12.6)	41.3 (13.6)	<0.001
Congestive heart failure, n (%)	1,473 (45.4)	355 (35.6)	489 (44.3)	629 (55.1)	<0.001
Cardiac arrhythmias, n (%)	1,311 (40.4)	345 (34.6)	439 (39.7)	527 (46.2)	<0.001
Hypertension, n (%)	1,970 (60.7)	608 (60.9)	680 (61.5)	682 (59.8)	0.685
Diabetes, n (%)	992 (30.6)	236 (23.6)	342 (31.0)	414 (36.3)	<0.001
Renal failure, n (%)	546 (16.8)	75 (7.5)	174 (15.7)	297 (26.0)	<0.001
Liver disease, n (%)	179 (5.5)	26 (2.6)	40 (3.6)	113 (9.9)	<0.001
Sepsis, n (%)	1,348 (41.6)	328 (32.9)	459 (41.5)	561 (49.2)	<0.001
Anemia, n (%)	1,969 (60.7)	398 (39.9)	650 (58.8)	921 (80.7)	<0.001
AKI, n (%)	1,761 (54.3)	487 (48.8)	604 (54.7)	670 (58.7)	<0.001
RRT, n (%)	88 (2.7)	5 (0.5)	15 (1.4)	68 (6.0)	<0.001
Vasopressor, n (%)	1,077 (33.2)	351 (35.2)	376 (34.0)	350 (30.7)	0.068
Ventilation, n (%)	1,743 (53.7)	569 (57.0)	614 (55.6)	560 (49.1)	<0.001

Continuous variables are presented as means (SDs) or medians (quartiles), while categorical variables are presented as absolute numbers (percentages). MBP, mean blood pressure; BUN, blood urea nitrogen; WBC, white blood cell; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; AKI, acute kidney injury; RRT, renal replacement therapy.

Results of subgroup analyses

To evaluate the underlying clinical heterogeneity, we used interaction and stratified analyses (Fig. 2). We assessed the relationship between RDW and 28-day mortality in different subgroups. Interaction and stratified analyses were not detected in terms of age (<75 and ≥75 years), sex, ethnicity, anemia, diabetes, hypertension, cardiac arrhythmias, renal failure, liver disease, congestive heart failure, sepsis, anemia, AKI, RRT, vasopressor use, ventilation, SAPS II (<37 and ≥37), and SOFA score (<4 and ≥4).

Table 2 Relationship between red blood cell distribution width and 28-day all-cause mortality in different models.

	Model 1	Model 2	Model 3
	OR (95% CI) P value	OR (95% CI) P value	OR (95% CI) P value
RDW, %	1.20 (1.15, 1.25) <0.0001	1.21 (1.16, 1.27) <0.0001	1.15 (1.09, 1.21) <0.0001
RDW, % tertile			
T1	Ref	Ref	Ref
T2	1.24 (0.98, 1.58) 0.0766	1.18 (0.93, 1.51) 0.1756	1.03 (0.78, 1.34) 0.8522
T3	2.36 (1.89, 2.96) <0.0001	2.37 (1.89, 2.98) <0.0001	1.70 (1.29, 2.22) 0.0001
P for trend	<0.0001	<0.0001	<0.0001

OR, odds ratio; CI, confidence interval; Ref, reference; RDW, red blood cell distribution width
Model 1 was not adjusted; Model 2 was adjusted for age, sex, and ethnicity; and Model 3 was adjusted for age, sex, ethnicity, weight, systolic blood pressure, mean blood pressure, heart rate, respiratory rate, percutaneous oxygen saturation, hematocrit level, platelet level, anion gap, creatinine, bicarbonate, chloride, glucose, blood urea nitrogen, white blood cell, potassium levels, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment score, cardiac arrhythmias, hypertension, sepsis, liver disease, vasopressor use, ventilation, renal replacement therapy, acute kidney injury, and anemia.

Discussion

In this retrospective cohort study, higher RDW values were independently related with increased risks of 28-day all-cause mortality in critically ill patients with COPD. In addition, the stratified result supports the consistent finding.

RDW is related to short- and long-term mortality in patients with internal diseases. In recent years, RDW has received substantial attention in patients with COPD. Seyhan et al.[38] retrospectively followed up 270 patients with stable COPD for a median period of 36 months (range, 20–52 months) and found that higher RDW levels are related to higher mortality risks (OR 1.12; 95% CI 1.01–1.24). After controlling for age, leukocyte count, mean corpuscular volume, thrombocytopenia, and anemia, results show that RDW was related to increased risk of in-hospital mortality in a study among 330 patients with acute COPD exacerbations.[39] Epstein et al.[40] discovered that high RDW at admission (>14.5%) was significantly related to the 60-day composite endpoint of readmission or mortality after discharge (OR 1.83; 95% CI 1.22–2.74) in a cohort of 539 patients with acute exacerbations of COPD. Hu et al.[41] conducted a prospective observational research among 442 patients with acute exacerbations of COPD and observed that increased RDW (≥13.75%) was strongly correlated with the risk of in-hospital death (relative risk 4.30; 95% CI 1.98–9.58) and the risk of 1-year mortality (HR 1.64; 95% CI 1.08–2.50). However, previous research involved limited sample sizes, and adjustments were not made for a large number of potentially confounding factors. Furthermore, to the best of our knowledge, limited research has focused on the correlation between RDW and mortality in critically ill patients with COPD. Our results support these earlier investigations.[38-41] In the present study, which included 3,244 critically ill patients with COPD, an increase in RDW was related to the increased risk of 28-day all-cause mortality based on multivariate logistic regression analysis.

Aging[48-51] and ethnicity[52,53] are associated with RDW values. Different epidemiological studies have reported inconsistent results in terms of the relationship between RDW and sex.[49-51] The correlation between RDW and 28-day mortality was constant across all subgroups in our analysis, regardless of age (<75 and ≥75 years), sex, or ethnicity. COPD comorbidities include hypertension, congestive heart failure, diabetes, and cardiac arrhythmias, and comorbidities mainly cause mortality among COPD patients.[54] Sepsis and AKI frequent occur in ICU patients and are related with poor outcomes.[55,56] The results of RDW and mortality were stable in these subgroups. RDW is commonly used for anemia differential diagnosis. Higher RDW levels are related to an increased risk of death, regardless of presence or absence of anemia. The effects of treatment and illness severity score should be considered. The results were consistent in different subgroups according to vasopressor use, ventilation, SAPS II (<37 and ≥37), and SOFA score (<4 and ≥4).

The mechanisms underlying the increase in RDW are unclear. To the best of our knowledge, high RDW level is correlated with an inflammatory state. Inflammation can affect iron metabolism and bone marrow function, thus inhibiting erythropoietin-induced erythrocyte maturation.[57,58] This condition results in the release of immature red blood cells into the circulation and disruption in red blood cell clearance, thus increasing RDW. Commonly, critically ill patients exhibit systemic inflammatory responses.[59] These mechanisms may assist in exploring the correlation between RDW and poor outcomes in COPD patients. Thus, RDW may be related to poor outcomes in patients with COPD.

Our study has some limitations. First, considering that the present study involves observational research, causal inferences cannot be detirmined. Moreover, the analysis was adjusted for the available confounders, but our observations may have been influenced by residual measured and/or unmeasured confounders. In addition, we excluded patients aged <18 years. Therefore, our findings cannot be generalized to these patients. Furthermore, RDW values could have been affected by many factors, such as erythropoietin use and iron or vitamin B12 deficiency, although considering the retrospective nature of the study, these situations could not be distinguished. Moreover, we only focused on the initial RDW value obtained within the first 24 h after ICU admission. The effect of RDW fluctuations on prognosis is unknown. In addition, the ICD-9 code-based definition of severe sepsis may underestimate the actual incidence of sepsis. Some cases of sepsis may not be covered by the codes. Finally, considering that this study was a single-center, retrospective

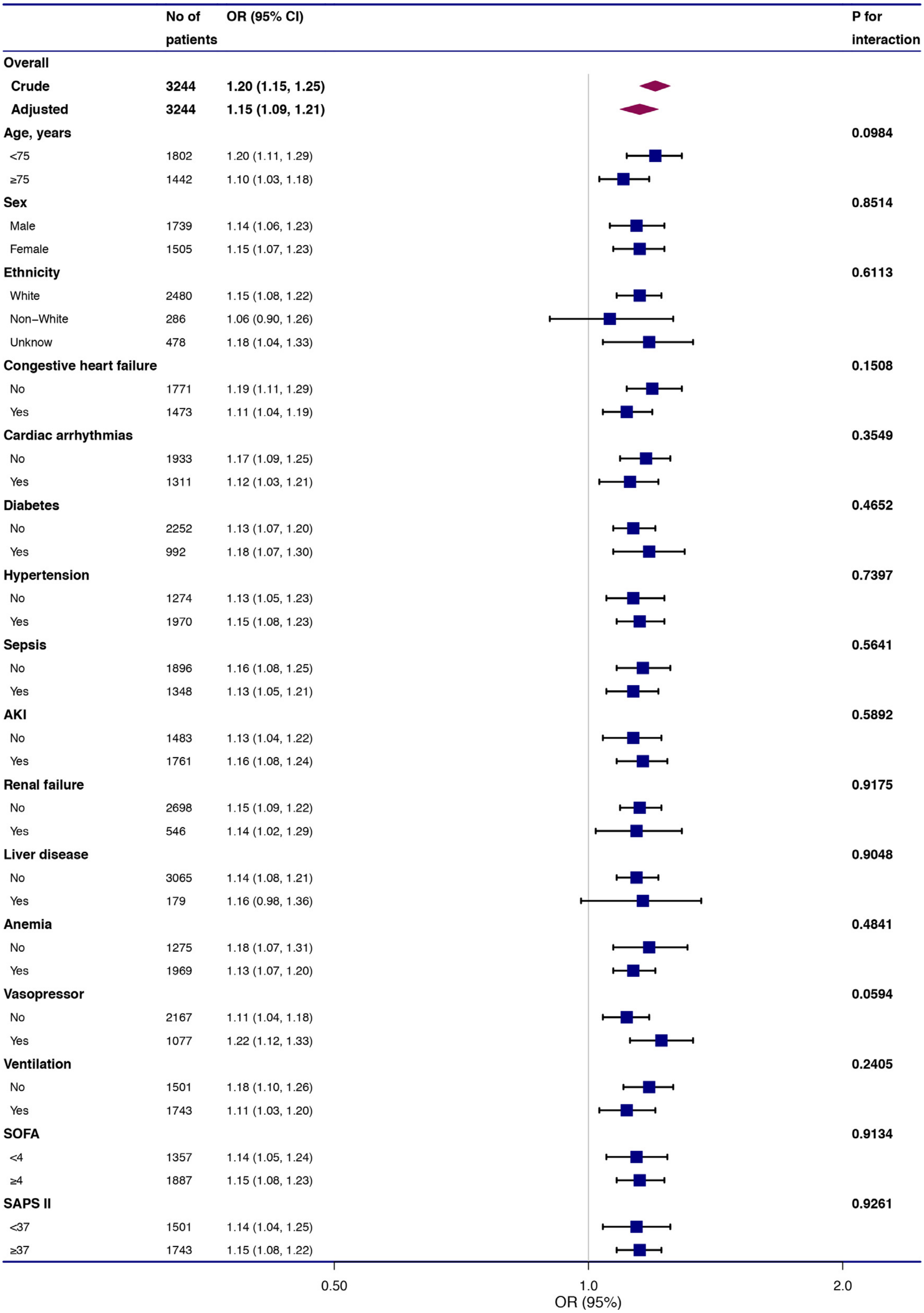

Fig. 2 Effect size of red blood cell distribution width on 28-day mortality in prespecified and exploratory subgroups. The effect size was adjusted for age, sex, ethnicity, weight, systolic blood pressure, mean blood pressure, heart rate, respiratory rate, percutaneous oxygen saturation, hematocrit level, platelet level, anion gap, serum creatinine, bicarbonate, chloride, glucose, blood urea nitrogen, white blood cell, and potassium levels, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment score, cardiac arrhythmias, hypertension, sepsis, liver disease, vasopressor, ventilation, renal replacement therapy, acute kidney injury, and anemia, except for the subgroup variable.

database analysis, our findings must be validated using a multicenter, prospective survey with a larger sample size.

Conclusions

This cohort study suggests that an increase in RDW is associated with a higher risk of 28-day all-cause mortality in critically ill patients with COPD.

Data availability

The data used in the present study may be obtained by sending an email to the author (jiangwx90@163.com). However, approval should be obtained from the MIMIC III Institute to re-analyze the complete data.

Contribution

LEQ was in charge of the study design and data collection. LWH analyzed data and contributed to writing this paper. SDB, LWW, ZJS, ZJH, and JM all joined in the discussion and examined the article. JWX designed and supervised the study. Finally, all writers approved the final manuscript.

Conflicts of interest

This paper has no conflicts of interest for any of the authors.

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ORIGINAL ARTICLE

Alpha1-antitrypsin deficiency in Greece: Focus on rare variants

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Abbreviations: A1antitrypsin, (AAT); AAT deficiency, (AATD); dried blood spot, (DBS); diffusing capacity for carbon monoxide, (DLCO); forced expiratory volume in 1 second, (FEV_1); Forced mid-expiratory flow, (FEF25—75%); Forced vital capacity, (FVC); isoelectric focusing, (IEF); polymerase chain reaction, (PCR).

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Abstract
Purpose: A_1Antitrypsin deficiency (AATD) pathogenic mutations are expanding beyond the PI*Z and PI*S to a multitude of rare variants.
Aim: to investigate genotype and clinical profile of Greeks with AATD.
Methods: Symptomatic adult-patients with early-emphysema defined by fixed airway obstruction and computerized-tomography scan and lower than normal serum AAT levels were enrolled from reference centers all over Greece. Samples were analyzed in the AAT Laboratory, University of Marburg-Germany.
Results: Included are 45 adults, 38 homozygous or compound heterozygous for pathogenic variants and 7 heterozygous. Homozygous were 57.9% male, 65.8% ever-smokers, median (IQR) age 49.0(42.5–58.5) years, AAT-levels 0.20(0.08–0.26) g/L, FEV_1(%predicted) 41.5(28.8–64.5). PI*Z, PI*Q0, and rare deficient allele's frequency was 51.3%, 32.9%,15.8%, respectively. PI*ZZ genotype was 36.8%, PI*Q0Q0 21.1%, PI*MdeficientMdeficient 7.9%, PI*ZQ0 18.4%, PI*Q0Mdeficient 5.3% and PI*Zrare-deficient 10.5%. Genotyping by Luminex detected: p.(Pro393Leu) associated with $M_{Heerlen}$ (M1Ala/M1Val); p.(Leu65Pro) with $M_{Procida}$; p.(Lys241Ter) with $Q0_{Bellingham}$; p.(Leu377Phefs*24) with $Q0_{Mattawa}$ (M1Val) and $Q0_{Ourem}$ (M3); p.(Phe76del) with M_{Malton} (M2), $M_{Palermo}$ (M1Val), $M_{Nichinan}$ (V) and $Q0_{LaPalma}$ (S); p.(Asp280Val) with P_{Lowell} (M1Val); P_{Duarte} (M4), $Y_{Barcelona}$ (p.Pro39His). Gene-sequencing (46.7%) detected $Q0_{GraniteFalls}$, $Q0_{Saint-Etienne}$, $Q0_{Amersfoort (M1Ala)}$, $M_{Würzburg}$, $N_{Hartfordcity}$ and one novel-variant (c.1A>*G*) named $Q0_{Attikon}$.Heterozygous included PI*MQ0$_{Amersfoort(M1Ala)}$, PI*MM$_{Procida}$, PI*Mp.(Asp280Val), PI*MO$_{Feyzin}$. AAT-levels were significantly different between genotypes (p = 0.002).
Conclusion: Genotyping AATD in Greece, a multiplicity of rare variants and a diversity of rare combinations, including unique ones were observed in two thirds of patients, expanding knowledge regarding European geographical trend in rare variants. Gene sequencing was necessary for genetic diagnosis. In the future the detection of rare genotypes may add to personalize preventive and therapeutic measures.
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Introduction

A_1Antitrypsin (AAT) which is mainly produced by hepatocytes, acts as major protease inhibitor in the serum and targets preferentially excessive human neutrophil elastase.[1] Normally its plasma levels range from 0.9 g/L to 2 g/L in the absence of an acute phase response. AAT deficiency (AATD) is characterized by a significant decrease of AAT plasma levels usually below the "protective level" of 0.57 g/L.[2,3] Low or absent plasma levels and/or dysfunctional AAT molecules increase risk to develop pulmonary emphysema, less commonly liver disease and rarely other systemic manifestations.[4–7] Cigarette smoking or equivalent is considered the major additional risk factor in these patients.[1,2] AATD is one of most common Mendelian disorders and PI*Z and PI*S variants account for the majority of cases worldwide.[8,9] However, the genetic repertoire of AATD pathogenic mutations is constantly expanding far beyond the PI*Z and PI*S variants to a multitude of rare alleles such as the deficient or dysfunctional ones leading to the production of misfolded AAT protein such as the M, N, P, O deficient and the null (Q0) variants without any production of AAT protein.[10,11]The prevalence of rare genotypes other than PI*ZZ and PI*SZ recorded so far ranges from 1.1% in countries like France to 20.4% in countries like Italy.[12–16] Their epidemiology and geographic distribution, pathogenetic role and clinical expression need further investigation. This study aimed to investigate for the first ever time in Greece genotype and clinical profile characteristics of AAT deficiency patients.

Patients and methods

In this retrospective collaborative Greek study, we assessed the genotype and clinical profile of AAT deficiency patients followed-up in 12 hospital centers all over Greece a country of 10.400.000 people [https://www.statistics.gr/press-kit_census_results_2021] in an effort to capture the entire population. For that purpose, after authorization by the Medical Ethics Committee of General University Hospital “Attikon”, Athens, Greece, a questionnaire was addressed to all Tertiary University Hospitals as well as Referral Centers of the National Health System (NHS) and dedicated private clinics to enroll symptomatic adult patients with early emphysema defined by fixed airway obstruction and computerized tomography scan findings and lower than normal serum AAT levels documented by two consecutive measurements in the absence of an acute reaction condition verified by normal CRP levels. The overlap presence of bronchiectasis, bronchial asthma and liver disease was also reported in addition to routinely collected epidemiologic, clinical and functional data. This case-finding program is still ongoing. The data of the present study correspond to the time period from September 2018 to October 2021. Normal serum AAT levels were considered at 0.9—2 g/L by nephelometry by local laboratory standards. Following genetic results, analysis considers adults as homozygous or compound heterozygous for pathogenic variants. All adult patients included in the study fulfilled the criteria of the European Respiratory Society for the diagnosis and treatment of pulmonary disease in AATD.[3]The AATD genetic analysis was performed at the German AAT Laboratory at the University of Marburg (MV, CFV, TG). For that analysis dried blood spot (DBS) samples were tested using the Progenika AAT genotyping kit (Progenika Biopharma, S, A, Derio, Spain) which can simultaneously identify and genotype 14 deficiency variants of the SERPINA1 gene based on Luminex xMAP-Technology (Luminex, Austin, TX, USA). For samples in which we suspected the presence of other mutations, due to low serum AAT levels, isoelectric focusing (IEF) was performed.[17,18] If the results from Luminex technology and IEF tests did not correlate or an indication of a rare mutation existed, gene sequencing (Next Generation Sequencing) was done. For sequencing the DBS samples were shipped to a reference laboratory [Progenika Biopharma, Spain]. We have described the laboratory methods in detail elsewhere.[17] Epidemiological, clinical, laboratory and functional data were collected in a standardized manner. Death data were recorded until October 2021, except for cases lost to follow-up. Rare and ultra-rare mutations were discussed systematically with experts from the German AAT Laboratory at the University of Marburg (MV, CFV, TG) in collaboration, when necessary, with the expert Center for Diagnosis of Inherited Alpha1-antitrypsin Deficiency at the University of Pavia on web meetings (IF, SO). Selected patients were discussed monthly in a web-based multidisciplinary meeting dedicated to AATD (www.respifil.fr) for consultation (MB, CL, VC, JFM). All patients signed written informed consent and the study was approved by the Medical Ethics Committee of General University Hospital “Attikon”, Athens, Greece (EBΔ 633/24—09—2018).

Statistical analysis

Normality of the distributions was checked with Kolmogorov-Smirnov test. Categorical variables are presented as n (%), whereas numerical variables are presented as median (interquartile ranges) since the distribution of data was skewed. Comparisons between AAT levels in the different groups were performed using Kruskal Wallis test. Statistical significance was established at the level of $p \leq 0.05$. Data were analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and graphs were created using Graph Pad Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Included are 45 adults, 38 homozygous or compound heterozygous for pathogenic variants and 7 heterozygous. The former was 57.9% male, 65.8% ever-smokers, diagnosed at a median age (IQR) of 49.0 (42.5—58.5) years, AAT levels of 0.20(0.08—0.26) g/L, FEV_1(% predicted), FEV_1/FVC%, FEF25—75% and DLCO (% predicted) of 41.5 (28.8—64.5), 49.6 (38.2—61.1), 14 (9.6—28.5) and 45.8 (31.7—58.3), respectively. Overall, 26.3% of patients presented overlapping emphysema and bronchiectasis and 2.6% bronchial asthma. Only 2.6% presented with liver disease. All patients were treated with a combination of LABA/LAMA bronchodilators in the addition of inhaled corticosteroids in 50%. Augmentation therapy was provided in 26 (68.4%) patients although 30 of them (78.9%) fulfilled all 3 criteria for treatment (age <70 years old, FEV_1< 70% and AAT levels less than 0.57 g/L).[19] No vasculitis was reported in the present cohort analysis. PI*Z, PI*Q0, PI*Mdeficient and PI*N allele’s frequency was 51.3%, 32.9%, 14.5% and 1.31%, respectively. PI*ZZ genotype was found in 36.8% of patients, PI*Q0Q0 in 21.1%, PI*MdeficientMdeficient in 7.9%, PI*ZQ0 in 18.4%, PI*Q0Mdeficient in 5.3% and PI*Zrare-deficient in 10.5% (Table 1, Fig. 1).

Distribution of patients all over Greece and in Cyprus is shown in Fig. 2. Using genotyping by Luminex the following mutations were detected: p.(Pro393Leu) which is associated with $M_{Heerlen}$ (M1Ala/M1Val); p.(Leu65Pro) which is associated with $M_{Procida}$; p.(Lys241Ter) which is associated with $Q0_{Bellingham}$; p.(Leu377Phefs*24) which is associated with $Q0_{Mattawa}$ (M1 Val) and $Q0_{Ourem}$ (M3); p.(Phe76del) which is associated with M_{Malton} (M2), $M_{Palermo}$ (M1Val), $M_{Nichinan}$ (V) and $Q0_{LaPalma}$ (S); p.(Asp280Val) which is associated with P_{Lowell} (M1Val) ; P_{Duarte} (M4), $Y_{Barcelona}$ (p.Pro39His) (Table 2). However, this method does not detect the background, as is the case with sequencing. Therefore, in the following text the mutations are written as follows:

$M_{Heerlen}$ (M1Ala/M1Val) =*p*.(Pro393Leu), $Q0_{Mattawa}$ (M1 Val)/$Q0_{Ourem}$ (M3) = p.(Leu377Phefs*24),M_{Malton}(M2)/$M_{Palermo}$(M1Val)/$M_{Nichinan}$(V)/$Q0_{LaPalma}$(S)= p.(Phe76del), P_{Lowell} (M1Val) ; P_{Duarte} (M4), $Y_{Barcelona}$ (p.Pro39His)= p.(Asp280Val).[8]

Gene-sequencing in 46.7% of patients detected $Q0_{Granite-Falls}$, $Q0_{Saint-Etienne}$, $Q0_{Amersfoort}$ (M1Ala), $M_{Würzburg}$, $N_{Hartfordcity}$ and one novel-variant (c.1A>*G*) named $Q0_{Attikon}$. This mutation has never been described before; it relates to the codon of initiation of translation of the gene completely inhibiting AAT production. The variant was characterized as a null variant. A new name is planned in a separate paper (Table 2). Investigation of the study population by genotyping and next-generation sequencing approaches revealed that 24 out of 38 homozygous or compound heterozygous adult patients (63.2%) presented a multiplicity of rare variants and a diversity of rare combinations. PI*$Q0_{GraniteFalls}$$Q0_{Granite-Falls}$ was encountered in 4 patients and PI*$Q0_{Amersfoort}$

Table 1 Epidemiological, clinical and laboratory data of adults homozygous or compound heterozygous for pathogenic variants.

Parameter	All (*n* = 38)	PI*ZZ (*n* = 14)	PI*Q0Q0 (*n* = 8)	PI*Mdeficient /Mdeficient (*n* = 3)	PI*ZQ0 (*n* = 7)	PI*Q0/ Mdeficient (*n* = 2)	PI*Z/rare-deficient (*n* = 4)
Gender (Male, n (%)	22.0 (57.9)	7.0 (50.0)	4.0 (50.0)	2.0 (66.7)	5.0 (71.4)	1.0 (50.0)	3.0 (75.0)
Age at diagnosis, years	49.0 (42.5–58.5)	46.5 (42.0–64.0)	47.0 (34.0–52.0)	49.0 (37.0–49.0)	50.0 (47.0–54.0)	46.5 (26.0–46.5)	61.0 (44.0–61.0)
Ever smoker, n (%)	25.0 (65.8)	10.0 (71.4)	5.0 (62.5)	2.0 (66.7)	4.0 (57.1)	1.0 (50.0)	3.0 (75.0)
Pack-years (n)	20.0 (0.0–25.0)	20.0 (2.5–22.5)	12.5 (0.0–20.0)	9.0 (0.0–9.0)	22.5 (0.0–40.0)	10.0 (0.0–10.0)	20.0 (12.0–20.0)
A_1Antitrypsin level (g/L)	0.20 (0.08–0.30)	0.25 (0.20–0.30)	0.04 (0.01–0.05)	0.13 (0.04–0.13)	0.20 (0.14–0.24)	0.16 (0.07–0.16)	0.33 (0.20–0.48)
Survival 12 months, n (%)	34.0 (89.5)	12.0 (85.7)	7.0 (87.5)	3.0 (100.0)	7.0 (100.0)	2.0 (100.0)	2.0 (66.7)
Augmentation therapy, n (%)	26.0 (68.4)	11.0 (78.6)	5.0 (62.5)	2.0 (66.7)	7.0 (100.0)	2.0 (100.0)	1.0 (33.3)
All 3 criteria, n (%)	30.0 (78.9)	10.0 (71.4)	8.0 (100.0)	2.0 (66.7)	6.0 (85.7)	1.0 (50.0)	3.0 (75.0)
FEV_1% predicted	41.5 (28.8–64.5)	46.0 (32.0–78.5)	33.9 (28.0–72.0)	35.0 (21.0–35.0)	37.5 (21.0–41.0)	72.9 (50.0–72.9)	57.0 (47.0–57.0)
FVC% predicted	80.5 (54.6–102.3)	92.1 (64.5–101.1)	75.0 (48.0–102.0)	75.0 (54.0–75.0)	43.0 (34.0–63.4)	112.8 (106.6–112.8)	103.0 (81.0–103.0)
FEV_1/ FVC%	49.6 (38.2–61.1)	46.5 (37.4–59.2)	48.6 (47.0–60.4)	52.0 (36.0–52.0)	51.0 (46.0–71.0)	54.8 (32.0–54.8)	57.7 (35.6–57.7)
FEF_{25-75}% predicted	14.0 (9.6–28.5)	15.5 (11.6–28.3)	9.0 (7.9–27.0)	30.0 (30.0–30.0)	14.0 (8.4–16.0)	38.7 (14.0–38.7)	25.0 (14.0–25.0)
DLCO% predicted	45.8 (31.7–58.3)	58.8 (31.7–88.5)	41.5 (30.2–47.5)	32.0 (32.0–32.0)	40.3 (27.9–61.4)	68.3 (55–68.3)	47.0 (42.0–47.0)
Bronchiectasis, n (%)	10.0 (26.3)	4.0 (28.6)	2.0 (25.0)	0.0	3.0 (42.9)	0.0	1.0 (25.0)
Bronchial asthma, n (%)	1.0 (2.6)	0.0	0.0	0.0	1.0 (14.3)	0.0	0.0
Liver disease, n (%)	1.0 (2.6)	1.0 (7.1)	0.0	0.0	0.0	0.0	0.0

Values are presented as median (IQR) unless otherwise indicated; IQR= interquartile range; p-values <0.05 were considered statistically significant, *M*=male; COPD= chronic obstructive pulmonary diseases; FEV_1= Forced expiratory volume in one second FVC= forced vital capacity; FEF_{25-50}= forced expiratory flow at 25–75% of forced vital capacity or forced mid-expiratory flow; DLCO= diffusing capacity of the lung for carbon monoxide; all 3 criteria: age <70 years old, FEV1$<$ 70% and AAT levels less than 0.57 g/L.

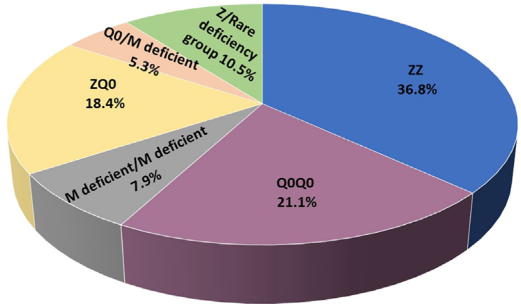

Figure 1 Pie chart displaying the proportions of different genotype groups in the cohort of 38 adult Greek patients with AATD homozygous or compound heterozygous for pathogenic variants.

$_{(M1Ala)}$Q0$_{Amersfoort(M1Ala)}$ in 2, the rest of the ultra-rare combinations being represented singularly. Exceptional combinations included PI*Q0$_{Amersfoort(M1Ala)}$p.(Leu377Phefs*24), (a unique one), p.(Phe76del p.(Leu377Phefs*24), and p.(Leu65-Pro)p.(Pro393Leu).Genetic analysis of heterozygous patients showed 4 PI*MQ0$_{Amersfoort(M1Ala)}$, 1 PI*MM$_{Procida}$, 1 PI*Mp.(Asp280Val) and 1 PI*MO$_{Feyzin}$. Five patients were female and three ever-smokers. Age at diagnosis had a range (minimum-maximum) of 42 (34−76) years, AAT levels of 0.16 (0.62−0.78) g/L and FEV$_1$% predicted of 64 (40−104)% (Table 3). Consanguinity was reported only once in an index-case PI*Q0$_{Granitefalls}$Q0$_{Granitefalls}$ patient where both parents were second cousins. AAT levels were significantly different between genotypes (p = 0.002) with PI*Q0Q0 presenting the lowest levels (Fig. 3).

Discussion

The present study expands knowledge about the geographical distribution of genotype variants in AATD in Europe. In Greece PI*ZZ genotype was found in only 36.8% of patients while in the rest a multiplicity of rare variants and a diversity of rare combinations, including some unique ones were observed, confirming an established South-North European geographical trend in rare variants.[7,20,21] Rare variants observed in 63.2% of patients embraced the null variants PI*Q0$_{Bellingham}$, PI*Q0$_{Amersfoort}$, PI*Q0$_{Granite\ Falls}$, PI*Q0$_{Saint\text{-}Etienne}$, PI*Q0$_{Mattawa}$ and the novel PI*Q0$_{Attikon}$ (c.1A>*G*) allele; and the deficient variants PI*M$_{Heerlen}$, PI*M$_{Procida}$, PI*M$_{Malton}$, PI*M$_{Würzburg}$, and PI*N$_{Hardfordcity}$. All genotypes included in the study proved pathogenic since they were clinically encountered in patients with early emphysema and lower than normal AAT levels. To define genotypes 46.7% of patients required gene sequencing. PI*Q0Q0 genotype was associated with the lowest AAT serum levels.

Historically, among patients with severe AATD, the PI*ZZ genotype appeared to predominate almost exclusively (98%) in Northern Europe and in Caucasians of European descent living in the USA. A smaller although significant number of homozygous PI*ZZ patients are also found in Canada, Australia, New Zealand and some countries of South America. However, more recent studies in Europe have discovered wide geographical differences, where Northern Europe, the Iberian Peninsula and Ireland present the highest prevalence of PI*ZZ genotype, Southern and Eastern Europe the lower ones and Great Britain intermediate prevalence.[20,21] In more detail and based on recent epidemiological evidence, the PI*ZZ genotype mean prevalence is 4.5 to 10 times higher in Denmark compared to countries like Serbia and North Macedonia, whereas data were completely lacking for Greece.[20,21]

The present study by demonstrating that in Greece only one third of patients with early emphysema and severe AATD presented the PI*ZZ genotype confirms for the first time, to the best of our knowledge in Greece, the already established North-South European geographical trend in PI*Z variant. Many theories have been developed so far to explain this observation including the Scandinavian origin of the PI*Z allele and the association of its dispersal to the Viking migration history. Updated knowledge of human genetic diversity tends to explain the observed gradients in prevalence through another perspective, the one of "South-North cline of genetic diversity".[8] Differences might result from population movements the Neolithic times from the Southern European populations historically larger and genetically more diverse to the Northern ones.[22,23]

The present study also expands knowledge about the geographical distribution of genotype variants in AATD in Europe by discovering in Greece a multiplicity of rare variants including six null variants (one novel one) and six rare deficiency ones in an exceptional diversity of rare combinations both homozygous and compound heterozygous rarely described before in one cohort. Interestingly the PI*S allele and the PI*SZ genotype considered as the second most prevalent ones worldwide were not represented in our study population.[24] This could be partly explained by the fact that the threshold of AAT serum levels used to select affected cases could not "capture" some of those patients and that only a fraction of PI*SZ (smokers) shows respiratory symptoms and emphysema.[24] In the Spanish registry of 469 patients with AATD, only 3.4% were carriers of rare variants in homozygous or compound heterozygous state.[12] In the Italian registry of 422 adult subjects with severe AATD, 20.4% of patients were found with one rare deficient/null allele in combination with an PI*S or PI*Z allele or with rare deficient/null alleles, the highest so far recorded prevalence in national registries and the closest one to our findings.[13] In the US AATD registry of 1129 subjects, 97% of them were PI*ZZ and only 1.8% presented rare variants such as PI*Q0$_{GraniteFalls}$, PI*Q0$_{Bellingham}$, PI*M$_{Malton}$, PI*M$_{Heerleen}$ and PI*P$_{Lowell}$.[14] In the German registry of 548 individuals, 8.5% of patients were carriers of rare variants.[15] Finally, in the French cohort of 312 patients, only 3 patients (1.1%) were found to carry a PI*Q0/Z genotype, whereas 84.6% were PI*ZZ and 5.5% PI*SZ.[16]The comparison of our study with others in Europe and the USA delineates the singularity of our findings showing 63.2% of AATD patients with rare, ultra-rare and almost unique variants and raises fascinating questions about migration patterns and adaptation procedures that could explain such a genetic diversity in a small but historical land of Eastern Europe, Greece. The fact that rare alleles almost segregated in a restricted geographical area, are also observed sporadically in different geographic populations both European and American provides evidence of their ancestry.[25−39] In the present cohort, the identification of null, rare-deficiency as well as a novel null variant was possible thanks to DNA-

Table 2 Biological characteristics of the alleles of the study population.

SERPINA1 mutation	Marker ID	Allele name (Molecular Background)	DNA Sequence	Intron/Exon	Mechanism	Mutation effect on the protein	Refs.
p.(Thr62Cys)		O_{Feyzin}	c.185A>*G*	Exon 4	Missense mutation	unknown	http://www.a1at-variantdatabase.com/detail-page-display-260.html
p.(Leu65Pro)	rs28931569	$M_{Procida}$	c.194T>C	Exon 2	Missense mutation	Protein deficiency	[28]
p.(Phe76del)	rs775982338	M_{Malton} (M2) $M_{Palermo}$ (M1 Val) $M_{Nichinan}$ (V) $Q0_{la\ palma}$ (S)	c.227_229delTCTdel	Exon 2	In-frame-deletion Single amino acid deletion at position 76	Protein deficiency	[30,36–38]
p.(Asp280Val)	rs121912714	P_{Lowell} (M1Val) P_{Duarte} (M4) $Y_{Barcelona}$ (p.Pro39His)	c.839A>*T*	Exon 5	Missense mutation	Protein deficiency	[8]
p.(Tyr184Ter)	rs199422210	$Q0_{Amersfoort}$ (M1Ala) $Q0_{Bredevoor}$ (Unknown)	c.552C>G	Exon 2	Nonsense mutation This sequence change creates a premature translational stop signal (p.Tyr184Ter) in the SERPINA1 gene. It is expected to result in an absent or disrupted protein product	Protein absence	[8,27]
p.(Tyr184Ter)	rs267606950	$Q0_{Granite\ Falls}$	c.552del	Exon 2	Frameshift mutation This frameshift results in a premature stop signal (p.Tyr184Ter) in the SERPINA1 gene. It is expected to result in an absent or disrupted protein product	Protein absence	[29]
p.(Lys187Ter)		$Q0_{Saint\text{-}Etienne}$	c.559A>*T*	Exon 2	Nonsense mutation This sequence change creates a premature translational stop signal (p.Lys187Ter) in the SERPINA1 gene. It is expected to result in an absent or disrupted protein product.	Protein absence	[26]
p.(Lys241Ter)	rs199422211	$Q0_{Bellingham}$	c.721A>*T*	Exon 3	Nonsense mutationThis sequence change creates a premature translational stop signal (p.Lys241Ter) in the SERPINA1 gene. It is expected to result in an absent or disrupted protein product.	Protein absence	[31]
p.(Thr292Ile)	rs745624643	$N_{Hartford\ City}$	c.875C>T	Exon 5	Missense mutation	Protein deficiency	[32]
p.(Leu377Phefs*24)	rs763023697	$Q0_{Mattawa}$ (M1 Val) $Q0_{Ourem}$ (M3)	c.1130dup	Exon 5	Frameshift mutation An insertion of 1 nucleotide at position 353 of the protein resulted in a premature stop codon of 24 amino acids downstream. It is expected to result in an absent or disrupted protein product.	Protein absence	[33,39]
p.(Pro393Ser)	rs61761869	$M_{Würzburg}$	c.1177C>T	Exon 5	Missense mutation	Protein deficiency	[34]
p.(Pro393Leu)	rs199422209	MHeerlen** (M1 Ala) $M_{Heerlen**}$ (M1 Val)	c.1178C>T	Exon 5	Missense mutation	Protein deficiency	[35]
p.Met1?	rs1057516555	**c.1A>G$Q0_{Attikon}$**	c.1A>*G*	Exon 4	Missense mutation	unknown	it will be fully characterized in a next paper.

* Genetic background: M1: p.(Val237Ala), M2: p.(Arg125His), M3. p.(Glu400Asp).

** MHeerlen might be considered also a null allele given its extreme low levels in serum, however in the present study it was included in the group of Mdeficient variants.

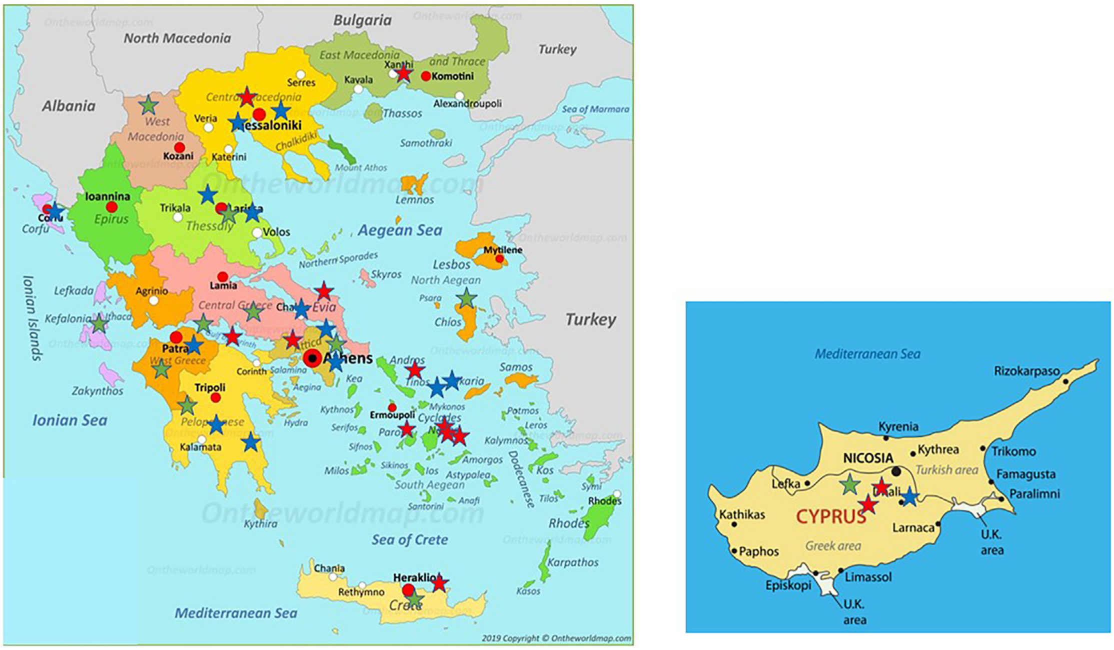

Figure 2 Distribution of the 38 patients depicted as stars of different colors in their area of origin on the map of Greece and Cyprus. Blue stars correspond to PI*ZZ patients, red stars to any combination homozygous or compound heterozygous including PI*Q0 or/and rare-deficient variants and green stars correspond to the combination of PI* Z with any PI*Q0 or rare-deficient variant.

sequencing technology which was the only one compared to IEF and PCR techniques that provided an accurate and unambiguous genotyping final result.

The sequencing protocol includes the seven exons of SERPINA1 gene (NM_001127701.1): 3 first exons corresponding to 5′ UTR region and the 4 coding exons. Full exons plus intronic sequences around exon (at least 30 bp intron sequences around exons) are amplified and sequenced by Next Generation Sequencing (MiSeq, Illumina).[17,40] This is in accordance with the recent literature which is increasingly highlighting the importance of whole *SERPINA1* gene next-generation sequencing to explain new mechanisms of AATD pathophysiology in a personalized medicine era.[41,42]

The clinical profile of our patients corresponded to the already described one of early emphysema even in the absence of smoke exposure.[43] In addition to PI*Z, null and rare-deficiency variants are considered factors increasing the risk for the development of early lung disease.[2,44,45] Pathogenicity is attributed to lower-than-normal AAT levels leading to unopposed proteolytic activity (loss of function) but also to stimulation of endoplasmic reticulum stress and inflammation pathways related to polymerization of misfolded proteins especially in some of the Mdeficient variants whose biologic and molecular behavior resembles that of PI*Z deficient ones (gain of function).[46]

The fact that our study also discovered rare variants in a small number of symptomatic early emphysema patients found to be heterozygous only for rare variants such as PI*Q0$_{Amersfoort (M1Ala)}$ in four patients and PI*M$_{Procida}$, p.(Asp280Val) and PI*O$_{Feyzin}$ further confirms our findings showing the predominance of rare variants in the Greek population. In the literature there is very little data about heterozygotes showing that PI*MZ individuals are at increased risk to develop early disease and that PI*MQ0 subjects may present with emphysema, asthma or

Table 3 Clinical and molecular characteristics of adult patients heterozygous for pathogenic variants.

Patient #	gender	Age at diagnosis, years	Clinical profile	FEV$_1$% predicted	Smoking status	AAT levels (g/L)	Genotype
1	M	76.0	E, B	40.0	Ex	0.67	PI*MQ0$_{Amersfoort(M1Ala)}$
2	F	53.0	B	75.0	Ex	0.78	PI*MQ0$_{Amersfoort(M1Ala)}$
3	F	44.0	BA	101.0	No	0.62	PI*MQ0$_{Amersfoort(M1Ala)}$
4	F	42.0	BA	98.0	No	0.72	PI*MM$_{Procida}$
5	M	34.0	B	75.0	No	0.70	PI*MQ0$_{Amersfoort(M1Ala)}$
6	F	58.0	BA	84.0	Ex	0.63	PI*MO$_{Feyzin}$
7	F	55.0	E	104.0	No	0.66	PI*Mp.(Asp280Val)

M=Male, *F*=Female, *E*=Emphysema, *B*=Bronchiectasis, BA=Bronchial asthma, FEV$_1$= Forced expiratory volume in one second, A$_1$AT=A$_1$-antitrypsin, age at diagnosis (years), Ex=ex-smoker.

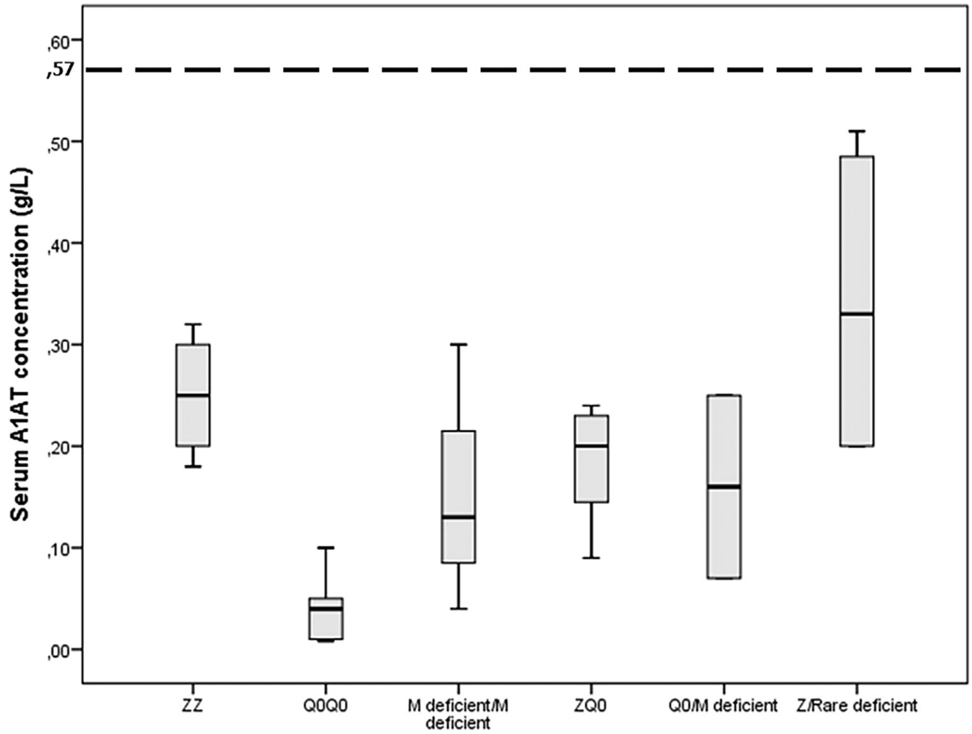

Figure 3 Serum A_1 antitrypsin (AAT) levels in g/L for 38 homozygous or compound heterozygous for pathogenic variants Greek patients with early emphysema and AAT deficiency. Horizontal bars correspond to the median value (interquartile range) for each group based on the genetic analysis. The dashed line corresponds to the protective level of 0.57 g/L.

chronic bronchitis over 45 years of age, irrespective of their smoking habit.[47–49]

The major limitation of our study is that it could be subject to selection or reporting bias and thus underscore the scale of AATD in Greece. Based on international epidemiological data,[1] the estimated number of cases in Greece approaches approximately 2500. Given the high under-recognition rate reported worldwide at 0.35 to 4%[1] the clinically identified patients should range from 9 to 100. Considering that the populations of Spain, Italy, the USA, Germany and France are 5, 6, 33.2, 8.3 and 6.7 times greater, respectively compared to Greece, the number of 45 patients included in the study may be regarded as very comparable to the "registry-based" cohorts of the countries cited-above.[12–16] Indeed in the epidemiologic study of de Serres and Blanco the authors estimate a number of 43 PI*ZZ for Greece.[50] We consider that this calculation could be imprecise for the Greek population. The authors of the epidemiologic study themselves comment on the potential important limitations and bias of their calculations based on the methods of selection of the cohorts and on the fact that the analysis had not taken into consideration rare variants given the paucity of data. In fact, many AATD patients in Greece were considered by their treating physicians to be "PI*ZZ" without documentation before a specific and detailed evaluation of pathogenic variants was performed with the contribution of the expert laboratory of the University of Marburg in collaboration with another 3 expert centers in Europe for the Greek patients in the present study.

Conclusion

Genotyping AATD in Greece, a multiplicity of rare variants and a diversity of rare combinations, including unique ones were observed in two thirds of patients, expanding knowledge regarding European geographical trend in rare variants. Gene sequencing was necessary for genetic diagnosis. In the future the detection of rare genotypes may help to personalize preventive and therapeutic measures.

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CRediT authorship contribution statement

S.A. Papiris: Conceptualization, Visualization, Funding acquisition, Formal analysis, Methodology, Writing – review & editing, Supervision. **M. Veith:** Formal analysis, Methodology, Writing – original draft. **A.I. Papaioannou:** Formal analysis, Methodology, Writing – original draft. **V. Apollonatou:** Funding acquisition, Methodology, Writing – review & editing. **I. Ferrarotti:** Methodology, Writing – review & editing. **S. Ottaviani:** Methodology, Writing – review & editing. **A. Tzouvelekis:** Funding acquisition, Methodology, Writing – review & editing. **V. Tzilas:** Funding acquisition, Methodology, Writing – review & editing. **N. Rovina:** Funding acquisition, Methodology, Writing – review & editing. **G.**

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REVIEW

Unsupervised physical activity interventions for people with COPD: A systematic review and meta-analysis

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KEYWORDS
COPD;
Physical activity;
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Meta-analysis

Abstract
Introduction and objectives: Unsupervised PA interventions might have a role in the management of chronic obstructive pulmonary disease (COPD) but their effectiveness is largely unknown. Thus, we aimed to identify and synthesise data on the effects of unsupervised PA interventions in people with COPD.
Material and methods: Databases were systematically searched in April 2020, with weekly updates until September 2021. Randomised controlled trials and quasi-experimental studies comparing unsupervised PA with usual care, were included. Primary outcomes were dyspnoea, exercise capacity and physical activity. The effect direction plot was performed to synthesise results. Meta-analysis with forest plots were conducted for the Chronic Respiratory Disease questionnaire – dyspnoea domain (CRQ-D), 6-minute walk distance (6MWD) and incremental shuttle walk distance (ISWD).
Results: Eleven studies with 900 participants with COPD (68±10 years; 58.8% male, FEV_1 63.7±15.8% predicted) were included. All interventions were conducted at home, most with daily sessions, for 8-12 weeks. Walking was the most common component. The effect direction plot showed that unsupervised PA interventions improved emotional function, fatigue, health-related quality of life, muscle strength and symptoms of anxiety and depression. Meta-analysis showed statistical, but not clinical, significant improvements in dyspnoea (CRQ-D, MD=0.12, 95% CI 0.09-0.15) and exercise capacity, measured with 6MWD (MD=13.70, 95% CI 3.58-23.83). Statistical and clinical significant improvements were observed in exercise capacity, measured with ISWD

PROSPERO registration number: CRD42020162311.

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(MD=58.59, 95% CI 5.79-111.39). None to minor adverse events and a high adherence rate were found.
Conclusions: Unsupervised PA interventions benefits dyspnoea and exercise capacity of people with COPD, are safe and present a high adherence rate. Unsupervised PA interventions should be considered for people with COPD who cannot or do not want to engage in supervised PA interventions or as a maintenance strategy of PA levels.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a global public health concern.[1] People with COPD present higher sedentary behaviour and lower levels of physical activity (PA) than their healthy peers.[2] Physical inactivity has been associated with poor health outcomes (e.g., dyspnoea, exercise intolerance, reduced health-related quality of life [HRQoL]) in people with COPD,[3,4] being an independent risk factor for hospitalisations due to acute exacerbations and early mortality.[5,6] Therefore, improving PA levels in this population is imperative.[1,7]

Physical activity has well-established physiological, social and psychological benefits in people with COPD.[1,8] Despite these unequivocal benefits,[1] increasing PA levels in this population is often challenging.[9] Barriers to engage in PA include low motivation,[10,11] physical (e.g., symptoms-related) and psychological (e.g., fear) disease limitations,[11] limited access to[12] or lack of perceived benefit of PA interventions,[13,14] time requirements and[14] travel issues.[13,14]

Unsupervised PA may contribute to overcome some of these barriers as it: i) is low cost;[15] ii) presents a broad application (e.g., specialised equipment is not required);[15] and iii) can be undertaken in any environment and/or at any time, whatever suits the individuals best,[16] hence may enhance adherence to PA in people with COPD. Nevertheless, unsupervised PA interventions are still underused in this population.[15] One possible explanation could be the lack of synthesis of the most common unsupervised PA interventions and respective evidence.

Recently, a systematic literature review of unsupervised exercise-based interventions in this population was published.[17] However, they focussed on exercise interventions, which is just a subset of PA.[18] PA refers to all movement performed by an individual, which means other components besides exercise, such as everyday tasks, are included.[18] In fact, people with COPD reduce their participation in PA and adopt a sedentary lifestyle to avoid exertional dyspnoea,[11] leading to muscle deconditioning and accentuating exercise capacity impairment.[19,20] Therefore, synthesising evidence of the benefits obtained with unsupervised PA interventions and also including activities integrated in individuals' daily life may be highly meaningful for participants, and provide relevant information to healthcare professionals for the management of COPD, especially in limited resource settings.

Therefore, this systematic review aimed to identify which unsupervised PA interventions have been used for people with COPD and explore their effectiveness.

Material and methods

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO – registration no. CRD42020162311) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[21] and the Synthesis Without Meta-analysis (SWiM)[22] recommendations.

Eligibility criteria

Studies were included if: i) their sample was composed of adult (≥18 years) people with COPD in a stable phase of the disease (i.e., 4 weeks without hospital admissions or exacerbations, nor changes in medication, according to Global Initiative for Chronic Obstructive Lung Disease – GOLD report[1]); ii) included unsupervised PA interventions for people with COPD compared to usual care (i.e., had not received any PA intervention in the study period); iii) they were original randomised controlled trials (RCT) or quasi-experimental studies; iv) written in Portuguese, English, Spanish or French languages. Studies were excluded if they: i) involved proxy versions; ii) were qualitative studies; iii) included other treatments/activities as an intervention while performing PA; iv) included any directly supervised training (other than a single session), i.e., face-to-face or remote contact (e.g. video-conference); and, v) were performed in hospital-based settings.

For the purpose of this review, the following definition of PA was used: "any bodily movement produced by skeletal muscles that requires energy expenditure."[18] Unsupervised PA interventions were defined as any PA without any supervision, undertaken in any environment and/or at any time, which best suits the person.[16] It could include a single supervised session to explain and/or demonstrate the activities; and, remote contact with healthcare professional using technologies, such as, telephone, mobile phone and/or tablet devices, to check patients' health and monitor their evolution, without being used to interactively coach/instruct the patient (e.g., video-conference).

Information sources

A systematic literature search was conducted in April 2020, on the following electronic databases: Cochrane Library, PubMed, Scopus, Web of science, EBSCOhost. Electronic search was supplemented by weekly automatic updates retrieved from the databases until September 2021, and hand-searches of references in key systematic reviews.[17] The search strategy was performed by title, abstract, keywords/MESH term. The full search strategy is presented in Supplementary material - Appendix 1.

Study selection

After removing duplicates, two reviewers (CP and VR) independently screened the potential studies (title and abstract), according to the eligibility criteria. The full-text of each potentially relevant study was then independently screened by the same reviewers to decide on its inclusion. Discrepancies were solved by consensus, and if agreement could not be reached, the other authors' opinion was obtained. Primary outcomes were dyspnoea, exercise capacity and PA. Secondary outcomes included body composition, emotional function, fatigue, health behaviours, healthcare utilisation, HRQoL, mastery, muscle strength, self-efficacy, symptoms of anxiety and depression, adverse events and, dropouts and adherence to interventions.

Data extraction

One reviewer independently extracted the data from included studies, and the other authors checked the accuracy and completeness of information. Data extraction was performed using a pre-developed and structured table-format covering the following topics: characteristics of the study (first author, year of publication, country and study design); setting (i.e., home-based); population (number of participants, sex, age, forced expiratory volume in one second percentage of predicted [FEV_{1pp}], severity of airway limitation [GOLD grades 1-4][1] and comorbidities [type and severity, classified with Charlson Comorbidity Index-CCI]; intervention (type, frequency and duration); outcome and outcome measures; and, results obtained in each outcome measure. Studies with multiple publications were identified to avoid duplicate reports (e.g., number of participants). Corresponding authors of the included studies were contacted via e-mail to request additional data (i.e., means and SD), whenever needed.

Quality assessment

Two reviewers independently assessed the methodological quality of each study using the Quality Assessment Tool for Quantitative Studies, developed by the Effective Public Health Practice Project, Canada.[23] This tool is comprised of six domains of methodological quality: 1) selection bias; 2) study design; 3) confounders; 4) blinding; 5) data collection methods; and, 6) withdrawals and dropouts.[23] Each domain is rated as "strong", "moderate" or "weak", according to a standardized guide.[24] The overall rating of each study is determined by the total number of "weak" scores, i.e., if the study presented: i) no weak scores, it was rated as strong quality; ii) one weak rating - moderate quality; and, iii) two or more weak ratings - weak quality.[23]

Data analysis and synthesis

Inter-rater agreement analysis was assessed using Cohen's kappa to explore the consistency of the quality assessment performed by the two reviewers. The Cohen's kappa ranges from 0 to 1 and agreement was interpreted as: slight ($\leqslant$0.2), fair (0.21−0.4), moderate (0.41−0.6), substantial (0.61−0.8), or almost perfect ($\geq$0.81).[25]

Studies were grouped according to the outcome measures reported. An effect direction plot was computed to deal with the diversity of outcome measures used in the included studies, following the SWiM recommendations.[26] This plot considers the study design, effect estimates of each outcome (represented with arrows, i.e., upward arrow ▲= positive health impact, downward arrow ▼= negative health impact, sideways arrow ◄►= no change/mixed effects/conflicting findings), sample size and studies quality (using a traffic light system, i.e., green for studies of high quality, amber for moderate and red for weak quality of evidence).[26] The effect estimates were analysed with the Cohen's d effect sizes (ES) based on the Pre/Post means and SD, according to the formula of Morris.[27] The ES were interpreted as very small ($\geq$0.01), small ($\geq$0.20), medium ($\geq$0.50), large ($\geq$0.80), very large ($\geq$1.20) and huge ($\geq$2.0).[28,29] Results were analysed by counting the effect direction and interpreted using the proportion of effects favouring the intervention [30] Proportions higher than 50% were considered as an improvement in the respective outcome measure.[30]

Meta-analysis, with forest plots, only included studies reporting the mean changes between the experimental (EG) and control (CG) groups and the respective SD or data allowing the calculation of these estimates. Between-study heterogeneity was quantified using I-squared (I^2) statistic. Statistical homogeneity was defined as $\leq$40%.[30]

Some data transformation occurred to compute ES. Data presented as 95% of confidence intervals (95% CI) [31] were transformed into SD, using the formula: SD=$\sqrt{n} * (upper\ limit - lower\ limit)/3.92$, where n is the sample size.[30] Additionally, data presented as median and interquartile range (IQR) [31] were converted into mean and SD using the summary table proposed by Wan and colleagues.[30,32]

Data analysis were performed using IBM SPSS 24.0 (IBM, Armonk, New York, USA) and RStudio, V1.2.5033 (RStudio, Inc; Boston, MA, USA).

Results

Study selection

The literature search provided 738 studies. After duplicates removed, 396 records were screened and 303 were excluded. The full-text of 93 articles was assessed and four studies were included. Seven additional studies were identified and retrieved, two from the databases weekly automatic updates and five from the reference list of a key systematic review [17] (Fig. 1). A total of 11 articles were included.

Quality assessment

Four studies were rated as strong [33-36] (36%), three [31,37,38] (28%) as moderate and four [39-42] (36%) as weak quality. Inter-rater agreement was substantial (Cohen's Kappa=0.72; 95% CI=0.37-1.07; p = 0.003; percentage of agreement= 82%). Quality assessment details can be found in Supplementary material (Table S1).

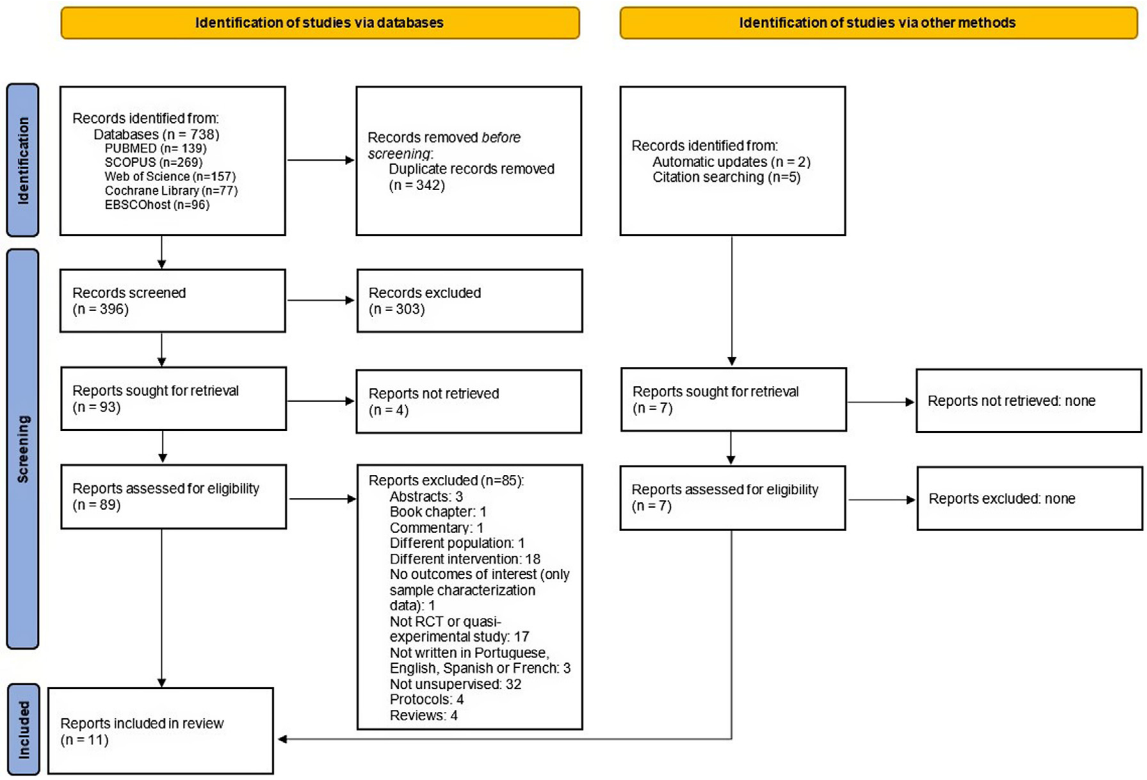

Fig. 1. Flow diagram of the articles screened and included in the study (*n* = 11) according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA).
Abbreviations: RCT – randomised controlled trial.

Studies characteristics

Included studies were published between 1977[42] and 2020[31], and were mostly conducted in the United States of America,[33,34] Australia,[31,39] United Kingdom [36,38] and Taiwan.[35,41] A total of 900 participants with COPD, 446 in the EG and 454 in the CG, were included. Sample sizes ranged between 20[38] to 305 participants.[33,34] Participants were on average 68±10 years old (*n* = 6), 541 (59%; *n* = 9) were male, presented a mean FEV_1 of 63.7±15.8 %predicted (*n* = 3) and the majority had moderate to severe (GOLD grades 2-3) grades of the disease (*n* = 4). Comorbidities reported (*n* = 3) included: cardiovascular disease (hypertension, heart failure, myocardial infarction, and peripheral vascular diseases), metabolic syndrome (e.g., diabetes), depression, musculoskeletal disease (e.g., arthritis) and ulcer disease.[33,34,36] Table 1 presents detail characteristics of the included articles.

Design of the interventions

Interventions lasted from 6 [36,38] to 66 weeks,[33,34] being 8-12 weeks [31,35,37,39-42] the most common range duration, and were performed 3 days/week,[37] 4 days/week [38] or daily.[31,33-36,39-42] All interventions were designed by health professionals (i.e., general practioners,[35,42] nurses[35,37,39-41], physiotherapists[31,36,38] and health coachs[33,34]) and performed at home.[31,33-42]

Interventions were single-component in seven [33-35,37,39,41,42] and multi-component in four [31,36,38,40] studies. Aerobic exercise [31,35,36,38,39,41,42] (e.g., walking) and muscle strength [31,36-38,40] were the main training components. Two studies [33,34] focused on promotion of lifestyle PA (i.e., promotion of activities of daily living). Interventions also included diaries;[31,41,42] action plans;[39,41] information about healthy behaviours;[39] phone calls to support the intervention, promote healthy behaviours or deliver self-management training;[31,33,34,36,39,40] distribution of handbook/manual;[33,34,41] workbook activities;[33,34] reading assignments;[33,34] and nutritional and psychosocial support.[40] More details are presented in Table 1.

Effectiveness of unsupervised PA interventions

A total of 14 outcomes, evaluated by 44 different measurement tools were found in the included studies (Table S1, Figs. 2 and 3).

Primary outcomes

Dyspnoea

Dyspnoea was measured in seven studies, with the modified Borg scale (MBS)– dyspnoea,[35] the Chronic Respiratory Questionnaire - dyspnoea domain (CRQ-D) [31,34,36,38] and the modified British Medical Research Council (mMRC).[31,41]

Unsupervised PA interventions had a positive effect on dyspnoea, with four [34,35,38,40] of six studies [31,34-36,38,40] favouring the EG (67%, 95% CI 22-96%) (Fig. 2). Meta-analysis of the CRQ-D[34,35,38,40] showed this significant improvement (MD=0.12, 95% CI 0.09-0.15). Statistical heterogeneity was

Table 1 Design and effects of unsupervised physical activity interventions for people with chronic obstructive pulmonary disease (*n* = 11).

Study, country and design	Setting	Participants	Intervention	Outcome	Outcome measure	Results
McGavin *et al*. 1977 Scotland Non-RCT	Home-based	n_{Total}= 24 EG: *n* = 12 (61.4±5.6 yrs; FEV_1: 0.97±0.33 L) CG: *n* = 12 (57.2±7.9 yrs, FEV_1: 1.15±0.72 L)	**EG:** Description: • Graded stair-climbing exercises. ○ Most disabled participants (walking distance <800m in 12 MWD): started with 2 steps up/down for 2 min. ○ Less disabled (walking distance >800m in 12 MWD): started with 5 steps up/down for 5 min. ○ Final aim: 10 steps (up/down) in 10 min. ○ Progress: assessed after 2 weeks of the baseline and then monthly, at an outpatient clinic. Frequency: Once a day, at least 5 days/week. Duration: 3 months **CG:** Description: Regular assessments Frequency: Monthly clinic visits Duration: 3 months	Body composition	Weight, kg	EG: Pre 65.9±7.3 Post 66.7±8.4, p>0.05; CG: Pre 66±11.1 Post 65±10, p>0.05; $ES_{EG\ vs\ CG}$=0.19
				Exercise capacity	12MWD, m	EG: Pre 1018±313 Post 1082±292, *p* < 0.001; CG: Pre 1053±132 Post 1034±141, p>0.05; $ES_{EG\ vs\ CG}$=0.35
					HR_{ex}, bpm	EG: Pre 118±14 Post 125±10, p>0.05; CG: Pre 123±10 Post 119±11, p>0.05; $ES_{EG\ vs\ CG}$=0.95
					HR_{st}, bpm	EG: Pre 118±15 Post 120±11, p>0.05; CG: Pre 119±10 Post 116±14, p>0.05; $ES_{EG\ vs\ CG}$=0.39
					$R_{ex,}$ cpm	EG: Pre 0.94±0.082 Post 0.97±0.059, p>0.05; CG: Pre 0.95±0.117 Post 0.96±0.150, p>0.05; $ES_{EG\ vs\ CG}$=0.18
					VE_{ex}, l/min	EG: Pre 35±13 Post 39±10, p>0.05; CG: Pre 36±14 Post 34±13, p>0.05; $ES_{EG\ vs\ CG}$=0.45
					VE_{st}, l/min	EG: Pre 35±4 Post 34±9, p>0.05; CG: Pre 32±12 Post 33±13, p>0.05; $ES_{EG\ vs\ CG}$=-0.19
					VO_{2ex}, mmol/min	EG: Pre 43.2±13.4 Post 50.0±15.3, p>0.05; CG: Pre 45.6±7.7 Post 40.3±8.4, *p* < 0.05; $ES_{EG\ vs\ CG}$=1.02
					WL_{ex}, W	EG: Pre 62.6±22.9 Post 77±26.7, *p* < 0.05; CG: Pre 63.9±14.7 Post 61.3±15.7, p>0.05; $ES_{EG\ vs\ CG}$=0.81
					Stride, mm	EG: Pre 790±90 Post 830±75, *p* < 0.01; CG: Pre 780±80 Post 760±89, p>0.05; $ES_{EG\ vs\ CG}$=0.70
Elçi *et al*. 2008 Turkey Prospective RCT	Home-based	n_{Total}= 78 (58.9±10,1 yrs; 84.6% male) EG: *n* = 39 (59.7±8.6yrs; 84.6% male; FEV_1pp: 47.8±18.8; GOLD 1-7.7%, GOLD 2-30.8%, GOLD 3-51.3%, GOLD 4-10.3%) CG: *n* = 39 (58.1±11.5yrs; 84.6% male; FEV_1pp: 46.3±15.5; GOLD 1-7.7%, GOLD 2-30.8%, GOLD 3-51.3%, GOLD 4-10.3%)	**EG:** Description: • Home-based PR: ○ Endurance training (75% of 6MWT speed) ○ Abdominal, upper and lower limb strengthening ○ Nutritional and psychosocial counselling ○ Weekly phone calls Frequency: 5 days/week, 90 min/day Duration: 3 months **CG:** Description: Usual care Duration: 3 months	Anxiety and depression	HADS total score, pts	EG: Pre 17.5±6.2 Post 13.5±3.9, *p* = 0.001; CG: Pre 20.4±7 Post 21.2±6.2, *p* = 0.065; $ES_{EG\ vs\ CG}$=-0.80
				Dyspnoea	mMRC, pts	EG: Pre 3.2±0.6 Post 2.9±0.7, *p* = 0.001; CG: Pre 3.1±0.5 Post 3.0±0.6, *p* = 0.324; $ES_{EG\ vs\ CG}$=-0.31
				Exercise capacity	6MWD, m	EG: Pre 312.4±51.3 Post 328.9±48.8, *p* = 0.001; CG: Pre 305.1±54.6 Post 298.2±52.8, *p* = 0.001; $ES_{EG\ vs\ CG}$=0.45
				HRQoL	SF-36, pts	EG: Pre 37.6±9.7 Post 49.3±8, *p* < 0.05; CG: Pre 34.1±10.9 Post 32±9, p>0.05; $ES_{EG\ vs\ CG}$=1.45
					SGRQ total score, pts	EG: Pre 60.3±18.2 Post 45.9±11.6, *p* < 0.05; CG: Pre 61.7±19.9 Post 65.5±17.4, p>0.05; $ES_{EG\ vs\ CG}$=-1.06

Table 1 (*Continued*)

Study, country and design	Setting	Participants	Intervention	Outcome	Outcome measure	Results
Moore *et al*. 2009 UK Pilot RCT	Home-based	n_{Total}= 20 (50% male) EG: *n* = 10 (70 [13]yrs, 60% male, FEV_1pp: 40 [36.5-49]) CG: *n* = 10 (70.5 [57.5-78.5] yrs, 40% male, FEV_1pp: 41.5 [30-55])	EG: Description: • Home exercise video/DVD programme: ○ Warm-up ○ High-intensity interval exercise (upper and lower limb strengthening, aerobic exercise) ○ Cool-down Frequency:4 days/week, 30 min/day Duration: 6 weeks CG: Description: Usual care, educational COPD booklet Duration: 6 weeks	Dyspnoea	CRQ-D, pts	EG: Pre Median 3.3 [1.8-4.1] Post Median 3.6 [2.6-4.4], *p* = 0.027; CG: Pre Median 2.7 [2.1-4.8] Post Median 2.5 [2-3.2], *p* = 0.326; ES $_{EG\ vs\ CG}$=0.68
				Emotional function	CRQ emotional function domain, pts	EG: Pre Median 4.4 [3.2-5] Post Median 5.4 [4.8-6], *p* = 0.002; CG: Pre Median 4 [2.4-5.8] Post Median 4 [2.9-5.9], *p* = 0.73; ES $_{EG\ vs\ CG}$=0.45
				Exercise capacity	ISWD, m	EG: Pre Median 110 [35-265] Post Median 200 [69-333], *p* = 0.021; CG: Pre Median 160 [48-288] Post Median 175 [39-215], *p* = 0.256; ES $_{EG\ vs\ CG}$=0.43
				Fatigue	CRQ fatigue domain, pts	EG: Pre Median 2.9 [2-4.4] Post Median 4.9 [4-5.1], *p* = 0.004; CG: Pre Median 2.5 [2-4.6] Post Median 2.5 [1.9-4.5], *p* = 0.74; ES $_{EG\ vs\ CG}$=0.82
				Mastery	CRQ mastery domain, pts	EG: Pre Median 4.8 [4.1-5.5] Post Median 5.4 [4.6-5.9], *p* = 0.06; CG: Pre Median 3.5 [2.9-5.6] Post Median 4.5 [3-5.4], *p* = 0.64; ES $_{EG\ vs\ CG}$=0.11
Ho *et al*. 2012 Taiwan Prospective RCT	Home-based	n_{Total}= 41 (74±10.3 yrs, 95.1% male) EG: *n* = 20 (73.1±11.2 yrs, 95% male, FEV_1pp: 60.6±18.9) CG: *n* = 21 (75.1±9.6 yrs, 95.2% male, FEV_1pp: 61.2±26.3)	EG: Description: • Pace walking to music: ○ Endurance training walk: ▫ 80% VO_2 peak based on ISWD, increasing gradually each month ▫ Participants should match their walking speed to the tempo of their favourite songs Frequency: 5 days/week, 30 min/day Duration: 12 weeks CG: Description: Usual care Duration: 12 weeks	Dyspnoea	MBS – dyspnoea, pts	EG: Pre 2.2±1.3 Post 0.8±1.1, *p* < 0.001; CG: Pre 1.4±1.6 Post 1.5± 1.6, p>0.05; ES $_{EG\ vs\ CG}$=-1.05
				Exercise capacity	ISWD, m	EG: Pre 243.5±135.4 Post 306±107.3, *p* < 0.001; CG: Pre 237.6±124.4 Post 218.5±119.4, p>0.05; ES $_{EG\ vs\ CG}$=0.79
				Health care utilisation	Emergency visits, no	EG: Mean Pre/Post 0.03±0.2; CG: Mean Pre/Post 0.04±0.3; p $_{EG\ vs\ CG.}$=0.52
					Hospitalisations, no	EG: Mean Pre/Post 0.03±0.2; CG: Mean Pre/Post 0.04±0.2; p $_{EG\ vs\ CG.}$=0.11
					Length of hospitalisations, days	EG: Mean Pre/Post 0.2±1.4; CG: Mean Pre/Post 0.3±1.3; p $_{EG\ vs\ CG.}$=0.64
					Unscheduled clinic visits, no	EG: Mean Pre/Post 0.03±0.2; CG: Mean Pre/Post 0±0; p $_{EG\ vs\ CG.}$=0.001
				HRQoL	SGRQ activity domain, pts	EG: Pre 45.2±14.9 Post 34.5±8.4 *p* = ND; CG: Pre 44.8±20 Post 52.7±24.2 *p* = ND; ES $_{EG\ vs\ CG}$=-1.02
					SGRQ impact domain, pts	EG: Pre 22.7±18.1 Post 10.2±13.5, *p* = ND; CG: Pre 18.4±15.2 Post 21.7±15, *p* = ND; ES $_{EG\ vs\ CG}$=-1.01
					SGRQ symptoms domain, pts	EG: Pre 34.5±20.5 Post 14.5±9.6, *p* = ND; CG: Pre 27.5±21.1 Post 24.7±20.5 *p* = ND; ES $_{EG\ vs\ CG}$=-0.91
					SGRQ total score, pts	EG: Pre 31.6±14.4 Post 18.3±12.7 *p* = ND; CG: Pre 27.9±15.7 Post 31.6±16.3 *p* = ND; ES $_{EG\ vs\ CG}$=-1.13
Mitchell *et al*. 2014 UK RCT	Home-based	n_{Total}= 184 (54.9% male) Comorbidities: Hypertension, Diabetes, Heart Failure, Arthritis EG: *n* = 89 (69±8 yrs, 60.7% male, FEV_1pp: 56±16.8; GOLD 1-7, GOLD 2-51, GOLD 3-22, GOLD 4-9; CG: *n* = 95 (69±10.1yrs, 49.5% male, FEV_1pp: 59.6±17.4; GOLD 1-8, GOLD 2-60, GOLD 3-20, GOLD 4-7)	EG: Description: • SPACE for COPD: ○ Home-based manual: ▫ Education material ○ Exercise programme (walking, resistance training of upper limb and lower limb using free weights); ○ Biweekly phone calls using motivational interview. Frequency: Daily (walking), 3x/week (resistance training) Duration: 6 weeks CG: Description: Usual care Duration: 6 weeks	Anxiety	HADS-A, pts	EG: Mean difference -0.73 [-1.28;-1.17] 95% CI; CG: Mean difference 0.12 [-0.38;0.62]95% CI; p $_{EG\ vs\ CG}$=0.04; ES $_{EG\ vs\ CG}$=-0.24
				COPD-related knowledge	BCKQ, pts	EG: Mean difference 2.79 [0.97;4.6] 95% CI; CG: Mean difference 0.44 [-1.02;1.9] 95% CI; p $_{EG\ vs\ CG}$=0.04; ES $_{EG\ vs\ CG}$=0.20
				Depression	HADS-D, pts	EG: Mean difference -0.5 [-1.03;0.03] 95% CI; CG: Mean difference 0.22 [-0.3;0.75] 95% CI; p $_{EG\ vs\ CG}$=0.1; ES $_{EG\ vs\ CG}$=-0.16
				Dyspnoea	CRQ-D, pts	EG: Mean difference 0.71 [0.45;1] 95% CI; CG: Mean difference 0.72 [0.2;0.65] 95% CI; p $_{EG\ vs\ CG}$=0.049; ES $_{EG\ vs\ CG}$=-0.01

Table 1 (*Continued*)

Study, country and design	Setting	Participants	Intervention	Outcome	Outcome measure	Results
				Emotion	CRQ-emotion domain, pts	EG: Mean difference 0.34 [0.11;0.57] 95% CI; CG: Mean difference -0.07 [-0.27;0.11] 95% CI; $p_{EG\ vs\ CG}$=0.011; $ES_{EG\ vs\ CG}$=0.22
				Exercise capacity	ESWT, s	EG: Mean difference 209.7 [122.3;297.1] 95% CI; CG: Mean difference 92.1 [32.8;151.4] 95% CI; $p_{EG\ vs\ CG}$=0.006; $ES_{EG\ vs\ CG}$=0.30
					ISWD, m	EG: Mean difference 9.4 [-5;24] 95% CI; CG: Mean difference -6.7 [-17.9;4.5] 95% CI; $p_{EG\ vs\ CG}$=0.017; $ES_{EG\ vs\ CG}$=0.08
				Fatigue	CRQ-fatigue domain, pts	EG: Mean difference 0.49 [0.24;0.66] 95% CI; CG: Mean difference 0.01 [-0.21;0.22] 95% CI; $p_{EG\ vs\ CG}$=0.013; $ES_{EG\ vs\ CG}$=0.26
				Mastery	CRQ-mastery domain, pts	EG: Mean difference 0.15 [-0.06;0.37] 95% CI; CG: Mean difference 0.11 [-0.35;0.13] 95% CI; $p_{EG\ vs\ CG}$=0.1; $ES_{EG\ vs\ CG}$=0.02
				Self-efficacy	PRAISE, pts	EG: Mean difference 0.9 [-0.34;2.15] 95% CI; CG: Mean difference -1.08 [-2.67;0.51] 95% CI; $p_{EG\ vs\ CG}$=0.32; $ES_{EG\ vs\ CG}$=0.17
Cameron-Tucker *et al*. 2016 Australia Parallel-group RCT	Home-based	n_{Total}= 65 (69±9 yrs, 45% male) EG: *n* = 35 (68±10 yrs, 46% male; GOLD 1-3, GOLD 2-12, GOLD 3-10, GOLD 4-4) CG: *n* = 30 (70±7 yrs, 43% male; GOLD 1-1, GOLD 2-10, GOLD 3-14, GOLD 4-3)	EG: Description: • Home-based walking program: ○ Walk at a moderate intensity to accumulate 30 minutes daily ○ Personal walking action plan ○ Personal SNAPPS summary ○ Information concerning health behaviours ○ 2 phone calls weekly, with a minimum of 4 during the study, to support the home-walking action plan and any other health behaviour plan. Frequency: All week days, preferably Duration: 8-12 weeks CG: Description: Usual care Frequency: None Duration: 8-12 weeks	Exercise capacity	6MWD, m	EG: Median Pre/Post 0 [41]; CG: Median Pre/Post 12 [39]; $p_{EG\ vs\ CG<0}$=0.01
				Health behaviours	"SNAPPS" snapshot questionnaire, scale 0-60	EG: Median Pre/Post 2 [6]; CG: Median Pre/Post 1 [4]; $p_{EG\ vs\ CG<0}$=0.42
					"SNAPPS" snapshot domains, scale 0-10: Smoking	EG: Median Pre/Post 0 [0]; CG: Median Pre/Post 0 [0]; $p_{EG\ vs\ CG<0}$=0.99
					Nutrition	EG: Median Pre/Post 0 [0]; CG: Median Pre/Post 0 [0]; $p_{EG\ vs\ CG<0}$=0.989
					Alcohol	EG: Median Pre/Post 0 [0]; CG: Median Pre/Post 0 [0]; $p_{EG\ vs\ CG<0}$=0.28
					Physical activity	EG: Median Pre/Post 0 [4]; CG: Median Pre/Post 0 [4]; $p_{EG\ vs\ CG<0}$=0.4
					Psychosocial	EG: Median Pre/Post 0 [0]; CG: Median Pre/Post 0 [0]; $p_{EG\ vs\ CG<0}$=0.737
					Symptom management	EG: Median Pre/Post 0 [1]; CG: Median Pre/Post 0 [2]; $p_{EG\ vs\ CG<0}$=0.85
				HRQoL	CAT, scale 0-40	EG: Median Pre/Post 0 [6]; CG: Median Pre/Post 0 [6]; $p_{EG\ vs\ CG<0}$=0.48
				Physical activity	SNAPPS snapshot self-reported walking, days/week	EG: Median Pre/Post 0 [5]; CG: Median Pre/Post 0 [0]; $p_{EG\ vs\ CG<0}$=0.64
					SNAPPS snapshot self-reported walking, min/day	EG: Median Pre/Post 14 [26]; CG: Median Pre/Post 16 [40]; $p_{EG\ vs\ CG<0}$=0.10
Coultas *et al*. 2016 USA Pragmatic RCT	Home-based	n_{Total}= 305 (70.3±9.5 yrs, 49.5% male) Comorbidities: Hypertension, heart failure, myocardial infarction, peripheral vascular diseases, depression, diabetes, ulcer disease EG:	EG: Description: • Lifestyle PA intervention: ○ Weeks 1-6: self-management education (manual, weekly phone calls) ○ Weeks 7-26: PA self-management (activation phase): ▫ Accumulate, at least, 30 min of moderate PA intensity	Dyspnoea	CRQ-D, pts	EG: Pre 4.48±1.30 Post 4.50±1.39, *p* = 0.82; CG: Pre 4.33±1.35 Post 4.23±1.49, *p* = 0.43; $ES_{EG\ vs\ CG}$=0.09
				Exercise capacity	6MWD, m	EG: Pre 342.8±91.03 Post 343.1±99.81, *p* < 0.001; CG: Pre 337.5±96.37 Post 324.1±107.5, *p* < 0.001; $ES_{EG\ vs\ CG}$=0.14

Table 1 (*Continued*)

Study, country and design	Setting	Participants	Intervention	Outcome	Outcome measure	Results
		n = 149 (70.8±9.5 yrs, 49.7% male; GOLD 2-59, GOLD 3-71, GOLD 4-19; CCI 3.1±2.2 pts) CG: *n* = 156 (69.8±9.5 yrs, 49.4% male; GOLD 2-75, GOLD 3-59, GOLD 4-22; CCI 2.9±1.7 pts)	(4-5 on MBS-dyspnoea), taking 1-2 minutes to recover ▫ Those who not achieve the recommendations were instructed to strive for multiple intervals of moderate PA intensity (weekly workbook activities) ▫ Phone calls once every other week alternated by text messages; ○ Weeks 27-66 (Maintenance phase): ▫ Maintenance of PA lifestyle ▫ 5 reading assignments; ▫ 1 monthly phone call. Frequency: Weeks 7-26, daily Duration: 66 weeks CG: Description: ○ Weeks 1-6: self-management education (manual, weekly phone calls) ○ Usual care (regular FU with their physician) Frequency: NA Duration: 66 weeks			
Chen *et al*. 2017 China Prospective RCT	Home-based	n_{Total}= 47 (67.1±10 yrs, 78.7% male, FEV_1pp: 54.7±24.3) EG: *n* = 25 (69±8.1 yrs, 88% male, FEV_1pp: 54.5±23.6) CG: *n* = 22 (65±11.6 yrs, 68.2% male, FEV_1pp: 54.9±25.6)	EG: Description: • Home-based lower-limb resistance training, through theraband and self-gravity resistance. ○ 6 different sets of exercises: straight-leg lifting, prone hip extension, thigh abduction, posterior muscle group, anterior muscle group and standing calf raise. ○ Best effort, not exceeding MBS-dyspnoea of 5. Frequency: 3 day/week, 20-30 minute each day Duration: 12 weeks CG: Description: Usual care: Frequency: NA Duration: 12 weeks	Exercise capacity	6MWD, m	EG: Median Pre 450 [367.5-504] Post 488.29±92.66, *p* = 0.014; CG: Pre 441.19±98.62 Post 484.2±97.29, *p* = 0.018; $ES_{EG\ vs\ CG}$=0.05
				HRQoL	CAT, pts	EG: Pre 18.48±4.92 Post 15.28±4.7, *p* = 0.002; CG: Pre 16.41±4.88 Post 15.14±4.25, *p* = 0.203; $ES_{EG\ vs\ CG}$=-0.41
				Muscle strength	5STS, s	EG: Pre 7.88±2.09 Post 6.77±1.85, *p* = 0.01; CG: Median Pre 7.62 [6.38-8.64] Post 7.11±1.74, *p* = 0.065; $ES_{EG\ vs\ CG}$=-0.36
					Isokinetic knee extension PT, Nm	EG: Pre 69.1±24.22 Post 83.41±19.44, $p < 0.001$; CG: Median Pre 75.35 [57.13-95.95] Median Post 79.95 [59.43-108.8], *p* = 0.058; $ES_{EG\ vs\ CG}$=0.26
					Isokinetic knee extension PT/BW, Nm/Kg	EG: Pre 0.97±0.4 Post 1.17±0.34, *p* = 0.003; CG: Median Pre 0.95 [0.84-1.23] Median Post 1.1 [0.91-1.49], *p* = 0.05; $ES_{EG\ vs\ CG}$=0.08
					Isometric knee extension PT, Nm	EG: Pre 82.41±28.57 Post 99.5±26.16, $p < 0.001$; CG: Median Pre 82.79 [63.69-110.57] Median Post 94.56 [68.95-132.38], *p* = 0.017; $ES_{EG\ vs\ CG}$=0.12
					Isometric knee extension PT/BW, Nm/Kg	EG: Pre 1.31±0.41 Post 1.57±0.39 *p* = 0.001; CG: Pre 1.42±0.57 Post 1.57±0.58, *p* = 0.055; $ES_{EG\ vs\ CG}$=0.22
Coultas *et al*. 2018 USA Single-site, parallel RCT	Home-based	n_{Total}= 305 (70.3±9.5 yrs, 49.5% male, FEV_1pp: 46.5±13.1) EG: *n* = 149 (70.8±9.5 yrs, 49.7% male, FEV_1pp:45.5±12.6) CG: *n* = 156 (69.8±9.5 yrs, 49.4% male, FEV_1pp: 47.3±13.5)	EG: Description: • Lifestyle PA intervention: ○ Weeks 1-6: self-management education (manual, weekly phone calls) ○ Weeks 7-26: PA self-management (Activation phase): ▫ Accumulate, at least, 30 min of moderate PA intensity (4-5 on MBS-dyspnoea), taking 1-2 minutes to recover ▫ Those who not achieve the recommendations were instructed to strive for multiple intervals of moderate PA intensity (weekly workbook activities)	Lung-related health care utilisation	Prevalence, at 18 months	EG: 24% [17;32] 95% CI; CG: 34% [28;43] 95% CI
					Risk ratio, at 18 months	EG: 0.68 (95% CI 0.47;1.00); CG: reference
					Rate ratio, at 18 months	EG: 0.64 (95% CI 0.42;0.99); CG: reference
				Physical activity	RAPA, Sedentary (%)	Mean absolute difference$_{EG\ vs\ CG}$ (%) -10.6 [-20.4;-0.8] 95% CI
					RAPA, Underactive (%)	Mean absolute difference$_{EG\ vs\ CG}$ (%) -5.2 [-14.4;3.9] 95% CI
					RAPA, Active (%)	

Table 1 (*Continued*)

Study, country and design	Setting	Participants	Intervention	Outcome	Outcome measure	Results
			▫ Phone calls once every other week alternated by text messages; ▫ Weeks 27-66 (Maintenance phase): ▫ Maintenance of PA lifestyle ▫ 5 reading assignments; ▫ 1 monthly phone call. Frequency: Weeks 7-26, daily Duration: 66 weeks CG: Description: ○ Weeks 1-6: self-management education (manual, weekly phone calls) ○ Usual care (regular FU with their physician) Frequency: NA Duration: 66 weeks			Mean absolute difference$_{EG\ vs\ CG}$ (%) 15.8 [4.0;27.7] 95% CI
Lin *et al*. 2019 Taiwan RCT	Home-based	n_{Total}= 78 (95.2% male) EG: *n* = 38 (70.92±7.89 yrs) CG: *n* = 40 (73.5±8.31 yrs)	EG: Description: • Breathing-based walking: ○ Combination of breathing, mediation and walking ○ One-to-one breathing-based walking guidance by the researcher until they practice correctly. ○ Handbook with instructions, pictures and a diary to practice breathing-based walking in daily life; ○ Home diary, progress the exercise prescription and deliver self-management training. Frequency: 30 min/day, 5x/week. Duration: 2 months CG: Description: Usual care Frequency: None Duration: 2 months	Anxiety	HADS-A, pts	EG: Pre 3.03 Post 1.16, $p < 0.05$; CG: Pre 1.63 Post 2.45, $p < 0.05$; p-value$_{EG\ vs\ CG}$<0.05
				Depression	HADS-D, pts	EG: Pre 7.0 Post 2.37, $p < 0.05$; CG: Pre 5.71 Post 5.90, p-value NS; p-value$_{EG\ vs\ CG}$<0.05
				Dyspnoea	mMRC, pts	EG: Pre 1.16 Post 0.89, $p < 0.05$; CG: Pre 1.32 Post 1.35, p-value NS; p-value$_{EG\ vs\ CG}$<0.05
				HRQoL	CAT, pts	EG: Pre 11.63 Post 5.11, $p < 0.05$; CG: Pre 9.82 Post 11.33, p-value NS; p-value$_{EG\ vs\ CG}$<0.05
Lahham *et al*. 2020 Australia RCT	Home-based	n_{Total}= 58 (68±9 yrs, 58.6% male, FEV_1pp: 90±7) EG: *n* = 29 (68±9 yrs 58.6% male, FEV_1pp: 90±8) CG: *n* = 29 (67±10 yrs 58.6% male, FEV_1pp: 92±7)	EG: Description: • Home-based PR: ○ Endurance training: ▫ Initial walking speed: 80% of the speed walked during a 6-minute walk test (6MWT). The distance walked was recorded using a pedometer. ○ Strength training ▫ Resistance training for the arms and legs used equipment available at home (e.g. home stairs for step ups and sealed water bottles as weights). • Initial exercise prescription was established during a home visit by a physiotherapist to ensure safety and understanding of the exercise program. • Participants were encouraged to exercise for 30 min, 5x/week and to record the completion of this activity in a home diary. • 7 phone calls (1/week) to review the home diary, progress the exercise prescription and deliver self-management training. Duration: 8 weeks	Dyspnoea	mMRC, pts	EG: Mean difference -0.3 [-0.7;0.1] 95% CI; CG: Mean difference -0.1 [-0.5;0.3] 95% CI
					CRQ-D, pts	EG: Mean difference 2.6 [-0.9;5.8] 95% CI; CG: Mean difference 2.2 [-1.1;5.6] 95% CI; ES $_{EG\ vs\ CG}$=0.03
				Emotional function	CRQ-emotional function domain, pts	EG: Mean difference 2.6 [-1.6;6.9] 95% CI; CG: Mean difference -0.6 [-4.8;5.6] 95% CI; ES $_{EG\ vs\ CG}$=0.21
				Exercise capacity	6MWD, m	EG: Mean difference 15 [-43;76] 95% CI; CG: Mean difference 29 [-28;87] 95% CI; ES $_{EG\ vs\ CG}$=-0.07
				Fatigue	CRQ fatigue domain, pts	EG: Mean difference 3.8 [1.0;6.5] 95% CI; CG: Mean difference 1.0 [-1.7;3.7] 95% CI; ES $_{EG\ vs\ CG}$=0.28
				HRQoL	CRQ total, points	EG: Mean difference 11.3 [1.8;20.8] 95% CI; CG: Mean difference 4.6 [-4.8;14] 95% CI; ES $_{EG\ vs\ CG}$=0.19
				Mastery	CRQ mastery domain, pts	EG: Mean difference 2.3 [-0.2;4.8] 95% CI; CG: Mean difference 2.0 [-0.5;4.5] 95% CI; ES $_{EG\ vs\ CG}$=0.03
				Physical activity	METs/day	

Table 1 (*Continued*)

Study, country and design	Setting	Participants	Intervention	Outcome	Outcome measure	Results
			CG: Description: Usual care (counselling to keep active and to follow medication) Frequency: 8 weekly phone calls to control for attention- Duration: 8 weeks			EG: Mean difference 0.1 [-0.1;0.2] 95% CI; CG: Mean difference 0 [-0.2;0.2] 95% CI; ES $_{EG\ vs\ CG}$=0.05
					MVPA bouts, no/day	EG: Mean difference -0.3 [-1.6;1.0] 95% CI; CG: Mean difference -0.6 [-1.9;0.7] 95% CI; ES $_{EG\ vs\ CG}$=0.07
					MVPA time, min/day	EG: Mean difference -5 [-301;290] 95% CI; CG: Mean difference -211 [-497;76] 95% CI; ES $_{EG\ vs\ CG}$=0.34
					Sedentary bouts, no/day	EG: Mean difference -0.6 [-1.6;0.4] 95% CI; CG: Mean difference 0.2 [-0.8;1.1] 95% CI; ES $_{EG\ vs\ CG}$= -0.31
					Sedentary time, min/day	EG: Mean difference 32 [-63;128] 95% CI; CG: Mean difference 8 [-84;101] 95% CI; ES $_{EG\ vs\ CG}$= 0.08
					Steps/day, no	EG: Mean difference 303 [-1607;2215] 95% CI; CG: Mean difference -106 [-1962;1749] 95% CI; ES $_{EG\ vs\ CG}$= 0.06
					Time spent in MVPA bouts, min/day	EG: Mean difference -4 [-29;22] 95% CI; CG: Mean difference -13 [-38;12] 95% CI; ES $_{EG\ vs\ CG}$= 0.11
					Time spent in sedentary bouts, min/day	EG: Mean difference 4 [-55;63] 95% CI; CG: Mean difference - 21 [-37;78] 95% CI; ES $_{EG\ vs\ CG}$= 0.13
					Total EE	EG: Mean difference -4 [-1425;1418] 95% CI; CG: Mean difference 82 [-1299;1463] 95% CI; ES $_{EG\ vs\ CG}$= -0.02

5STS, five times sit-to-stand test; 6MWD, 6-minute walking distance; 6MWT, 6-minute walk test; 12MWD, 12-minute walking distance; 95% CI, 95% of confidence intervals; %, percentage; ADLs, activities of daily living; BCKQ, Bristol COPD Knowledge Questionnaire; bpm, beats per minute; CAT, COPD assessment test; CCI, Charlson Comorbidity Index; CG, control group; cpm, cycles per minute; CRQ, Chronic Respiratory Questionnaire; CRQ-D, CRQ — dyspnoea domain; EE, energy expenditure; EG, experimental group; ES, effect size; ESWT, endurance shuttle walk test; FEV1pp, forced expiratory volume in 1 second — percentage predicted; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS — anxiety; HADS-D, HADS — depression; HR_{ex}, heart rate during the greatest work load that a subject could maintain for 1 minute; HRQoL, health-related quality of life; HR_{st}, heart rate during the greatest work load that was common to both the initial and follow-up exercise in any one subject; ISWD, incremental shuttle walk distance; kg, kilograms; l/min, litres per minute; m, meters; MBS, modified Borg scale; min/day; minutes per day; mm, millimetres; mmol/min, millimole per minute; mMRC, modified British Medical Research Council; MVPA, moderate-vigorous physical activity; NA, Not applicable; ND, Not described; Nm, Newton meters; no, number; PA, physical activity; PR, pulmonary rehabilitation; PRAISE, Pulmonary Rehabilitation Adapted Index of Self-Efficacy; PT, peak torque; pts, points; PT/BW, peak torque/body weight; pts, points; RAPA, Rapid Assessment of Physical Activity questionnaire; R_{ex}, respiratory exchange ratio during the greatest work load that a subject could maintain for 1 minute; RCT, randomised controlled trial; s, seconds; SF-36, 36-item short form survey; SGRQ, St. George's respiratory questionnaire; TDI, Transition Dyspnea Index; UK, United Kingdom; W, Watts; WL_{ex}, work load during the greatest work load that a subject could maintain for 1 minute; VE_{ex}, minute ventilation during the greatest work load that a subject could maintain for 1 minute; VO_{2ex}, oxygen uptake during the greatest work load that a subject could maintain for 1 minute.

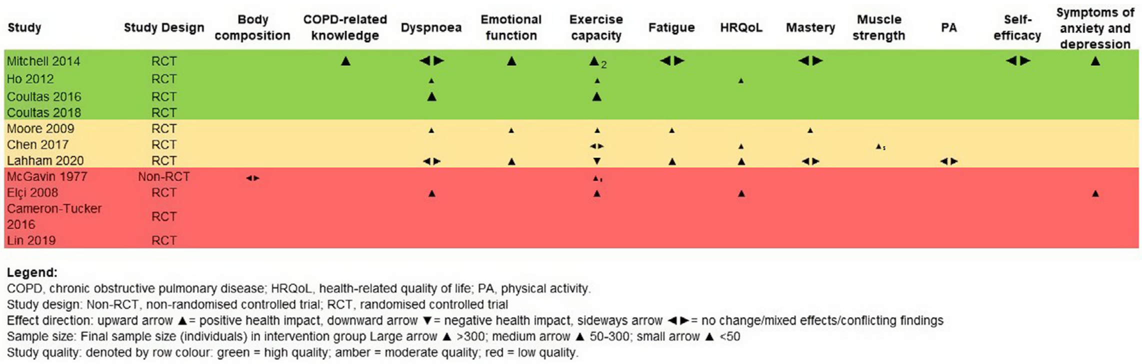

Fig. 2. Effect direction plot of unsupervised physical activity interventions in people with chronic obstructive pulmonary disease (n = 11).

not apparent (I^2=0%) however, the intervention effect was heavily weighted towards one trial[34] (Fig. 3).

Exercise capacity

Exercise capacity was measured in nine studies.[31,34-40,42] Most common measures used were the 6-minute walk distance (6MWD)[31,34,37,39,40] and the incremental shuttle walk distance (ISWD).[35,36,38] The 12-minute walk distance,[42] the heart rate,[42] the respiratory exchange ratio,[42] the minute ventilation,[42] the oxygen uptake,[42] the work load,[42] the stride[42] and the endurance shuttle walk test[36] were also reported. A positive effect on exercise capacity was observed, with six[34-36,38,40,42] of the eight studies[31,34-38,40,42] favouring the EG (75%, 95% CI 35-97%) (Fig. 2). These positive effects were also observed in meta-analysis of the 6MWD[31,34,37,40] (MD=13.70, 95% CI 3.58-23.83) and ISWD[35,36,38] (MD=58.59, 95% CI 5.79-111.39). However, a substantial heterogeneity was observed in both meta-analysis (I^2=98%, $p < 0.01$; I^2=86%, $p < 0.01$; respectively) (Fig. 3).

Physical activity

Physical activity was assessed in three studies,[31,33,39] using METs/day,[31] moderate-vigorous PA (MVPA) bouts and time,[31] Rapid Assessment of Physical Activity questionnaire,[33] "SNAPPS" (Smoking, Nutrition, Alcohol, Physical activity, Psychosocial wellbeing and symptom management) snapshot

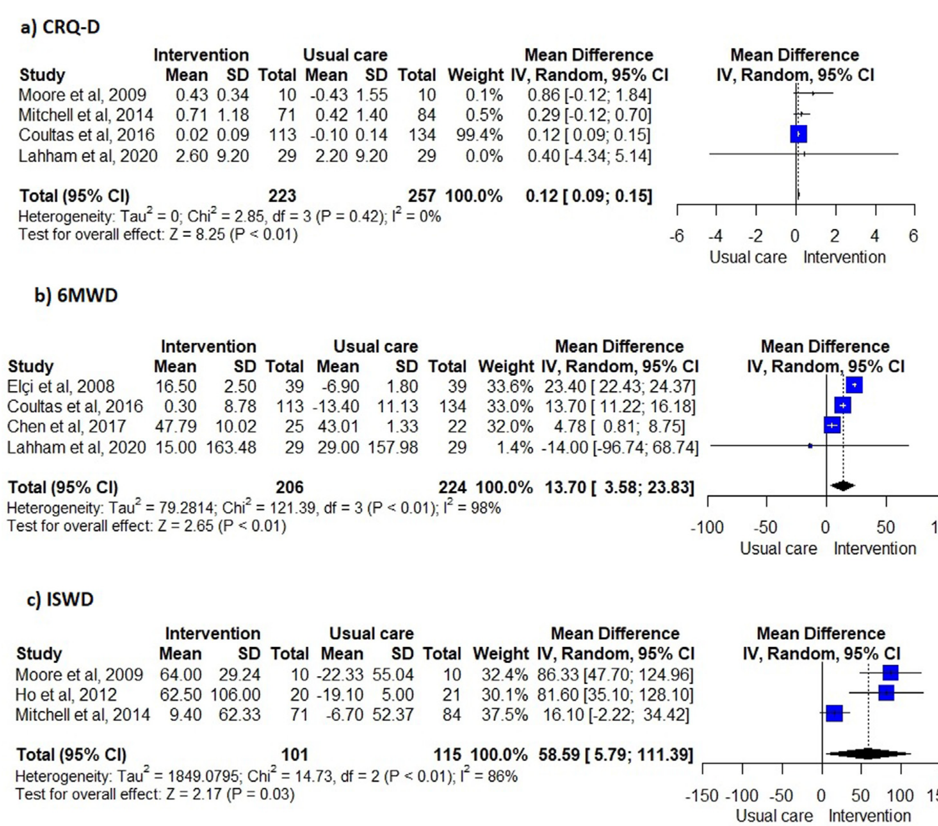

Fig. 3. Forest plots illustrating the effect of unsupervised PA interventions on: a) Chronic respiratory questionnaire − dyspnea domain (CRQ-D), b) 6-minute walk distance (6MWD), and c) incremental shuttle walk distance (ISWD), in comparison to usual care.

questionnaire self-reported walking,[39] sedentary bouts and time,[31] steps/day,[31] time spent in MVPA[31] and in sedentary bouts[31] and total energy expenditure.[31] The direction of effect was only evaluated in one study,[31] however a consistent direction of the effect was not determined.

Secondary outcomes

Body composition

Body composition was assessed in one study using weight and no differences were observed between groups.[42]

Emotional function

Emotional function was assessed with the CRQ-emotional function domain, in three studies[31,36,38] and positive effects were observed, favouring the EG (100%, 95% CI 29-100%).

Fatigue

Fatigue was assessed with the CRQ-fatigue domain in three studies,[31,36,38] and a positive effect was found in two[31,38] of these studies, favouring the EG (67%, 95% CI 9-99%) (Fig. 2).

Health behaviours

Health behaviours were evaluated using the SNAPPS snapshot questionnaire, total score and per domains, in one study.[39] Direction of the effect was not possible to be determined and no significant differences were observed between groups.[39]

Healthcare utilisation

Healthcare utilisation was assessed in two studies.[33,35] One used the number of emergency visits, hospitalisations, unscheduled clinic visits and length of hospitalisations[35] and the other the lung-related health care utilisation.[33] No differences were observed between groups, although lung-related health care utilisation was lower in the EG after the intervention (risk ratio=0.68, 95% CI 0.47-1 and rate ratio=0.64, 95% CI 0.42-0.99).[33]

Health-related quality of life

Health-related quality of life was evaluated in six studies,[31,35,37,39-41] using the 36-item short form survey,[40] the COPD assessment test,[37,39,41] the CRQ total score[31] and the St. George's Respiratory Questionnaire.[35,40] Direction of effect was only possible to be determined in four studies.[31,35,37,40] Unsupervised PA interventions had a positive effect on HRQoL, favouring the EG (100%, 95% CI 40-100%) (Fig. 2).

Mastery

Mastery was assessed with the CRQ-mastery domain, in three studies[31,36,38] and no effects were observed, with only one study [38] favouring the EG (33%, 95% IC 1-96%) (Fig. 2).

Muscle strength

Lower-limb muscle strength was evaluated in one study,[37] with the five times sit-to-stand test, isokinetic and isometric peak torque and adjusted for body weight. Improvements were observed in all outcome measures (ES= -0.36 to 0.26) for the EG after the intervention.[37]

Self-efficacy

Self-efficacy was assessed in one study[36] with the Pulmonary Rehabilitation Adapted Index of Self-Efficacy and no differences were observed between groups.

Symptoms of anxiety and depression

Symptoms of anxiety and depression were measured in three studies[36,40,41] with the Hospital Anxiety and Depression Scale. Positive effects were observed, with two[36,40] studies favouring the EG (100%, 95% IC 16-100%) (Fig. 2).

Adverse events

Four studies[33,34,37,41] explored the adverse events of unsupervised PA interventions. Two[33,34] of these studies found that 63% (n = 192) of participants had no adverse events and 37% (n = 106) had, at least, one adverse event. The most common adverse event was acute exacerbation of COPD, with a twice higher prevalence in the CG (15%, n = 47) than in the EG (9%, n = 28) ($p < 0.01$).[33,34]

Dropouts and adherence to interventions

Nine studies[33-39,41,42] reported dropouts, ranging between 7.1%[41] to 38.5%.[39] Reasons to dropout included: abrupt dizziness,[37] acute exacerbation of COPD,[35,38] cataract surgery,[37] comorbidities,[36] death,[42] failure to keep appointments,[39] intercurrent depressive illness,[42] knee pain,[38] lack of enthusiasm,[42] lost to follow-up,[36,38,41] non-COPD related hospital admission,[35,37] poor health,[39,41] social reasons,[36] programme was too easy or not so serious,[36,37] time constraints,[35,39] travel issues,[37,39] too busy to participate [41] and work commitement.[36]

Only four studies reported adherence to the intervention,[31,35,37,39] which varied between limited[39] to 93%.[31]

Discussion

This systematic review provided an overview of the unsupervised PA interventions implemented in people with COPD and showed that these interventions are effective in improving dyspnoea and exercise capacity.

Unsupervised PA interventions were conducted at home,[31,33-42] in most cases lasted 8-12 weeks[31,35,37,39-42] and were performed daily.[31,33-36,39,41,42] Aerobic training was the most common component,[31,35,36,38,39,41,42] namely, walking, however strength training [31,36-38,40] was also included and done in isolation[33-35,37,39,41,42] or with others.[31,36,38,40] These findings are of special importance, since people with COPD spend most of their day in a sedentary behaviour and at home.[2,43] Therefore, conducting these interventions in patients' home-environment, integrated into their daily routines (e.g., aerobic training through walking[31,35,39] or home stairs[31]) and using everyday resources (e.g., water bottles as weights[31]), may be a person-centred and feasible approach to increase participation in PA for people with COPD. Therefore, such interventions should be considered for those people with COPD who cannot or do not want to be involved in supervised PA interventions, either by limited access or disease restrictions, or as a strategy for maintaining PA levels (e.g., after pulmonary rehabilitation), with regular assessments and/or phone calls for monitoring the individuals' progress.[44]

Furthermore, these interventions were effective in improving dyspnoea and exercise capacity in people with COPD. Nevertheless, some caution is needed when interpreting the effects of unsupervised PA interventions in dyspnoea for several reasons. First, the meta-analysis for the CRQ-D was greatly weighted by one large study,[34] with other studies showing no effects. This might have led to an underestimation of the effect. Also, the observed improvement (0.12 points) in the CRQ-D was statistically significant but not clinically relevant, based on the minimal clinically important difference (MCID) of 0.5 points of CRQ-D.[45] Therefore, further studies with higher sample sizes assessing the effects of unsupervised PA interventions in dyspnea should be conducted, since this outcome is a cardinal symptom for people with COPD.[1] In terms of exercise capacity, unsupervised PA interventions lead to statistical improvements under the MCID (25m[46]) in the 6MWT, but statistical and meaningful improvements above the MCID (47.5m[46]) in the ISWT. Heterogeneity of the interventions might explain this finding. Interventions included in the 6MWD meta-analysis were heterogeneous, whilst all the interventions included in the ISWD meta-analysis were walking-based. Integrating a walking component into the unsupervised PA interventions seems therefore important to improve exercise capacity clinically.

Similar results, for dyspnoea and exercise capacity (measured with 6MWD), were found recently in a systematic review of unsupervised exercise-based interventions in this population.[17] This is of special importance for clinical practice and research communities, which have been increasingly focusing on the promotion of PA and can now see benefits in these outcomes also obtained with unsupervised PA interventions integrating activities of individuals' daily life.[8,47]

We were unable to draw conclusions using the effect direction plot for PA. Indeed, it is surprising that PA, a strong predictor of COPD progression,[48] was just assessed in three studies. Thus, studies assessing the effects of unsupervised PA interventions in PA levels of individuals with COPD are urgently needed.

Our findings also showed that unsupervised PA interventions were effective in improving emotional function, fatigue, HRQoL, lung-related healthcare utilisation, muscle strength, self-efficacy and symptoms of anxiety and depression. Prior studies have shown that these parameters play a role in the disease management and progression[1,49-53] however, evidence is still scarce. Given the social, economic and health burden of COPD worldwide,[1] further research focusing on the effects of unsupervised PA interventions on these outcomes is needed.

Overall, unsupervised PA interventions were shown to be safe, with no or minor adverse events being reported. Most of the included studies reported a high adherence to unsupervised PA interventions. Compared with supervised PA interventions, unsupervised PA interventions showed a higher rate of adherence.[54] These interventions are adapted to each person's context and needs, are low cost and have broad applicability, being easy to perform at home, which might explain the high levels of adherence.[15] Future research should explore important variables such as GOLD grades and groups and its influence on the results obtained, as well as the long-term effects of such interventions.

Limitations

This systematic review has several limitations that need to be acknowledged. Firstly, the small number of existing studies; their large diversity of designs, outcomes and outcome measures; lack of consensus on the definition of unsupervised PA; and, the high heterogeneity observed in the meta-analysis, limited our conclusions. Nevertheless, a synthesis of the results, using the effect direction plot was computed which provided a thorough synthesis of data. Secondly, the imbalance between participants, i.e., more males than females and moderate to severe participants, limited the generalisation of results. Further studies including more people with COPD in mild and very severe grades and females should be conducted. Thirdly, our search was limited to studies published in English, Portuguese, Spanish or French included in databases. Additional studies may exist in the unpublished grey literature and may have been missed. A thorough search in different databases and scanning the references of key articles and systematic reviews were however conducted to minimise this limitation. Finally, approximately one third of the included studies were of low quality, nevertheless most studies presented moderate to high quality.

Conclusions

This systematic review showed that unsupervised PA interventions improved dyspnoea (statistically but not clinically) and exercise capacity in people with COPD. Overall, these interventions seem to be safe and present a high adherence rate. The inclusion of a walking component for 8-12 weeks in the unsupervised PA interventions is recommended to optimise results. Unsupervised PA interventions should be considered for people with COPD who cannot or do not want to engage in supervised PA interventions or as a maintenance strategy of PA levels. Future studies with robust methodologies should now be conducted to strengthen these promising results with potential to optimise COPD management.

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Disclosure of interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.01.007.

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LETTER TO THE EDITOR

Pulmonary rehabilitation: Publication rate of presentations to international congresses: Are the abstracts being published as journal articles?

Publication Rate on Pulmonary Rehabilitation

Dear Editor,

Research project findings have been disclosed more as conference abstracts than as articles in scientific journals.[1,2] However, conference abstracts aim beyond scientific dissemination to receive peer feedback so that the preparation of the complete manuscript can be refined and published in qualified scientific journals.[3] Publication as an article in a conference abstract appears to be based on the direction of the study results, leading to publication bias.[4] To prevent bias, researchers should be encouraged to publish their results in peer-reviewed scientific journals.[5]

The two largest scientific congresses in the field of pulmonology are held annually: the European Respiratory Society International Congress (ERSc), with approximately 4,000 abstracts accepted annually, and the American Thoracic Society International Conference (ATSc), with almost 7,000 abstracts accepted annually (Fig. 1). In pulmonology, pulmonary rehabilitation is a multidisciplinary field of knowledge that includes physicians and their respiratory allies.

This study aimed to evaluate the publication rate of scientific abstracts presented within the scope of pulmonary rehabilitation and related topics in ERSc and ATSc. Searches for abstracts were conducted during the electronic proceedings of the two conferences held from 2016 to 2018. The search was initially based on titles of abstracts that contained terms within the scope of pulmonary rehabilitation, such as "physical activity"; "physical training"; "exercise"; "exercise training"; "walking"; "physiotherapy"; "physical therapy"; "pulmonary rehabilitation"; "cardiopulmonary rehabilitation", but not limited to these words. The focus was exclusively on physical exercise, rather than mental or other forms of exercise. Abstracts pertaining to stress testing or physical exercise training were considered relevant. Education and behavioral modifications were considered only if they were related to physical activity or pulmonary rehabilitation. Conversely, educational topics that specifically targeted medication adherence or medical education were deemed ineligible. After screening based on the aforementioned keywords, the full text of the abstracts was read, and studies involving animals, *in vitro* or not related to pulmonary rehabilitation were excluded (Fig. 1). The remaining abstracts were categorized by presentation type: thematic posters, poster discussions, or oral presentations. The number of authors and country of origin of the corresponding author was recorded. We analyzed the number of abstracts published as full articles until five years after the abstract presentation.

After the abstract screening, full-text articles were searched in the Google Scholar and Medline databases. When a journal article was not found, up to three e-mails were sent to the authors to determine the publication status and obtain a copy of the article if it was published. When the journal article related to the presented abstract was not found, and no response from the author was obtained, it was classified as an "uncertain publication." If the abstract findings were published in two or more articles, only the article with the highest impact factor (IF) was considered. The following data was extracted from abstracts published as journal articles: name of the journal, IF, data on study design, affiliation, and whether the study result was statistically significant or with a positive direction from their primary outcome analysis.

A total of 964 potentially eligible abstracts were identified, of which 200 (20.7%) were excluded as they were not related to pulmonary rehabilitation, in *vitro,* or animal studies. Seven hundred sixty-four abstracts were analyzed for journal publication rates, with most being thematic posters 419 (54.8%) followed by posters, 276 (36.1%), and oral presentations 69 (9.0%). The median number of authors was six, and most were from the US 143 (18.7%). At the ERSc, the UK had the highest number of presentations 75 (16.4 %), while the US had the highest number of presentations at the ATSc.

The authors responded to e-mails regarding full-text publications after presenting the abstracts in 41.9% of the contacts. Among the authors who responded, the reasons for not publishing the studies in an article format were: not having funding; author lack of time; abandonment by the first author; interruption of research carried out by their students; lack of budget; authors assumed that their findings were not relevant; authors started another more interesting project; retirement; lack of control group; small sample;

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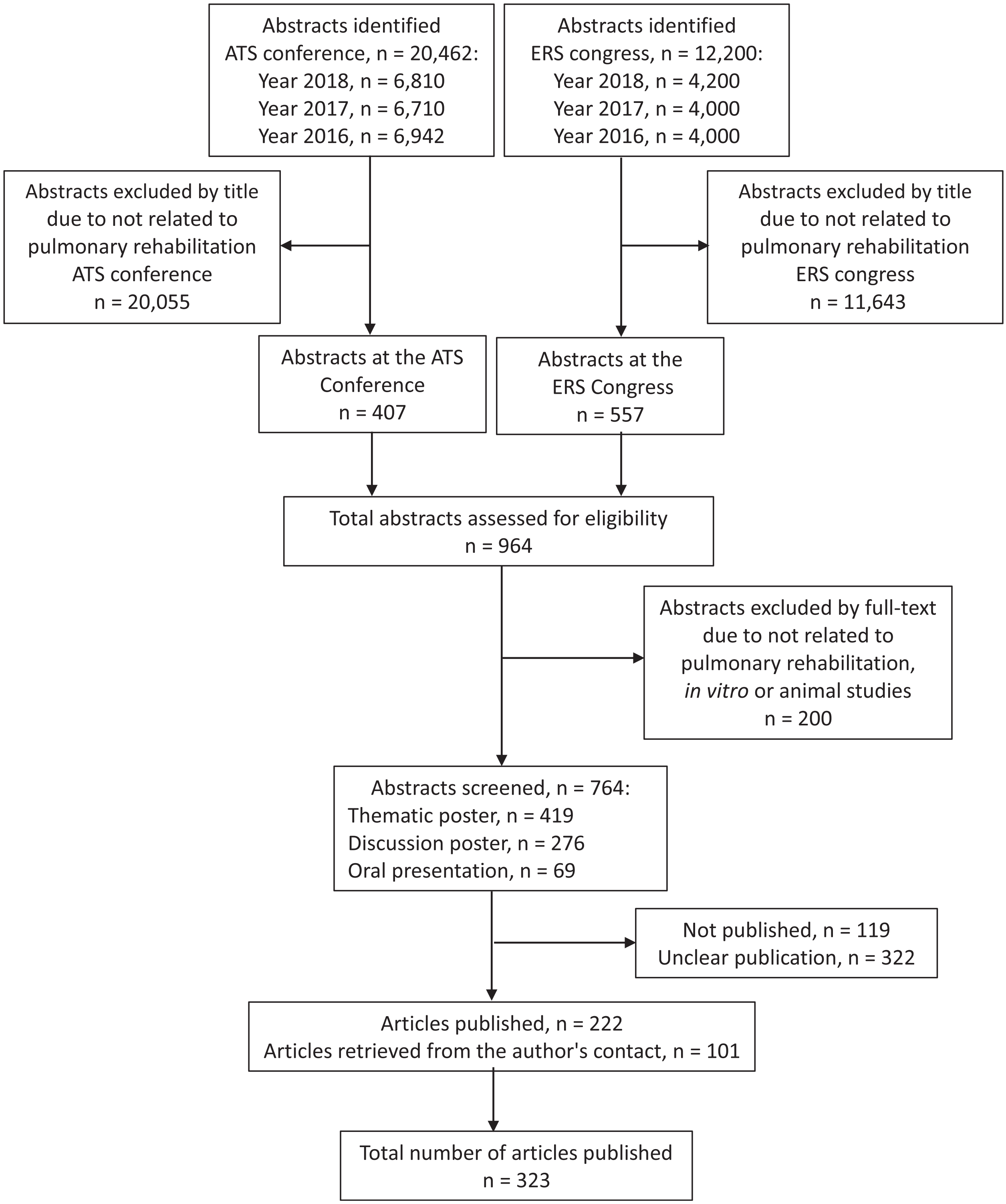

Figure. 1 Flow diagram of search strategy.

received a negative peer review and were rewriting to submit to another journal, and published as a book chapter or thesis. In 22 (4.0%) abstracts, the author's e-mail contacts could not be found. In 322 (42%) abstracts, no journal article was found related to the study and no response was obtained from the author, which was classified as "uncertain publication".

A total of 323 published articles related to pulmonary rehabilitation abstracts were identified, resulting in a publication rate of 42.3%. A flowchart of the study is presented in Fig. 1. Categorization by mode of presentation proportionally showed that 46 (66.7%) oral presentations, 128 (46.4%) poster discussions, and 149 (35.5%) thematic posters were published as articles. The median IF of the journals is 3.4

(2.6–6.4). Significant and positive results were reported in 253 (78.3%) of the identified articles.

The publication rate of 42.3% corroborates the publication rate variation for biomedical research described in the literature, ranging from 19 to 60%. Articles related to abstracts previously presented as oral presentations were the most published (66.7%). These results corroborate those of previous investigations in which oral presentations were published more often than posters.[2] In this study, researchers found that abstracts with statistically significant findings were more likely to be published than those with non-significant results. This observation supports the notion of potential publication bias in the literature. This is probably due to the strict selection criteria for oral presentations and dialogue between the authors and panelists.[6]

Although the searches were restricted to only two databases, this limitation was overcome by contacting authors who had the opportunity to inform the publication status of their abstracts.

This study found that only two of the five abstracts presented at scientific meetings were published in journals. Efforts must be made to increase the journal publication rate of studies presented at conferences. One suggestion is continuing education, which can be offered through various workshops during scientific events, aiming to improve editorial skills, especially for young researchers. Another strategy would be to encourage multicenter studies involving the collaboration of young researchers.

In conclusion, over half of the abstracts on pulmonary rehabilitation presented at the ERSc and ATSc from 2016 to 2018 remain unpublished. Strategies for improving the conversion of abstracts into journal articles are required.

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Authors' contribution

C.M., C.C.O., A.J., and T.M.D.O. participated in the conception and design of the study, data analysis, and interpretation, critical review of relevant intellectual content, and final approval of the manuscript to be submitted. G.S.G., E.F.T., D.F.S., and M.J.X.R. were involved in data acquisition, article writing, and final approval of the submitted version.

Conflicts of interest

All authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Coffee shops, a hub for TB clusters?

Stone quarry workers account for about 30% of the tuberculosis (TB) cases[1] in *Penafiel* and Marco de *Canaveses*, two municipalities in the northern region of Portugal that have the highest TB notification rates of the country.[2]

In high incidence areas, only a small number of reliable epidemiologically linked cases are identified using conventional contact investigations.[3] Whole-genome sequencing (WGS) is increasingly used to study transmission dynamics.

We conducted a retrospective study including all notified cases of TB in stone quarry workers from the municipalities of *Penafiel* and *Marco de Canaveses* from 1 January 2012 to 31 December 2019. First, we analysed classical epidemiological data from the stone quarry workers with TB diagnosed during 2012—2014. Secondly, all the available strains of *M. tuberculosis* isolated from 2015 to 2019 were sent for WGS in the National Reference Laboratory using a single nucleotide polymorphisms (SNP)-based approach.[4] Then we compared clustered and non-clustered cases using the Chi-squared test or Fisher's exact test.

According to local public health services' records, 11 stone quarry workers with confirmed TB were notified between 2012 and 2014. Work-related exposure led to universal screening initiatives in workplaces: 135 co-workers of the same companies were screened. TB disease screening included chest-X ray and symptom questionnaire (96.3% adherence; one case found in 130 screened) and TB infection screening was performed through Tuberculin Skin Test (36.3% adherence; 30 cases found in 49 screened; two initiated preventive treatment). During 2016—2017, eight new cases were found among those previously screened individuals, i.e., 5.9% of the co-workers developed TB disease in a period of three years. The results of their screening were not screened (one), incompletely screened (four), not treated TB infection (two), previous negative screen (one). TB infection screening was not performed in more than 60% of the contacts, which may have contributed to the high proportion of screened workers that developed TB. However, we hypothesize whether this could reflect that transmission occurred in other settings besides workplaces (namely social or familiar).

A total of 76 current or former stone quarry workers diagnosed with TB in the 2015—2019 period were found, i.e., 18.8% of the notified cases of TB in 2015—2019.[2] Three of those were excluded (not confirmed TB). Of the 73 included cases, 35 (47.9%) had available specimens. Genotyped and non-genotyped cases of TB had similar characteristics regarding the considered risk factors (Table 1).

All the cases were male, born in Portugal, with an average age of 50-years-old (median 51, interquartile range (IQR) 43—56), and had pulmonary TB. The main risk factors included tobacco use, silicosis and alcohol dependence (Table 1). No cases of HIV were found (six had not registered HIV status). Two of the genotyped TB strains were polyresistant to isoniazid and streptomycin, and 33 were susceptible to all first line drugs. The delay between onset of symptoms and diagnosis was on average of 78 days (median 63 days; IQR: 34.0—88.0).

A high molecular diversity of *M. tuberculosis* was found (Fig. 1). Clusters included cases from 2015 to 2019, suggesting ongoing active transmission. As we did not genotype all the strains of M. tuberculosis from the community, we could be missing the remaining strains from other clusters.

Median (IQR) time between successive cases in clustered cases was 205 (95.5—308.3) days. Clustered cases were more prone to have alcohol dependence and smoking habits, which could be associated with attending coffee shops regularly (Table 1). Likewise, being professionally inactive, having a previous episode of TB and a positive sputum smear were also more common among clustered cases. As positive sputum smear indicates higher infectiousness, that is expected. In a study that analysed MIRU-VNTR molecular clustering data from 7458 patients, cases in large molecular clusters were also more likely to have multiple social risk factors.[5]

Using a logistic regression analysis, none of the transmission settings was a significant predictor of clusters but attending public places was the better predictor (OR 1.8, 95% CI 0.254—12.449). Social contacts in community public places such as coffee shops seem to contribute to the maintenance of ongoing active transmission of TB. In other study, workers that converted from IGRA negative to positive had no co-workers with active TB and were not identified as close contacts, suggesting they could have been infected in social settings.[6]

In our opinion, the high molecular diversity found in a small sample of stone quarry workers cases suggests a complex scenario of transmission between them and the high-risk communities in which they live and work. Stone quarry workers are not only more prone to transmit TB to other people of the community; they are also more susceptible to

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Table 1 Characteristics of clustered and non-clustered TB cases.

	Non-genotyped cases (*n* = 38)	Genotyped cases (*n* = 35)	*p* value	Not clustered (*n* = 7)	Clustered cases (*n* = 28)	*p* value
Age groups years			*p* = 0.706			*p* = 0.517
21–44	8 (21.1%)	9 (25.7%)		1 (14.3%)	8 (28.6%)	
45–64	26 (68.4%)	24 (68.6%)		6 (85.7%)	18 (64.3%)	
≥65	4 (10.5%)	2 (5.7%)		0	2 (7.1%)	
Employment status			*p* = 0.284			*p* = 0.166
Active	25 (65.8%)	27 (77.1%)		7 (100.0%)	20 (71.4%)	
Inactive	13 (34.2%)	8 (22.9%)		0	8 (28.6%)	
Silicosis						*p* = 1.000
Yes		18 (51.4%)		4 (57.1%)	15 (53.6%)	
No		16 (45.7%)		3 (42.9%)	13 (46.4%)	
Alcohol dependence						*p* = 0.220
Yes		13 (37.1%)		1 (14.3%)	12 (42.9%)	
No		22 (62.9%)		6 (85.7%)	16 (57.1%)	
Tobacco use						p=0.652
Yes		24 (68.6%)		4 (57.1%)	20 (71.4%)	
No		11 (31.4%)		3 (42.9%)	8 (28.6%)	
Previous treatment of TB						*p* = 0.084
Yes		10 (28.6%)		0	10 (35.7%)	
No		25 (71.4%)		7 (100.0%)	18 (64.3%)	
Sputum smear						*p* = 0.155
Positive		25 (71.4%)		3 (42.9%)	22 (78.6%)	
Negative		10 (28.6%)		4 (57.1%)	6 (21.4%)	
Number of days between symptoms and diagnosis						*p* = 0.935
3–30		6 (17.1%)		1 (14.2%)	5 (17.9%)	
31–65		13 (37.1%)		3 (42.9%)	10 (35.7%)	
≥66		16 (45.7%)		3 (42.9%)	13 (46.4%)	
Attended public places			*p* = 0.683			*p* = 0.401
Yes	21 (55.3%)	21 (60.0%)		3 (42.9%)	18 (64.3%)	
No	17 (44.7%)	14 (40.0%)		4 (57.1%)	10 (35.7%)	
Close contact with relatives with TB			*p* = 0.468			*p* = 1.000
Yes	3 (7.9%)	5 (14.3%)		1 (14.3%)	4 (14.3%)	
No	35 (92.1%)	30 (85.7%)		6 (85.7%)	24 (85.7%)	

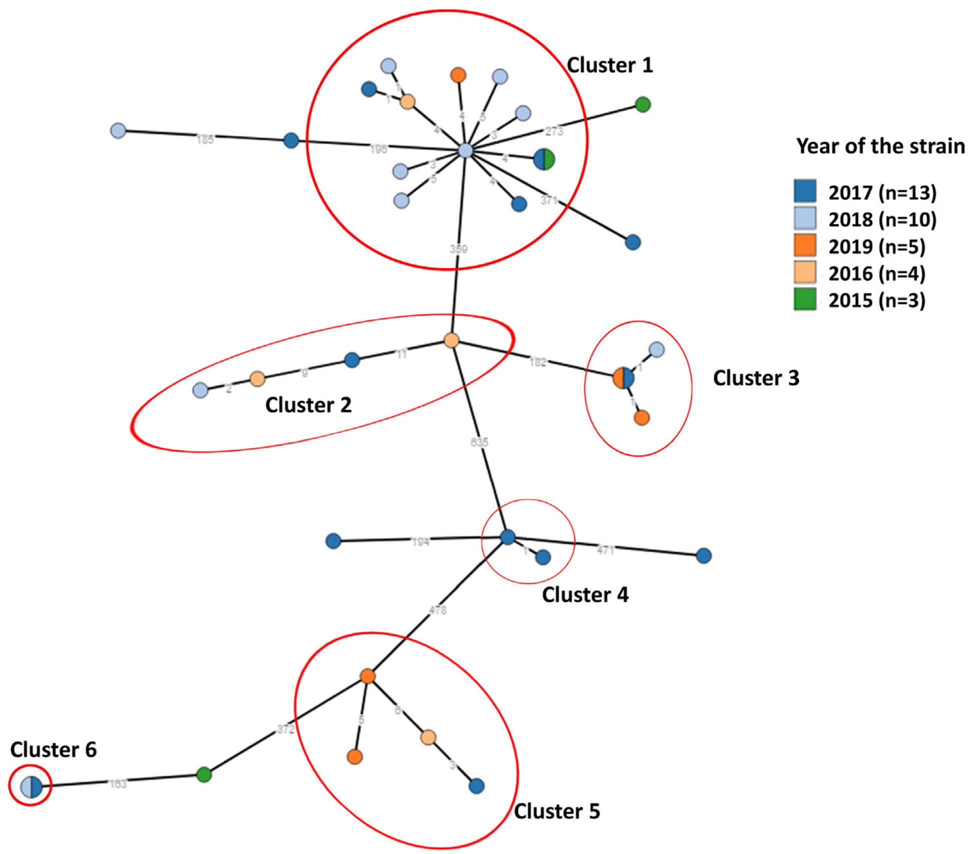

Fig. 1 Network of 35 *Mycobacterium tuberculosis* (MTB) isolates. Phylogeny of MTB isolates was determined based on a core single nucleotide polymorphisms (SNP) approach. Each node corresponds to a single or multiple isolates (i.e., nodes with slices). Nodes are coloured by year of strain isolation and genetic clusters of closely related isolates were defined whenever the strains had less than six SNP difference and are highlighted in red circles. Clades representing determined lineages from the global *M. tuberculosis* tree are indicated [cluster_1: lineage4.3.4.2 (100.0%, *n* = 12); cluster_2: lineage4.3.2 (100.0%, *n* = 4); cluster_3: lineage4.3.2 (100.0%, *n* = 3); cluster_4: lineage4.1.2.1 (100.0%, *n* = 2); cluster_5: lineage4.1.1.1 (100.0%, *n* = 4); cluster_6: lineage4.1.1.3 (100.0%, *n* = 2)].

infection and re-infection by *M. tuberculosis*, given their common and multiple risk factors, especially in places where epidemiological links are difficult to establish. WGS could routinely contribute to identifying public places that are hotspots of TB transmission.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Ethical approval

Ethical approval for this study was obtained (Ethics Boards of the Northern Regional Health Administration, 134/2022).

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LETTER TO THE EDITOR

Clinical impact of Xpert® MTB/RIF Ultra for pulmonary TB diagnosis under routine conditions in a reference center in Brazil

Dear Editor,

According to the literature, there is insufficient scientific data on the clinical impact, pre-post-analytical barriers, and health-care delivery, regarding the implementation of molecular tests for tuberculosis (TB) diagnosis recommended by World Health Organization (WHO) under field conditions in high burden countries.[1]

The molecular test Ultra assay (Xpert Ultra; Cepheid Inc., Sunnyvale, CA, USA) offers a lower limit of detection for *Mycobacterium tuberculosis* (MTB),[2] being particularly important to detect paucibacillary TB presentations - extrapulmonary TB, TB/HIV coinfection and pediatric TB.[5] Also, the test offers a semi-quantitative category of result named "trace", which is considered a concern.

We aimed to evaluate the performance of Ultra under routine conditions in respiratory specimens tested at Thorax Diseases Institute - Federal University of Rio de Janeiro, Brazil. A diagnostic test study using secondary data from the Mycobacterial Laboratory included all spontaneous sputum (SS), induced sputum (IS) and bronchoalveolar lavage (BAL) submitted to Ultra, smear microscopy and automatized culture, between December 2019 and December 2020 (Ethics Committee approval #01561018.3.0000.5257). Tests with indeterminate results, contaminated cultures, non-tuberculosis mycobacteria identification and those performed during patient's follow-up were excluded.

Cases were classified as Confirmed TB (MTB identification on culture), Non-confirmed TB (clinical/radiological diagnosis, treated and cured) or Not-TB (other diagnosis concluded). Data for HIV-*status* were performed searching on https://laudo.aids.gov.br/login.

Medcalc® Statistical Software (MedCalc Software Ltd, Ostend, Belgium) was used for statistical analysis.

722 specimens (330 BAL, 260 SS and 132 IS) were analyzed, with 59/105 known HIV status being positive. Ultra's overall diagnostic sensitivity was 93.5% with a specificity of 91.2%. In smear positive samples, Ultra was 100% sensitive *versus* 87.6% in smear negative.

For different pulmonary specimens, Ultra was more accurate on BAL (93.6%), followed by IS and SS [Accuracy (Acc) 90.9% and 89.6%, respectively] (Table 1).

The fifty false-positive Ultra results included 13 previous TB cases. In 10/154 TB cases, Ultra lead to false-negative results, and in all of them mycobacterial cultures identified MTB growth.

63/722 respiratory specimens presented trace results, five (7.9%) with confirmed TB and 14 (22.2%) with non-confirmed TB. 10/44 cases classified as not-TB had previous TB (Fig. 1). Therefore, Ultra was 93.5% sensitive and 91.2% specific. If trace results were considered as MTB not detected, sensitivity would fall to 81.1% with 98.9% of specificity. Whether the previous history was taken into consideration for classification of trace as MTB not detected and attributed to DNA fragments of non-viable bacilli, sensitivity and specificity would be both 93.5%.

To the best of our knowledge, this is the first study under routine conditions and in a scenario of high prevalence of TB, as Brazil, that analyzes the performance of Ultra in such a large sample, which turn this letter innovative and informative.

Recently, Xpert® MTB/RIF showed a good performance in different pulmonary specimens, with emphasis in IS (Acc=97%).[3] In the present study, Ultra on IS had a sensitivity of 96.5% and a lower specificity of 89.3%, which is compatible with what the new version proposes. Considering the differences between our sample and Zar's *et al*,[4] which addresses a pediatric sample, Ultra also presented a better performance on IS when compared to nasopharyngeal aspirate. Despite our results showing the greater accuracy on BAL, the performance of Ultra on IS deserves to be highlighted, considering the costs and safety of the method, which can be substituted for BAL for TB diagnosis.

For Mazzola and colleagues,[5] Ultra's proportion of true-positive results exceeds the false-positives: the latter being avoidable in scenarios with a low pretest probability. In our casuistry, considering only the false-positive results attributed to previous TB history, 70.6% presented trace-results.

Independently of HIV-*status*, trace category increased case detection by 2.1% without significant loss of specificity in the study of Andama *et al*.[6] In our research, if trace-results were considered negative in all cases, sensitivity would fall to 81.1%, with a higher specificity (98.9%). The other way, 44 cases would be false-positive, ten with previous TB. Therefore, if the history of previous pulmonary TB had been evaluated, and Ultra trace result considered as

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Table 1 Ultra performance according to the different respiratory specimens.

Respiratory Specimen	Ultra Results	TB Diagnosis: Not TB		TB N (%)		Xpert® Ultra MTB/RIF performance: Se	Sp	PPV	PLR	NPV	NLR	Acc
		Previous TB N (%)	No TB N (%)	Non Confirmed TB N (%)	Confirmed TB N (%)							
Spontaneous Sputum	**MTB not detected**	0	149 (90.9)	0	5 (6.3)	94.4 (87.4-98.1)	87.1 (81.2-91.8	79.2 (72.0-85.0	7.34 (4.95-10.87)	96.7 (92.7-98.6)	0.06 (0.03-0.15)	89.6 (85.2-93.0)
	MTB detected	3 (42.9)	2 (1.2)	5 (55.6)	74 (92.5)							
	Trace	4 (57.1)	13 (7.9)	4 (44.4)	1 (1.3)							
	Total	7 (100)	164 (100)	9 (100)	80 (100							
Induced Sputum	**MTB not detected**	0	92 (93.9)	0	1 (5.3)	96.5 (82.2-99.9)	89.3 (81.7-94.5)	71.8 (59.2-81.7)	9.04 (5.15-15.87)	98.9 (93.0-99.8)	0.04 (0.01-0.27)	90.9 (84.7-95.2)
	MTB detected	0	0	4 (40)	16 (84.2)							
	Trace	5 (100)	6 (6.1)	6 (60)	2 (10.5)							
	Total	5 (100)	98 (100)	10 (100)	19 (100)							
Bronchoalveolar Lavage	**MTB not detected**	0	277 (94.5)	0	4 (13.3)	88.9 (73.9-96.9)	94.2 (90.9-96.6)	65.3 (53.9-75.2)	15.37 (9.55-24.74)	98.6 (96.5-99.4)	0.12 (0.05-0.30)	93.6 (90.4-96.0)
	MTB detected	0	1 (0.3)	2 (33.3)	24 (80)							
	Trace	1 (100)	15 (5.1)	4 (66.7)	2 (6.7)							
	Total	1 (100)	293 (100)	6 (100)	30 (100)							
Total	**MTB not detected**	0	518 (93.3)	0	10 (7.8)	93.5 (88.4-96.8)	91.2 (88.6-93.4)	74.2 (68.8-79.0)	10.62 (8.13-13.89)	98.1 (96.6-98.9)	0.07 (0.04-0.13)	91.7 (89.4-93.6)
	MTB detected	3 (23.1)	3 (0.5)	11 (44)	114 (88.4)							
	Trace	10 (76.9)	34 (6.1)	14 (56)	5 (3.9)							
	Total	13 (100)	555 (100)	25 (100)	129 (100)							

Legend: TB – Tuberculosis; MTB – *Mycobacterium tuberculosis*; Se – Sensitivity; Sp – Specificity; PPV – Positive predictive value; NPV – Negative predictive value; PLR – Positive likelihood ratio; NLR – Negative likelihood ratio; Acc – Accuracy

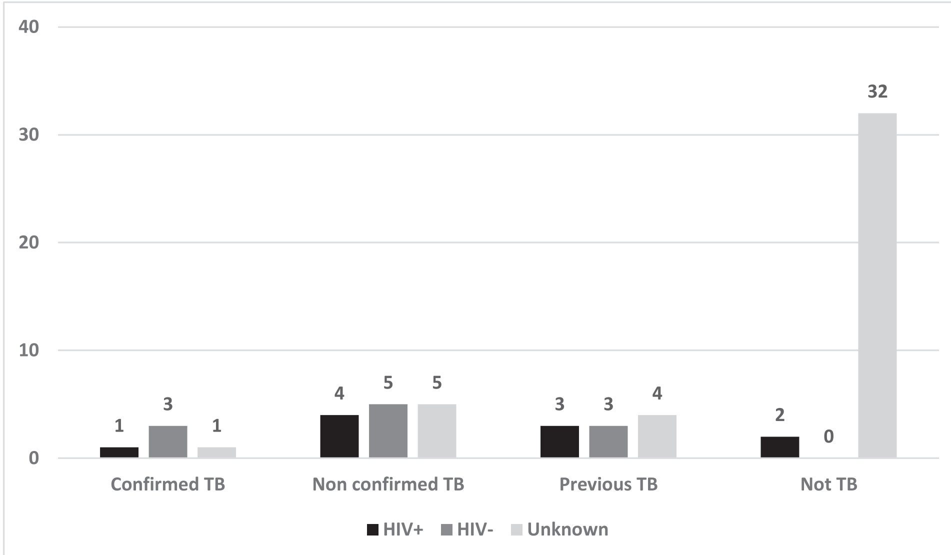

Fig. 1 Trace results in absolute numbers according to the HIV and TB status (n = 63).

MTB not detected in this situation, we would find a balance of both parameters (93.5%).

In Kendall's[7] publication, Ultra's trace results increased overtreatment by more than 50%, nonetheless it avoided 50% of deaths. Therefore, the interpretation of trace results requires a balance between case detection and overtreatment as established by Global Laboratory Initiative of the Stop TB partnership.

Our limitations were mostly attributed to diagnostic test studies conducted in routine conditions. We could not analyze Ultra results according to HIV-*status* in all specimens and we didn't have access to all previous TB history.

In conclusion, our study, conducted in a country with a high burden for TB, confirmed Ultra's good overall performance for pulmonary TB diagnosis. Other studies conducted in different scenarios are needed to confirm the correct interpretation of trace results in this specific tuberculosis presentation.

Authors contribution

APS and FCQM: conception and design of the study; APS, GD, JGR, MCFFA; FMR: acquisition of data; APS: analysis and interpretation of data, drafting the article; FM, AK and DRS: revision of the paper for important intellectual content and final approval of the version to be submitted.

Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Dynamic hyperinflation in patients with severe asthma compared to healthy adults

Despite current medical management, exertional breathlessness is commonly experienced by adults with severe asthma limiting their exercise tolerance. A cardiopulmonary exercise test may help identify the reasons for these symptoms to guide appropriate management and evaluate new interventions. For instance, exhalation can be interrupted by the next inspiration resulting in an increased end expiratory lung volume. Increasing end expiratory lung volume as ventilation increases is defined as dynamic hyperinflation.[1] Although there are reports of dynamic hyperinflation in asthma,[2-4] the frequency, severity and impact by exercise platform is unknown.

We aimed to assess: 1) the presence and magnitude of dynamic hyperinflation, and contribution to exercise intolerance in patients with severe asthma compared to healthy individuals; 2) whether dynamic hyperinflation was affected by the presence of exercise-induced bronchoconstriction and fixed airflow obstruction, or exercise modality. Some of the results of these studies have been previously reported in the form of an abstract.[5]

This study was a prospective (trial registration # ISRCTN96143888) cross-sectional study and part of a larger study investigating the feasibility of asthma-tailored pulmonary rehabilitation.[6] Adults with severe asthma (A_{group}) and MRC Dyspnoea ≥ 2, under the care of asthma specialists in a tertiary centre multi-disciplinary service were recruited at Glenfield Hospital, Leicester, UK. Fixed airflow obstruction was defined as an FEV_1/FVC less than the lower limit of normal despite medical management. Exclusion criteria were >10 pack-year smoking history with the presence of fixed airflow obstruction. Age, sex matched, self-reported healthy individuals with no known co-morbid conditions and <10 pack-year smoking history were recruited as controls (C_{group}). The study was approved by the National Research Ethics Service Committee of the East Midlands (Ref#127552) and written informed consent was obtained before participation.

All A_{group} performed spirometry, incremental treadmill ('treadmill') and cycle ('cycle') exercise tests, in random order, with bidirectional volume measures and expiratory gas analysis. Spirometry was repeated during recovery to assess exercise-induced bronchoconstriction.[7] The C_{group} performed spirometry and the treadmill test only.

During all exercise tests, inspiratory capacity manoeuvres were performed at rest, during warm up and every two minutes during exercise. Assuming the participant inspired to total lung capacity (TLC), inspiratory capacity was calculated as the difference in TLC and the average of the last five end expiratory lung volume values (end expiratory lung volume = TLC − inspiratory capacity) observed before the participant was prompted to inhale to TLC.[8] The presence and magnitude of dynamic hyperinflation was assessed through the linear regression of end expiratory lung volume

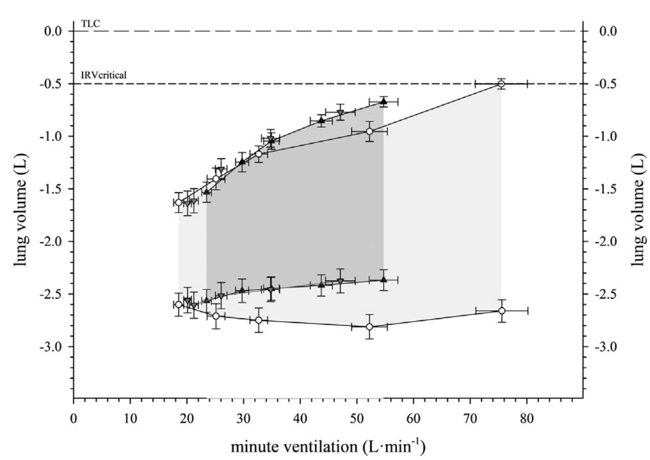

Fig. 1 Operational lung volumes plotted against ventilation on the incremental treadmill test in patients with severe asthma (black triangles) and healthy individuals (white circles). Tidal volume (greyed area) is bounded by the EELV (lower boundary) and EILV (upper boundary) for each group. Patients with severe asthma demonstrate DH whereas healthy individuals demonstrate the absence of DH (slope of EELV ≅ 0). Operational lung volumes in patients with severe asthma on the incremental cycle test are also shown (grey triangles). The error bars represent standard error. DH: dynamic hyperinflation, TLC: total lung volume, IRV: inspiratory reserve volume, EILV: end inspiratory lung volume, EELV: end expiratory lung volume, TLC: total lung capacity, IRV: inspiratory reserve volume.

Abbreviations: Agroup, Adults with severe asthma group; Cgroup, control group; TLC, total lung capacity; V̇E, minute ventilation; Vt, tidal volume; MVV, maximal voluntary ventilation.

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(ml) as a function of minute ventilation ($\dot{V}E$) with units ml·(L·min^{-1})$^{-1}$.[1,8] Using the average tidal volume (Vt) that preceded the prompt, end inspiratory lung volume = end expiratory lung volume + Vt and inspiratory reserve volume = TLC − end inspiratory lung volume were calculated. Maximal voluntary ventilation (MVV) was estimated FEV_1 x 40 and ventilatory limitation was defined as $\dot{V}E_{pk} > 80\%MVV_{pred}$.

Fifty-five patients with severe asthma and 30 controls were recruited (Table E1). Peak oxygen uptake (see Table E2) was significantly lower in A_{group} compared to C_{group} (1971 ml·min^{-1} versus 2471 ml·min^{-1} respectively, $p<0.001$). A greater proportion of A_{group} demonstrated a ventilatory limitation compared to C_{group} (49% versus 23% respectively, $p<0.05$).

Shown in Fig. 1, end expiratory lung volume increased during treadmill exercise in A_{group} (9 [23] ml·(L·min^{-1})$^{-1}$) whereas it did not increase in the C_{group} (−1 [8] ml·(L·min^{-1})$^{-1}$). The difference between groups was significant (difference = 10 [1 to 19] ml·(L·min^{-1})$^{-1}$). In the A_{group} there was no significant difference in dynamic hyperinflation during treadmill exercise compared to cycle exercise (difference = −4 [−9 to 2] ml·(L·min^{-1})$^{-1}$).

In contrast to the C_{group}, the A_{group} demonstrated an inflection of increased breathlessness before the critical inspiratory reserve volume (Fig. 2A). The slope of the relationship between $\dot{V}E$ and $\dot{V}CO_2$ (Fig. 2D) was not different between A_{group} and controls. However, A_{group} indicated more breathlessness as assessed by Borg scale[9] per absolute $\dot{V}E$ than C_{group} (Fig. 2B) but less of an effect when $\dot{V}E$ was expressed as percent predicted maximum voluntary ventilation (Fig. 2C).

In subgroup analyses, there was no significant difference in dynamic hyperinflation between: 1) A_{group} with and without fixed airflow obstruction (14 [37] ml·(L·min^{-1})$^{-1}$ versus 5 [9] ml·(L·min^{-1})$^{-1}$, respectively, $p = 0.17$); 2) A_{group} with and without exercise-induced bronchoconstriction (12 [43] ml·(L·min^{-1})$^{-1}$ versus 9 [10] ml·(L·min^{-1})$^{-1}$, respectively, $p = 0.72$).

We observed patients with severe asthma develop mild dynamic hyperinflation during incremental exercise whereas healthy controls maintained their end expiratory lung volume with increasing ventilation. In asthma, the dynamic hyperinflation was not affected by the exercise modality,

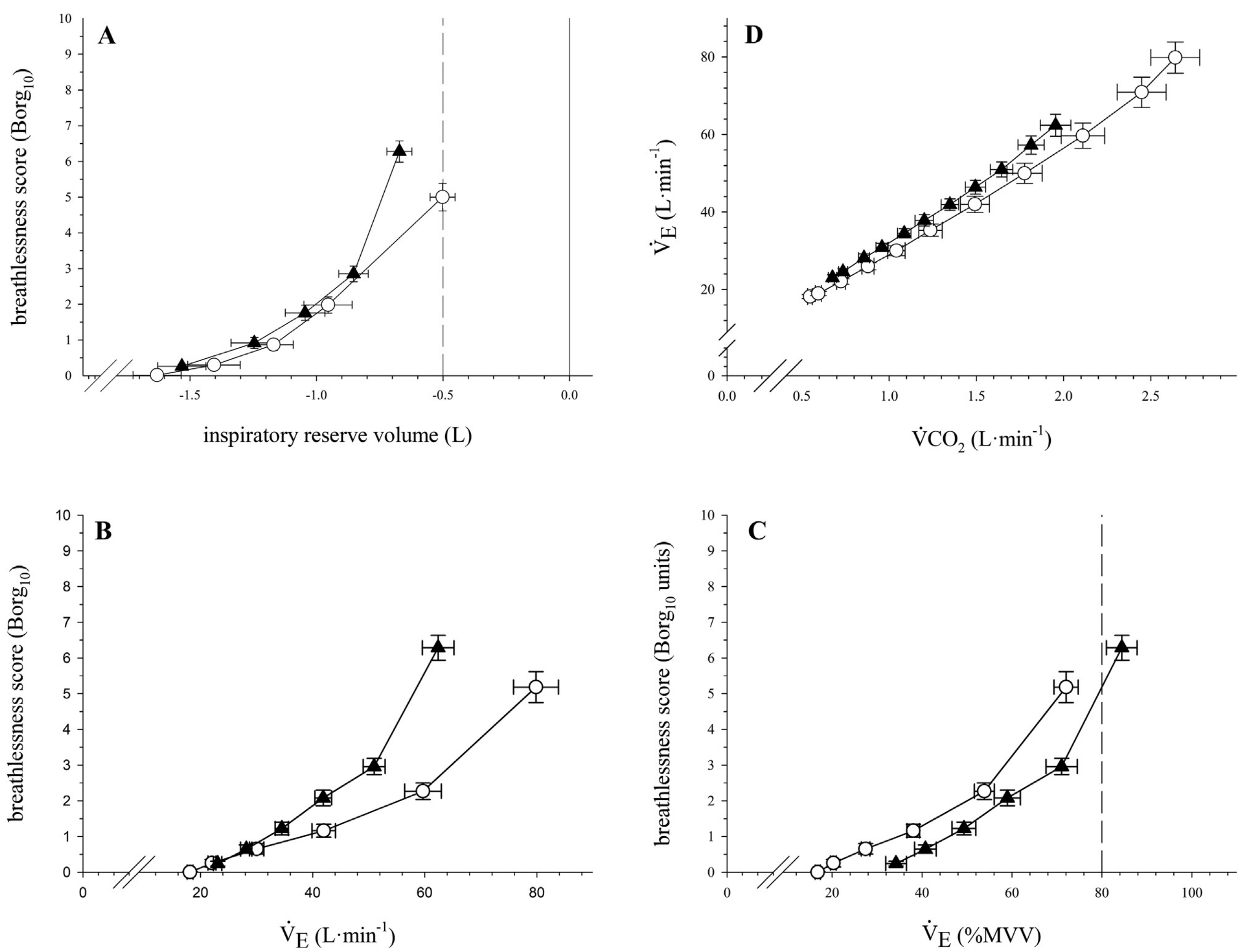

Fig. 2 A comparison of symptom response between patients with severe asthma (triangles) and healthy individuals (circles) on an incremental treadmill test including: breathlessness response as a function of inspiratory reserve volume (panel A) as well as a function of ventilation in absolute (panel B) and relative terms (panel C). The relationship of $\dot{V}E$ and $\dot{V}CO_2$ ventilation is shown in panel D. The error bars represent standard error.

exercise-induced bronchoconstriction or fixed airflow obstruction indicating evaluation of a physiological deficit not reflected by other physiological tests.

In the presence of mild dynamic hyperinflation, A_{group} limited Vt relatively early in the exercise and did not increase end inspiratory lung volume to achieve a critically low inspiratory reserve volume, likely to avoid mechanical and sensory consequences associated with expanding their lungs close to TLC. Under these circumstances they were obliged to increase their respiratory rate to increase minute ventilation. Their breathlessness rose sharply during exercise which may be associated with reaching their flow related breathing capacity and less to do with the mechanical consequences of volume expansion close to TLC. In contrast, the majority of healthy individuals reached their critical inspiratory reserve volume. However, perceived breathlessness was significantly higher in patients with severe asthma compared to healthy individuals at maximal exertion (see Table E1).

The magnitude of dynamic hyperinflation in this study was assessed through the slope of regression line between end expiratory lung volume against ventilation with the advantage that test duration, power or ventilation achieved do not affect the assessment of dynamic hyperinflation in contrast to pre-post measures only.[1] The magnitude of dynamic hyperinflation in patients with severe asthma in our study is similar to that in patients with mild COPD reported by O'Donnell et al.[10] We did not observe a difference in dynamic hyperinflation between treadmill and cycle exercise demonstrating that the primary determinant of the end expiratory lung volume is the magnitude of ventilation. It has been suggested that dynamic hyperinflation would be greater during walking because intercostal respiratory and abdominal muscles stabilize the trunk and compromise expiration[11] but our observations suggest this influence in inconsequential. We observed similar magnitude of dynamic hyperinflation in adults with severe asthma with and without exercise induced bronchoconstriction in contrast with a previous report[3] of younger patients with mild asthma and non-fixed airflow obstruction.

The underlying mechanisms of dynamic hyperinflation observed in adults with severe asthma are likely to be different to those driving dynamic hyperinflation in COPD and deserve further study. Furthermore, the resultant ventilatory limitation to exercise may translate to adults with severe asthma reducing their physical activity in daily life as dynamic hyperinflation has been observed during lower exercise challenges such as the six-minute walk test.[11] Whether optimal bronchodilation can ameliorate the dynamic hyperinflation remains to be determined.

Conclusions

This study identifies dynamic hyperinflation as an important quantifiable consequence of severe asthma contributing to exercise limitation. In addition to the mechanical constraint, our data suggest that some patients with severe asthma may have an altered perception of breathlessness. The underpinning pathophysiology requires further investigation, but both phenomena are potential treatable traits.

Author contributions

RE contributed to the conception and design, analysis and interpretation of data, drafting and revising the manuscript critically for important intellectual content. SM contributed to the design, analysis and interpretation of data, drafting and revising the manuscript critically for important intellectual content. TD contributed to the conception, analysis and interpretation of data; drafting and revising the manuscript critically for important intellectual content. RHG, PB and SS contributed to the interpretation of data; revising the manuscript critically for important intellectual content. All co-authors contributed and approved the final manuscript. RE is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2023.07.006.

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LETTER TO THE EDITOR

New insights in circulating peptidome to differentiate mild to severe COVID-19 patients: Preliminary report

Dear Editor,

Peptidomics is an innovative technique that allows the identification of endogenous or foreign peptides associated with pathogenic organisms and infective agents, potentially exploited to better understand COVID-19 pathophysiology. To date, the plasma peptidome of COVID-19 patients has been poorly characterized due to the challenging sample preparation requirements, peptide stability, and analytical issues including the wide range of peptide polarity and concentration.[1] For these reasons, in a recently published work, we applied for the first time an untargeted mass spectrometry-based peptidomic approach to plasma samples from patients infected by SARS-CoV-2 virus.[2] Since we already discussed the mainly observed peptidomic differences occurring between COVID-19 positive patients and negative controls, here we focus on the comparison of the peptidome of plasma samples from mildly symptomatic SARS-CoV-2 infected (*n* = 11) patients and critical ones (*n* = 10). Mildly symptomatic subjects required only low-flow oxygen supplementation, whereas critical patients were those admitted to the semi-intensive respiratory unit care with respiratory failure requiring at least non-invasive ventilation (continuous positive airway pressure, CPAP). The clinical characteristics and comorbidities of the patients are reported in Table 1. Other data of patients have been

Table 1 Clinical data of the patients.

	COVID-19 patients		
	Total (*n* = 21)	Mildly symptomatic (*n* = 11)	Severe (*n* = 10)
Demographic characteristics			
Female, *n* (%)	12 (57.1%)	6 (54.5%)	6 (60%)
Age, years (*mean* ± *SD*)	74.9 ± 16.1	71.9 ± 21.8	77.2 ± 7.7
Respiratory support, *n* (%)			
Continuous positive airway pressure (CPAP)	10 (47.6%)	0 (0%)	10 (100%)
Oxygen supplementation	11 (52.4%)	11 (100%)	0 (0%)
Dexamethasone regime, *n* (%)	4 (19.04%)	0 (0%)	4 (40%)
Outcome, *n* (%)			
Discharged	16 (76.2%)	11 (100%)	5 (50%)
Deceased	5 (23.8%)	0 (0%)	5(50%)
Comorbidity, *n*			
Hypertension	11	5	6
Diabetes	4	1	3
Respiratory system	2	1	1
Cardiovascular system	8	4	4
Other endocrine system	6	3	3
Chronic kidney	1	1	0
Digestive system	3	0	3
Time from disease onset to sample collection, days (mean ± SD)	6.45 ± 4.8	5.2 ± 4.7	7.7 ± 3.9
(min—max)	(1.0—11.0)	(1.0—11.0)	(2.0—10.0)

Sample collection carried out at admission to hospital. Data are presented as number and percentage for dichotomous values or mean ± SD for continuous values.

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published elsewhere.[2] The Institutional Review Board (Comitato Etico Interaziendale Novara) approved this study (no. RQ06320/25 March 2020) including all permissions taken from the patients.

QAE Sephadex A-25 strong anion exchange particles (Sigma—Aldrich St. Louis, MO, USA) were used to fractionate 200 μL of citrate plasma samples. After that, peptides were desorbed from highly abundant proteins by heating samples to 60 $^{\circ}$C for 15 min.[3] The circulating peptidome was investigated using the micro-LC Eksigent Technologies (Eksigent, Dublin, USA) system linked to a TripleTOF 5600+ mass spectrometer (AB Sciex, Concord, Canada). The plasma peptidome was then identified using a database search.

The subsequent statistical analysis based on a *t*-test and the ratio of the abundances of quantified peptides within each group (p-value $\leq$ 0.05, fold change $\geq$ 1.3), revealed the presence of only 9 regulated peptides in plasma samples from mildly symptomatic COVID-19 *vs* critical patients, 5 of which were overexpressed in the mild group and 4 in those experiencing the severe disease.

More specifically, mild symptomatic patients presented an overexpression of two peptides belonging to Isoform 2 of Fibrinogen alpha chain (FIBA_HUMAN), DSGEGDFLAEGGGV and DEAGSEADHEGTHST, one peptide deriving from Isoform 2 of Complement C4-A (CO4A_HUMAN), DDPDAPLQPVTPLQ, one Alpha-1-antitrypsin (A1AT_HUMAN) related peptide, EDPQGDAAQ, and a Complement C3 (CO3_HUMAN) peptide, IHWESASLL.

Conversely, the critical group was characterized by the up modulation of two peptides related to Isoform 2 of Haptoglobin (HPT_HUMAN), WVQKTIAEN and VDSGNDVTDIADD, one peptide from Transthyretin (TTHY_HUMAN), LSPYSYSTTAVVTNPKE, and one peptide belonging to Talin (TLN1_HUMAN), SGASGPENFQVG. In addition, these 9 peptides were not expressed by all the patients. In particular, the following peptides DSGEGDFLAEGGGV and DEAGSEADHEGTHST both from FIBA, DDPDAPLQPVTPLQ (from A1AT1) and EDPQGDAAQ (from CO4A) were not present in severe patients, while SGASGPENFQVG (from TLN1) was not expressed in mild patients.

We also investigated, using boxplots and ROC curves, the possibility of modulated peptides to be indicative of the clinical different course of SARS-CoV-2 infection, and we observed that 6 of them performed optimally in diagnostic tests (Fig. 1): FIBA_HUMAN-DSGEGDFLAEGGGV (AUC = 0.909), A1AT_HUMAN-EDPQGDAAQ (AUC = 0.773), CO4A_HUMAN-DDPDAPLQPVTPLQ (AUC = 0.864), CO3_HUMAN-IHWESASLL (AUC = 0.818), HPT_HUMAN-WVQKTIAEN (AUC = 0.818), and TLN1_HUMAN-SGASGPENFQVG (AUC = 0.75).

Our data show that the main regulated peptides in both mildly symptomatic and severe COVID-19 patients derive from inflammatory, immune-response and coagulation proteins and that specific peptide's overexpression suggest a correlation with severity of disease. In particular we found important differences among overexpressed peptides in mild symptomatic and severe patients. For example, we observed a stronger upregulation of transthyretin, of haptoglobin peptides and of a peptide derived from the cytoskeletal protein Talin, and conversely, a downregulation of fibrinogen, complement, and alpha-1-antitrypsin peptides in severe versus mild cases. Especially in the critical group the meaning of the up-regulated peptides (HPT_HUMAN, TTHY_HUMAN, TLN1_HUMAN) is not known and still needs to be addressed. Interestingly, the quantification of parental proteins show no modulation in mild vs severe COVID 19 patients[4] suggesting that the observed differences are due

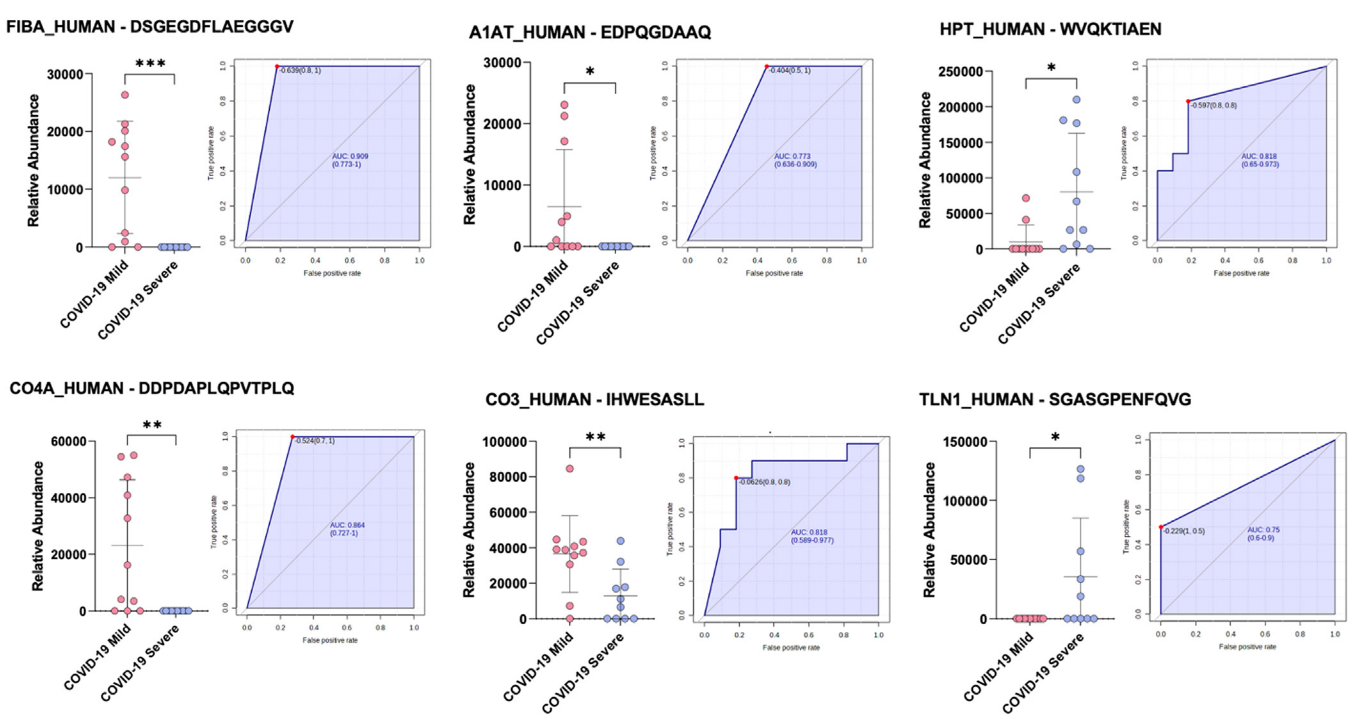

Fig. 1 Boxplots and ROC curves for the best potential biomarkers identified with peptidomic analysis (pink dots: COVID-19 mild, purple dots: COVID-19 severe). ***p <0.001; ** p < 0.01; * p < 0.05. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to modulation of peptides metabolism more than mirroring the levels of the full protein.

HPT_HUMAN peptide, for example, which is involved in neutralizing free heme directly linked to the infection's increased hemolysis seems to be overwhelmed in severe SARS-CoV-2 patients, therefore, leading us to postulate that infected subjects show high levels of the related protein unable to efficiently neutralize free heme, thus suggesting a modified degradation pattern.[5]

Transthyretin (TTHY_HUMAN) is an acute phase-reactant acting as a hormone transporter whose levels negatively correlate with inflammation, it is known to be a neuroprotective and oxidative-stress-suppressing factor and low concentrations of TTHY are indicative of a systemic inflammatory state.[6] In severe COVID-19 patients we observed an overexpression of this peptide that may be related to high-dose steroid treatment (glucocorticoids increase transthyretin plasmatic level)[7] or to an altered degradation pathway and could be an attempt of homeostasis correction of a very de-regulated background.

Talin-1 is a cytoskeletal protein central for the regulation of cell-matrix adhesion and its depletion is responsible of severely affected focal adhesion assembly. High plasma sTalin-1 levels in patients with coronary artery disease (CAD) were found to be associated with severity of CAD, suggesting a role of sTalin-1 in the progression of coronary atherosclerosis,[8] hence an overexpression of this peptide may have a potential role in cardiovascular consequences of severe COVID-19 infection.

To date this is the only study investigating how SARS-CoV-2 infection affects circulating peptides, further research would allow the identification of more specific pathways and peptides associated with the development of the disease.

Taken the limitations of a small sample and the preliminary value of our findings, it is interesting to observe that we found some modulated peptides to be good diagnostic tools in predicting different outcomes of COVID-19 infection.

In conclusion, the changes observed in circulating peptidome are the result of a complex balance between target abundance, protease activity, and clearance rate, all of which might be modulated by COVID-19 infection.

Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Risk factors of pulmonary relapse in microscopic polyangiitis and granulomatosis with polyangiitis

Dear Editor,

In a recent study the French Vasculitis Study Group identified overall predictive factors for AAV relapse, including PR3-ANCA, age under 75 years, and eGFR greater than 30 ml/min/1.73m2.[1] We aim to examine factors that specifically contribute to pulmonary relapse in patients with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA). This study included adult patients with MPA or GPA who were followed at Toulouse University Hospital (France) between 2004 and 2019. The local ethics committee approved the study and written consent was waived in accordance with French law on retrospective observational studies. Diagnosis of AAV was based on clinical and biological criteria of vasculitis and histological findings.[2] Patients were defined as relapsed when symptoms of active vasculitis returned, and other causes were excluded. Relapse-free survival was calculated from the diagnosis date to relapse date or the last follow-up date for patients who did not relapse. The Kaplan-Meier estimator was used to generate relapse-free survival probability curves and they were compared using log-rank tests. The Cox model was used to estimate relative risks of relapse based on potential prognostic variables. Variables associated with relapse with a statistical threshold of less than 20% were included in the models, except for variables for which more than 50% of the data was missing. Stata software version 14.2 (StataCorp) was used for analyses. A total of 274 patients with AAV were included in this study, of which 147 (53.6%) were male and 133 (48.5%) had GPA. PR3-ANCA positivity was observed in 81% GPA patients, while 76.6% of MPA patients were MPO-ANCA positive. The most commonly used treatments for induction-remission were intravenous cyclophosphamide (55%) and rituximab (39%) and for maintenance-remission rituximab (38%) and azathioprine (32%). No significant difference in therapeutic approaches was observed between MPA and GPA patients. The mean follow-up period was 70 months (SD: 53.0) and the median duration from diagnosis to the first relapse was 48 months (SD: 37.5). We observed 86 relapses (31.4%) and 33 with pulmonary relapse (12%). AAV patients' cumulative probability of relapse at 1-year, 3-year, and 5-year intervals was 2%, 17%, and 21%, respectively. There was no significant difference in relapse rate based on the patients' AAV diagnosis ($p=0.23$) or whether they had pulmonary involvement ($p=0.66$) or not (Fig. 1). However, relapse occurred more frequently in anti-PR3 patients ($p=0.0007$) and those who had not received rituximab as maintenance therapy ($p<0.0001$) (Fig. 1). The multivariate analysis excluded 24 patients (8.6%) due to lack of follow-up data. Risk factors associated with pulmonary relapse, as identified, included initial pulmonary involvement (HR 9.6; 95% CI [1.2; 74.6]; $p=0.03$), cardiac involvement (HR 6.4; 95% CI [1.7; 24.3]; $p=0.006$), mechanical ventilation (HR 21.6; 95% CI [1.9; 247.5]; $p=0.014$), and the presence of cavitary lung lesions (HR 5.2; 95% CI [1.7; 15.8]; $p=0.004$). Using rituximab as an induction-remission therapy was a protective factor, with a four-fold lower risk of pulmonary relapse (HR 0.23; 95% CI [0.06; 0.86]; $p=0.03$). Death rate was 10% without significant difference between MPA and GPA patients ($p=0.20$). Achieving remission in GPA or MPA patients is often challenging. One-third of patients experienced an AAV relapse in 4 years in our study consistent with long-term follow-up studies.[1,3] Previous reports have conflicting data on the association between pulmonary involvement and risk of relapse.[3,4] We found that pulmonary involvement is not associated with an increased risk of overall relapse but it is associated with a nearly 10-fold higher risk of pulmonary relapse. In multivariate analysis, a more severe diffuse alveolar hemorrhage (DAH) requiring mechanical ventilation and blood transfusions (indicative of active vasculitis disease) and the presence of cavitated nodules (indicative of active granulomatous disease) were specific predictive factors for pulmonary relapse. Previous studies suggested that cardiac involvement was associated with an overall risk of relapse[1,5] and our data are consistent with these studies (for pulmonary relapse). The underlying physiopathological mechanism remains unknown and caution is necessary due to the low rate of this condition. In our study, using rituximab in maintenance therapy is associated with reduced risk of relapse, consistent with results from randomized trials.[6,7] Furthermore, in multivariate analysis, using rituximab in induction therapy was associated with improved respiratory outcomes and a four-fold lower risk of pulmonary relapse. We restricted ourselves to ANCA-positive vasculitis through a classification bias present. The retrospective and monocentric design of the study, coupled with the potential for missing data and referral biases, poses a significant challenge to establishing causal relationships. However, the large sample size can help to reduce the impact of bias and enhance the generalizability of the findings. Risk factors for pulmonary relapse include pulmonary

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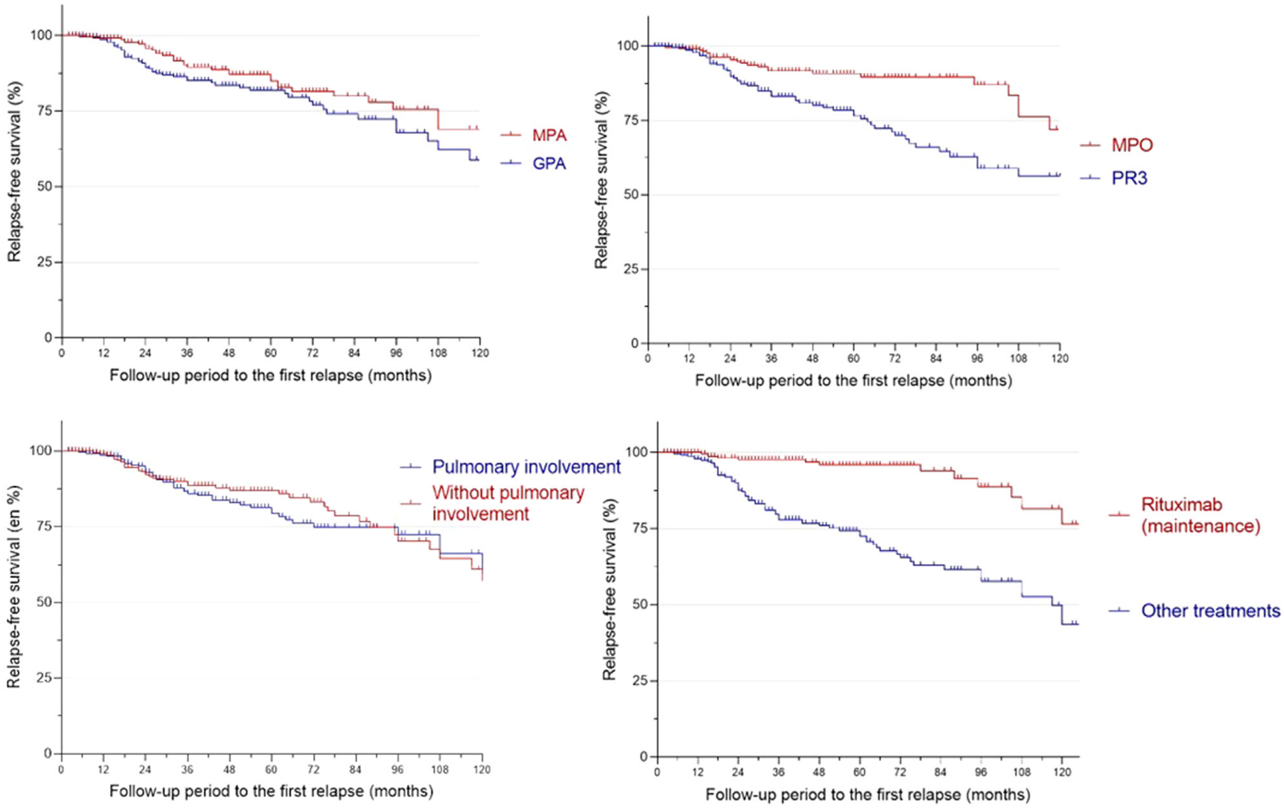

Figure 1 Overall relapse free survival according to (a) diagnosis of AAV, (b) ANCA subtype, (c) presence of pulmonary involvement, and (d) rituximab use in maintenance.

involvement with severe DAH or cavitary nodules at disease onset and cardiac involvement. Identifying these risk factors early can enable tailored treatment strategies with rituximab and monitoring pulmonary relapse risk during follow-up.

Conflicts of interest

TV has received consulting fees from Boeringer Ingelheim. SF has received consulting fees for Abionyx, Pharma, CSL-Vifor, Sanofi-Genzyme, Novartis SA, Alexion, Baxter. GPr , GPu and VLC have nothing to disclose.

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LETTER TO THE EDITOR

Lung disease in rheumatoid arthritis: Results from a national cohort

Dear Editor,

Lung involvement can occur in 10–80% of rheumatoid arthritis (RA) patients,[1,2] mostly within the first 5 years of RA diagnosis.[1] It includes interstitial lung disease (ILD), airways disease, pleural disease and nodules.[1] Pulmonary hypertension and direct toxicity from RA therapy have also been described.[1]

Despite therapeutic advances,[2] lung disease remains responsible for 10–20% of RA mortality.[1]

This observational, retrospective, multicenter study characterizes lung involvement in a nationwide cohort of RA patients, identifies factors associated with lung disease and describes treatments used in patients with RA-ILD. All RA patients aged ≥18 years at diagnosis prospectively followed in Rheumatic Diseases Portuguese Registry (Reuma.pt) were included from 2008 to February 2022.

Lung involvement diagnosis was based on high resolution computed tomography (CT) and/or histopathological data. The date of the exam was considered the date of lung disease diagnosis. Demographics and clinical data, including smoking habits, RA duration, rheumatoid factor (RF), anticitrullinated peptide antibodies (ACPA), secondary Sjögren's syndrome (SS2) and subcutaneous rheumatoid nodules, were retrieved at last visit. Erosive disease was based on X-rays performed at any time. Current/previous disease modifying antirheumatic drugs (DMARDs) and antifibrotics were recorded. Missing information was filled in from hospital records, whenever possible.

Continuous variables were expressed as mean ± S.D. or median with interquartile range (IQR) and categorical variables as absolute values and frequencies. Groups were compared using qui-square test and independent samples *t* test or Mann–Whitney test, as appropriate. Statistically significantly different variables were included in a logistic regression analysis for identifying features independently associated with lung disease. A significance level of 5% was considered. SPSS version 28.0 (IBM Corp, Armonk, NY, USA) was used. The study was approved by the Coordinator and Scientific Board of Reuma.pt and by the Ethics Committee of Hospital Garcia de Orta. All data registered on Reuma.pt is subjected to an informed consent signed by the patient.

From 9415 RA patients registered in Reuma.pt, 7473 (79.4%) were female, with mean age of 62.3 ± 13.6 years and median disease duration of 12.4 [IQR 6.5–20.6] years at last visit.

Lung disease was documented in 298 (3.2%) patients. The median interval between joint and pulmonary symptoms was 5 [IQR 1–15] years. Twenty-one (7.8%; 28 missing data) patients had lung disease as first manifestation.

Fig. 1 shows the distribution of different types of lung involvement. Thirteen patients had more than one type of lung involvement. None of the patients with rheumatoid lung nodules had subcutaneous nodules. Two patients with CT showing peribronchial micronodules and a fluffy "tree-in-bud pattern" had lung biopsy, which documented follicular bronchiolitis.

Table 1 shows clinical characteristics of patients with and without lung involvement.

Continuous variables are expressed as mean ± S.D. if they had a normal distribution, or median with interquartile range (IQR) if not normally distributed. Categorical variables are presented as absolute values (*n*) and frequencies (%).

In multivariate analysis, ever smoking (OR = 2.1; [95%CI:1.4–3.9], $p < 0.001$), positive ACPA (OR = 2.1; [95%CI:1.2–3.6], $p = 0.002$) and older age (OR = 1.05 per year; [95%CI:1.03–1.07], $p < 0.001$) were positively associated with lung disease, whereas previous treatment with methotrexate (MTX) (OR = 0.32; [95%CI:0.22–0.46], $p < 0.001$) and tumor necrosis factor inhibitors (TNFi) (OR = 0.48; [95%CI: 0.32–0.7], $p < 0.001$) had a negative association with RA-associated lung disease.

At lung disease diagnosis, 169 (56.7%) patients were taking MTX, 131 (44%) other conventional synthetic DMARDs, 49 (16.4%) TNFi, 13 (4.4%) tocilizumab, 9 (3%) rituximab, 2 (0.7%) abatacept and 2 (0.7%) Janus Kinase inhibitors. After lung disease diagnosis, 77 out of 169 patients (45.6%) were kept under MTX.

After ILD diagnosis, rituximab became the most prescribed biologic, in 62 (34.1%) patients, followed by tocilizumab (15 patients; 8.2%) and abatacept (7 patients; 3.8%). TNFi were used in 16 (8.8%) patients. Twelve RA-ILD patients received antifibrotics (6 nintedanib, 6 pirfenidone).

The involvement of several centers explains why the number of 6 authors has been exceeded.

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Table 1 Comparison of clinical characteristics between patients with and without lung involvement.

	With lung involvement (*N* = 298)	Without lung involvement (*N* = 9117)	Percentage of missing data	*p*-value
Male	89 (29.9%)	1853 (20.3%)	0%	<**0.001**
Age (years)	69.4 ± 10.5	62.2 ± 13.7	0%	<**0.001**
RA duration (years)	13.6 [IQR 7–22.8]	12.3 [IQR 6.5–20.5]	20.8%	0.066
Ever smoking	90 (30.2%)	1419 (15.6%)	40.6%	<**0.001**
Occupational exposure risk	38 (12.8%)	625 (6.9%)	61.2%	0.327
Positive RF	228 (76.5%)	4783 (52.5%)	24.5%	<**0.001**
Positive ACPA	217 (72.8%)	3802 (41.7%)	38%	<**0.001**
Erosive disease	155 (52%)	3171 (34.8%)	40.7%	0.058
SS2	22 (7.4%)	329 (3.6%)	46.8%	0.815
Previous treatment with MTX	169 (56.7%)	6112 (82.5%)	18.8%	<**0.001**
Previous treatment with TNFi	49 (20.3%)	2989 (40.4%)	18.8%	< **0.001**

RA, rheumatoid arthritis; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibody; SS2, secondary Sjögren's syndrome; MTX, methotrexate; TNFi, tumor necrosis factor inhibitor.

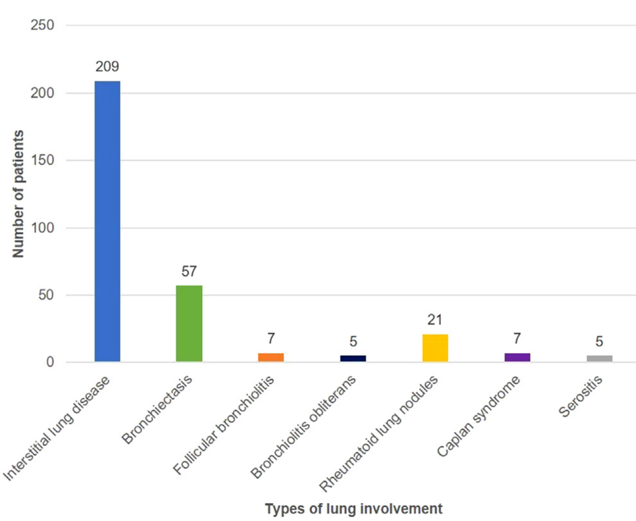

Fig. 1 Distribution of the different types of lung involvement in RA patients.

The proportion of RA patients with lung involvement in our cohort was lower than that reported in the literature,[1] which might be explained by underreporting in Reuma.pt and because in most cases lung disease was only screened after respiratory symptoms developed. High-resolution CT is now considered the gold-standard for diagnosis. Lung biopsy is only performed when imaging features are inconclusive or when the etiology of lung disease is unclear.[1,2]

Besides, taking into consideration the pathogenic role of RA-related autoantibodies, smoking and occupational dust in RA-associated lung disease[1,3] and the fact that articular disease activity seems to be higher in patients with RA-ILD,[1] the lower smoking prevalence rates in Portugal compared to other European countries[4] and the lower aggressiveness of RA in southern Europe than in other geographic areas[5] can also contribute to the lower prevalence of RA-associated lung disease in our cohort. In 7.8% of RA patients, lung disease was the first disease manifestation, with recent data suggesting that the lung may be a potential mucosal site of generation of RA-related autoimmunity.[3]

RA-ILD was the most prevalent type of lung involvement (70.1% of the patients with lung disease), which is in line with published data.[1]

Patients with RA-associated lung disease had a higher frequency of smoking habits, positive RF and ACPA and erosive disease, consistent with the literature.[1,3] However, 24 patients with lung disease were negative for RF and ACPA, with only 2 having smoking habits. This means that other factors may contribute to lung disease development.

Data on MTX and others DMARDs causing/worsening pre-existing ILD in RA patients is controversial,[2,6] with recent data demonstrating that controlling systemic inflammation can delay/prevent RA-ILD development.[3]

Despite being a retrospective study, this constitutes an extensive characterization of a considerable number of RA patients with lung involvement and confirms the reproducibility of classic risk factors for lung disease[7] in a national cohort. In the future, the identification of new risk factors and the validation of risk scores, could help identify patients at high risk of RA-associated lung disease that might benefit from a screening strategy including an HRCT at disease diagnosis, similar to what is already recommended for systemic sclerosis.[8]

Conflicts of interest

All authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2023.05.009.

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LETTER TO THE EDITOR

The “serial switcher” in severe asthma

Dear Editor,

Biologics represent an opportunity for severe, uncontrolled, T2-high asthmatic patients. Despite their careful prescription, response can be incomplete and a switch to another agent can be proposed.

A 69-year-old, never-smoker woman was admitted in 2009 to the Severe Asthma Unit with uncontrolled asthma symptoms. She was sensitized to dust mites and suffered from nasal polyps (NPs) relapsing 6 times after surgery. Daily maintenance treatment consisted of high ICS dose + long-acting beta-agonists and prednisone 5 mg. She also needed 6 bursts of OCS/year for asthma exacerbations (AEs). Pulmonary function was severely compromised (FEV_1 0.69 L, FEV_1/FVC 32%), and the other parameters showed F_ENO 18 ppb, Peripheral Blood Eosinophils (PBE) 1060 cells/μL, total IgE 198 UI/mL, ACT 11/25 and Sinonasal Outcome Test (SNOT-22) 58. She underwent fiberoptic bronchoscopy (protocol 1759/2008-14871/2009) and bronchial biopsies were collected (Fig. 1).

At cell count, eosinophils were 23.58 cells/mm^2 and neutrophils 108.49 cells/mm^2, both above the normality thresholds.[1] Other diagnoses were excluded. Asthma was classified as severe, late-onset, poorly controlled, frequently exacerbating with T2 phenotype[2] and mixed inflammatory profile.

Anti-IgE Omalizumab was prescribed and, after 8 years of treatment, ACT and SNOT-22 improved, PBE decreased as well as AEs (3/year), but FEV_1 unchanged. Daily ICS dose was reduced but still needing OCS. Therefore, Omalizumab was withdrawn due to an unsatisfying response.

In October 2017, after 3 months of washout, she started anti-IL5 Mepolizumab (1° switch) leading, after 3 years of treatment, to a good clinical and laboratory response with PBE falling to 130 cells/μL and further ICS dose reduction. Daily OCS was no longer needed and AEs were abolished. However, the patient still complained of bothering nasal symptoms due to recurrence of NPs. Mepolizumab was interrupted and, following 3 months of washout, anti-IL-4Rα Dupilumab was prescribed (2° switch).

After just 3 weeks of therapy the patient showed great amelioration in terms of ACT and SNOT-22 score, FEV_1 and F_ENO values. As expected, PBE mildly increased. In March 2021, after 2 months, the patient complained of persistent tachycardia and PBE raised to 2380 cells/μL. Based on these side effects, Dupilumab was interrupted.

After 4 months of a wash-out, asthma was uncontrolled and exacerbated, leading to starting anti-IL5Rα Benralizumab (3° switch). After 6 months, clinical and functional parameters improved, AEs were abolished and PBE dropped to 0 cells/μL (Table 1). Facial RM showed a residual inflammatory tissue in osteomeatal complexes.

Different biologics can be prescribed in severe, uncontrolled, T2-high asthmatics. Based on surrogate biomarkers our patient showed a T2-high phenotype, while bronchial biopsies demonstrated a mixed inflammatory profile configuring a more severe disease.[2,3] After prolonged Omalizumab treatment the patient could not suppress the risk of clinical worsening and couldn’t interrupt OCS, leading to the switch to Mepolizumab. Currently, there are no clear recommendations neither for switching from one biologic therapy to another nor about the length of the washout period between drugs.[4] Patients who failed Omalizumab treatment resulted in Real-life experiences to be good candidates for a successful anti-IL5 therapy.[5]

Mepolizumab seemed to be the correct treatment for our patient. However, recurrence of NPs, a well-known risk factor for poor asthma control and a cause of poor response to anti-IL-5 treatments, may cause physicians to switch between biologics.[4] Dupilumab, effective on both severe asthma and NPs,[6] was started leading to clinical improvement after only 3 weeks. Unfortunately, it was cautiously withdrawn after side effects occurred. Even if clinically mild, side effects significantly impact the quality of life, for

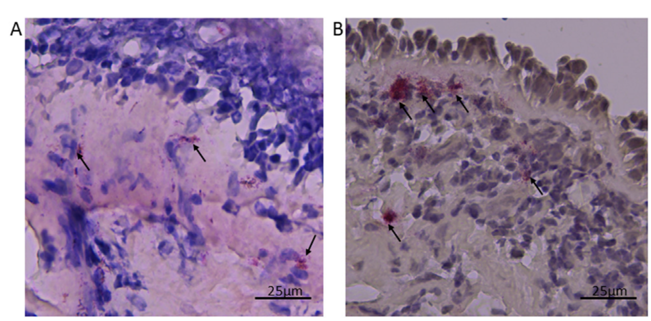

Fig. 1 Representative photomicrographs showing cells staining positively for the eosinophilic cationic protein (eosinophils, panel A) and neutrophil elastase (neutrophils, panel B) (40 × magnification). Arrows indicate positively stained cells.

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Table 1 Table showing the improvement over time in functional pulmonary parameters, clinical scores, decrease in asthma exacerbations (OCS bursts previous year) and maintenance treatment,switching from one biologic to another.

	Before Omalizumab (2009)	After 8 Years of Omalizumab (2017)	After 3 Years of Mepolizumab (Oct 2020)	After 3 Weeks of Dupilumab (2021)	After 6 Months of Benralizumab (2021)
ACT score	11/25	20/25	22/25	23/25	25/25
SNOT-22 score	58	36	26	4	6
FEV_1 (L)	0.69	0.67	0.81	1.24	1.10
FEV_1 (% pred.)	36	45	50	70	81
FVC (L)	2.18	1.97	2.10	2.71	2.29
FVC (% pred.)	95	106	131	117	134
FEV_1/FVC ratio (%)	32	31	29	45.7	42
FEV_1/FVC ratio (% pred.)	-	37	38	59	51
F_ENO (ppb)	18	-	42	28	58
PBE (cells/μL)	1060	630	130	1020	0
PBE (%)	12.6	7.7	1.9	14	0
Asthma exacerbations previous year (n)	6	3	0	**Asthma exacerbations from the start of Dupilumab:** 0	**Asthma exacerbations from the start of Benralizumab:** 0
Inhaled maintenance treatment (Budesonide/mcg/day)	1800	1200	800	800	800
Oral corticosteroid (Prednisone/mg/day)	5	2.5	-	-	-

ACT= Asthma control test, FEV_1= Forced expiratory volume in the first second, FVC= forced vital capacity, FEV_1/FVC ratio=Tiffeneau Index, F_ENO=Fractional exhaled nitric oxide, PBE=Peripheral blood eosinophils, SNOT-22=Sinonasal outcome test, % pred.= % predicted.

example tachycardia in an old lady already symptomatic for asthma. A mild to moderate increase in PBE is expected but usually transient following Dupilumab. However, high and sustained PBE suggests close monitoring and investigation of eosinophilic-related morbidity.[7]

Finally, Benralizumab caused complete control of nasal and asthmatic symptoms with evidence of mild inflammatory sinonasal tissue reduction.

This clinical case shows that the appropriate biologic should be selected according to the dominant severe asthma phenotype. Surrogate biomarkers are currently used for disease phenotyping, however, overlap between T2 endotypes is often evident, complicating the choice for the best treatment. In some specific cases, performing bronchial biopsy gives a more detailed profile of the underlying inflammatory pathway. Today the identification of treatable traits, more susceptible to a certain biologic, may guide the choice. The lack of biomarkers predictors of clinical response may justify the failure and a switch of treatment. An algorithm for appropriate switching has been proposed but its application in real life needs further observation.[8]

We evaluated 4 different biologics in the same patient, improving step-by-step from one biologic agent to another (Table 1). At the age of 82, she feels much better than when she was 69: FEV_1, ACT and SNOT improved over time such as the burden of daily treatment.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.12.004.

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LETTER TO THE EDITOR

Prevascular mediastinal angyomiolipoma. A case report

Angiomyolipomas are benign mesenchymal tumours that commonly arise in the kidney.[1,2,5,7,9] However, they can also occur in extrarenal sites, including the skin, oropharynx, abdominal wall, gastrointestinal tract, heart, lung, liver, uterus, penis, and spinal cord.[1,2,5,9] The occurrence of angiomyolipoma in the mediastinum is extremely rare,[1-4] with only a few documented cases in the medical literature. This article presents a case of angiomyolipoma detected in the prevascular mediastinum, which was accompanied by recurrent pleural effusion.

A 78-year-old male presented to our hospital with a large-volume and recurrent left pleural effusion. Cytologic examination of the effusion was negative for malignant cells. Routine haematologic, blood chemical and enzyme tests were within normal limits. Computed tomography (CT) (Fig. 1A) of the thorax revealed a mediastinal pleural mass associated with extensive pleural effusion on the left. Magnetic resonance imaging (MRI) (Fig. 1B) showed a solid, heterogeneous lesion in the mediastinal pleura, with well-defined limits and regular contours, measuring approximately 36 × 23 mm with the longest perpendicular axes. The lesion was mostly isointense on T1 and moderately hyperintense on T2, with central hypointense areas. Additionally, a lesion was identified at the level of the pectoralis major muscle sheath, measuring about 73 × 41 mm in the longest perpendicular axes. The two lesions, although undetermined by imaging, suggested the possibility of schwannomas. A biopsy of the lesion in the pectoralis major muscle sheath was performed, and the morphological and immunohistochemical findings were consistent with a diagnosis of schwannoma.

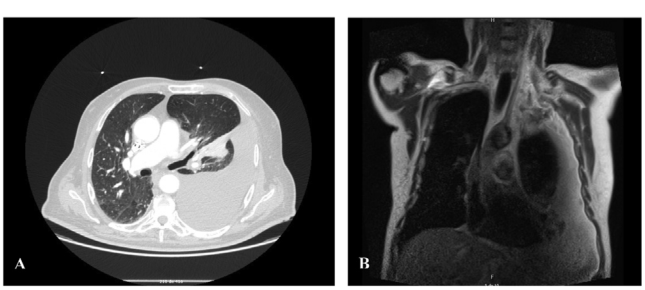

Fig. 1 Computed tomography (CT) scan (A), Chest MRI (B). Mediastinal pleural mass associated with extensive pleural effusion on the left.

To confirm the cause of the mediastinal lesion, the patient underwent medical thoracoscopy. A hypervascular, sessile mass was observed in the prevascular mediastinum and subsequently biopsied (Fig. 2). The tumour was not separated from the aorta during the procedure. Histological examination of pleural fragments showed vascular congestion, alveoli filled with macrophages, and compression of the alveoli by a fibroadipose tissue 'mass' (MDM2-) and smooth muscle (actin+), accompanied by capillary proliferation (CD34+). Thrombi were frequently present. No necrosis or mitoses were detected. Histochemical investigation for microorganisms, including PAS, Ziehl-Neelsen, and Grocott staining, yielded negative results. Immunohistochemical analysis was performed to explore other neoplasms, and results for calretinin, BER-EP4, S100, CD1a, Melan-A, HMB45, and p53 were negative (Fig. 3)

Angiomyolipoma of the mediastinum is an exceptionally rare mesenchymal tumour consisting of fat, smooth muscle cells, and abnormal, tortuous, thick-walled blood vessels.[1,2,3,6] Although angiomyolipomas are usually found in renal tissue and may be linked to tuberous sclerosis and lymphangioleiomyomatosis (LAM),[1,3,6,7] our patient had no prior history of either condition.

Angiomyolipomas are characterised by the expression of melanoma markers (HMB45 and melan-A) in tumour cells, as well as smooth muscle component positivity for muscle actin-specific marker (HHF35) and desmin.[2,8] Although the immunohistochemical study did not fully support the diagnosis, the observed morphological features strongly suggest that angiomyolipoma is likely the correct diagnosis, considering its rarity in the mediastinum and the limited number of reported cases in the literature. The histology was reviewed by three different pathologists.

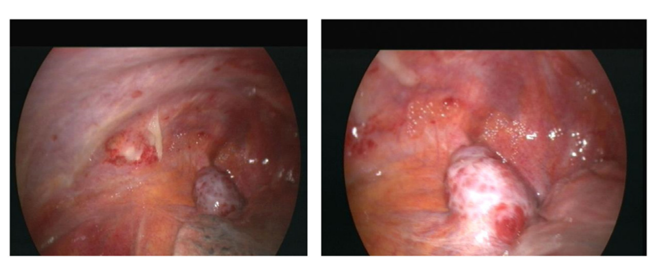

Fig. 2 Videothoracoscopy. Mediastinal pleural lesion.

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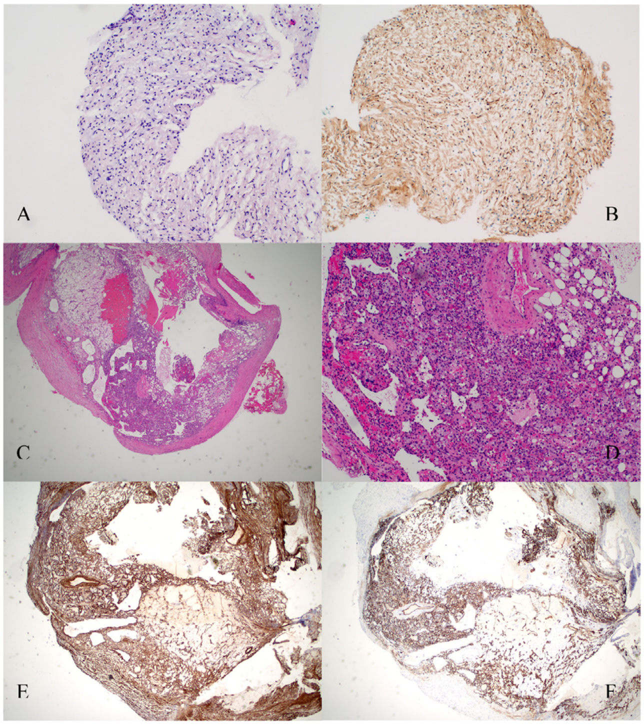

Fig. 3 Histopathology sections. A. Lesion in the pectoralis major muscle sheath. Hematoxylin and eosin staining. B. Lesion in the pectoralis major muscle sheath. Schwann cells are strongly positive for S-100 protein (×10). C. Hematoxylin and eosin staining revealing features of the excised pleural mass with mature adipose tissue, thick-walled blood vessels and smooth muscle cells. Pathological findings of angiomyolipoma. D. 10× magnification. E. Pleural lesion. Smooth muscle actin immunohistochemical showed diffuse positivity smooth muscle cells (×10). F. Pleural lesion. Immunostaining for CD34 antigen revealed many CD34-reactive capillaries combined with mature adipocytes (×10).

While renal angiomyolipomas typically exhibit a benign behaviour, there have been rare reported cases where they display more aggressive characteristics, including invasion into the renal vein and inferior vena cava.[11] Angiomyolipoma of the mediastinum is a recognised variant with malignant potential, as seen in renal angiomyolipomas.[3] However, due to the limited availability of long-term follow-up data for mediastinal angiomyolipomas, it remains challenging to fully understand their prognosis and potential for malignant behaviour.

The histology did not show evidence of pleural invasion. The pleural effusion was identified as an exudate and tested negative for malignant cells. The lungs exhibited no signs of lymphangioleiomyomatosis (LAM), and it was considered that the pleural effusion might be reactive.

The management of angiomyolipoma is controversial, and there is limited literature supporting the optimal treatment for pleural angiomyolipoma. However, available literature suggests that small, asymptomatic tumours can be managed conservatively with regular follow-up. For larger tumours with a high risk of spontaneous rupture and bleeding, surgical intervention or selective arterial embolization may be considered as treatment options.[3,4,10]

In conclusion, while angiomyolipoma in the mediastinum is extremely rare, with only a few reported cases in the literature, it should be considered in the differential diagnosis of mediastinal tumours. Unfortunately, further investigation was not possible as the patient passed away due to a complication of the procedure.

Ethical considerations

Written informed consent was obtained from the family for publication of the article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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PHOTO

Mixed squamous cell and glandular papilloma of the bronchus

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A 67-year-old man presented to the Department of Neurointerventional Surgery with a 3-month history of left limb weakness. Chest computed tomography (CT) revealed an endobronchial lesion in the left lingular segmental bronchus (Fig. 1A–C). No respiratory symptoms, such as cough and sputum, were reported, although he had a smoking history

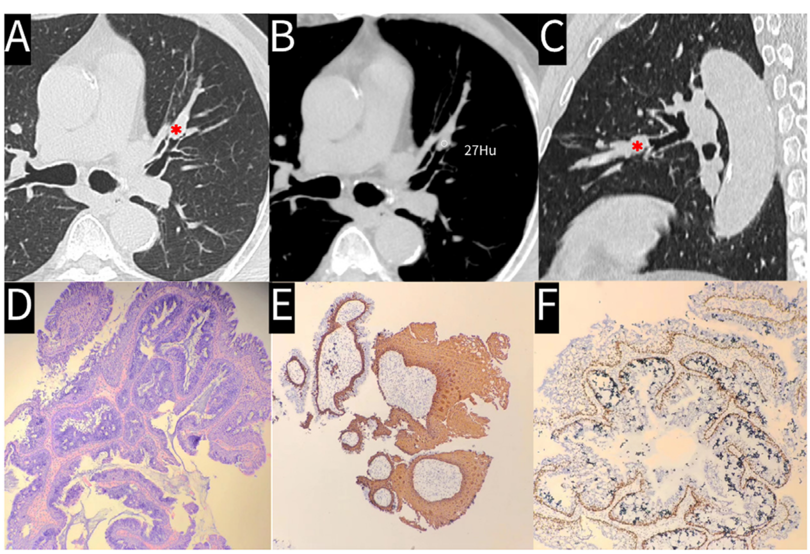

Fig. 1 (A) Axial computed tomography (CT) with lung window showing an endobronchial mass in the left lingular segmental bronchus (asterisk). (B) CT value measurement of the endobronchial mass. (C) Sagittal CT with lung window showing the endobronchial mass (asterisk). (D) Hematoxylin and eosin-stained image showing branched fibrovascular cores in the center of tumor papilla lined by squamous and glandular epithelium. (E) Immunohistochemical staining showing CK5/6 expression in squamous and basal cells. (F) Immunohistochemical staining showing P63 expression in basal cells.

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of 50 pack-years. Fiberoptic bronchoscopy was performed, and the endobronchial mass measuring 1.5 cm × 1.0 cm × 0.8 cm in size was easily electro excised. Histopathological examination led to the diagnosis of mixed squamous cell and glandular papilloma (MSGP) (Fig. 1D) with the following immunohistochemical staining observations: epithelial cell CK5/6 (+) (Fig. 1E), CK7 (+), TTF-1 (+), NapsinA (−), basal cell P63 (+) (Fig. 1F), P40 (+), Ki-67 (1%, +). The patient was feeling well at the 2-month follow-up.

MSGP is a rare endobronchial papillary tumor characterized by a mixture of squamous and glandular epithelial cells. MSGP occurs more frequently in men who smoke and is commonly found in the left lingular segment.[1] As the majority of MSGPs present with a lung mass on the CT image,[2] endobronchial presentation of this MSGP is uncommon. Surgical resection is the mainstay of treatment as MSGP can potentially advance to carcinoma.[2] In patients with limited endobronchial lesions, endoscopic therapy is an option.

Conflicts of interest

None.

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