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Volume 29. Number 4. July/August 2023

# CONTENTS

Pulmonology 29 (2023) 271−272

PULMONOLOGY

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EDITORIAL

# Antisynthetase syndrome with predominant lung involvement. An easy to miss diagnosis

Interstitial Lung Diseases can be extremely challenging in terms of diagnosis. Antisynthetase syndrome (ASYS) represents a major area of concern as it can present with isolated pulmonary involvement and can even mimic other diseases, notably hypersensitivity pneumonitis.[1] ASYS is a clinically distinct subset among the immune inflammatory myopathies, characterized by the presence of autoantibodies against aminoacyl-tRNA synthetases (anti-ARS) that are myositis-specific antibodies. The classic clinical triad of myositis, ILD and arthritis is referred to as complete ASYS. However, all triad findings are rarely found at presentation. Even after extended surveillance extending over one year, a complete ASYS is seen in no more than 50% of patients with anti-Jo1 and even less for patients with non-anti-Jo-1 autoantibodies. Organ involvement and thus clinical presentation depends on the type of anti-ARS antibody meaning that different medical specialties encounter different phenotypes. Rheumatologists are more likely to see patients in whom muscle and joint involvement predominates, while patients with predominant lung involvement are more likely to be referred to pulmonologists.[2] We analyze the diagnostic difficulties of ASYS from the pulmonologists perspective, focusing on four domains, clinical, laboratory, imaging and pathology.

Patients with ASYS, usually presenting to respiratory services are more likely to have isolated lung involvement. Myositis if present can be subclinical without muscle weakness. History is unhelpful and sometimes can be misleading as some patients report exposure to organic antigens, erroneously pointing towards hypersensitivity pneumonitis. Helpful physical findings as mechanic hands, Gottron papules, periorbital edema, and skin erythema, can easily go unnoticed by non experienced pulmonologists.

In cases of ASYS where lung is the first involved organ or in cases with subclinical myositis, muscle enzymes (creatine kinase and aldolase) can be normal. Aminoacyl-tRNA synthetases antibodies (anti-ARS) are located in the cytoplasm and result in a negative ANA test which does not indicate autoantibody negativity in the context of ASYS.[3] Furthermore, the extractable nuclear antigen (ENA) panel includes only anti-Jo-1 out of the eight known anti-ARS antibodies.[4] A negative ENA panel cannot exclude the diagnosis of ASYS and can miss patients that are at high risk for developing isolated or predominant lung involvement (e.g. anti-PL-7, anti-PL-12 and anti-EJ) [4]. A prominent bronchoalveolar lavage lymphocytosis ($\geq$30%), usually pointing towards hypersensitivity pneumonitis has been reported in ASYS.[1]

Imaging findings of ASYS based on high resolution computed tomography (HRCT) are not specific. They include bilateral areas of ground glass, consolidation, and reticulation. Traction bronchiectasis points to the presence of underlying fibrosis. The corresponding patterns are Non Specific Interstitial Pneumonia (NSIP), Organizing Pneumonia (OP), mixed NSIP/OP, while a Usual Interstitial Pneumonia pattern (typical or probable) has only rarely been described.[5] In some patients there are diffuse areas of ground glass, alternating with normal parenchyma, resulting in a mosaic pattern. Also, consolidative areas tend to have a peribronchial distribution. The presence of mosaic attenuation and peribronchial distribution, especially when there is a history of exposure to an inciting antigen, can be strongly deceptive in favor of hypersensitivity pneumonitis. Coronal reformations can be helpful as they can highlight the predominant location of findings to the lung bases with sharp demarcation in the craniocaudal plane. This is known as the “straight edge” sign and is considered to be indicative of an underlying connective tissue-interstitial lung disease.

Lung biopsy findings in ASYS are also not specific. The presence of dense lymphocytic inflammation with peribronchial distribution, predominance of plasma cells, lymphoid aggregates with or without germinal centers, follicular bronchiolitis and pleuritis raise suspicion of an underlying collagen tissue disease. However, these findings are by no means pathognomonic of ASYS or connective tissue-interstitial lung disease in general. Furthermore, there can be significant overlap with other diseases with HP being a characteristic example.[1] In a patient with ASYS and avian exposure, prominent bronchoalveolar lavage lymphocytosis, mosaic pattern on HRCT, pathology could be considered compatible with HP, leading to a false diagnosis.

Timely diagnosis of ASYS has significant impact on patients’ outcome. Lung involvement in the context of ASYS is not only one of the most common manifestations but also a major factor of increased morbidity and mortality. Delayed diagnosis has

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**Table 1** Diagnostic challenges in amyopathic lung predominant idiopathic inflammatory myositis.

| | |
|---|---|
| Clinical<br>• Idiopathic inflammatory myositis with predominant lung involvement is rare.<br>• Musclesymptomsareabsent.<br>• Exposure toan inciting antigen can be misleading.<br>• Skin findings or arthritis can be overlooked. | Laboratory<br>• Muscle enzymes are within normal range.<br>• ANA can be negative/lowtiterpositive.<br>• ENA panel tests only for anti-Jo-1.<br>• BAL lymphocytosis is not pathognomonic |
| Imaging<br>• Imaging patterns (NSIP, OP, mixed NSIP/OP) are not specific.<br>• Mosaicattenuation orpredommant peribronchial distribution can be present pointing to more common diagnoses. | Pathology<br>• Pathology findings (dense lymphocytic inflammation with peribronchial distribution, lymphoid aggregates with or without germi nal centers) are not specific. |

been associated with worst prognosis and not surprisingly is most commonly observed in non-anti-Jo-1 patients.[6] The significance of this observation is twofold. First, ENA panel does not test for non-anti-Jo-1 autoantibodies. Second, patients with non-anti-Jo-1 autoantibodies, mainly anti-PL-7, anti-PL-12 and anti-EJ are most often associated with clinically isolated pulmonary involvement and thus more easily to be misdiagnosed. ASYS has the perfect camouflage recipe (Table 1). It can present with isolated pulmonary involvement, skin manifestations can be absent or go unnoticed by the non-experienced pulmonologist, and muscle involvement can be present, but subclinical, resulting in normal muscle enzymes. ANA can be negative and ENA panel does not test for anti-ARS except for anti-Jo-1. Furthermore, ASYS can notoriously masquerade as hypersensitivity pneumonitis in the presence of an inciting antigen, prominent bronchoalveolar lavage lymphocytosis, mosaic attenuation of the lung parenchyma and/or bronchocentric distribution on HRCT, and pathology findings exhibiting bronchiolocentric lymphocytic inflammation with lymphoid aggregates and peribronchiolar metaplasia.

In the above-mentioned clinical scenario imaging holds a key role. The presence of radiological NSIP and/or OP pattern should always raise suspicion of underlying ASYS even in the presence of a working diagnosis, as HP. It is impossible to exclude ASYS unless testing for anti-ARSs. Biomarkers are the basis of personalized medicine. Thankfully, in ASYS we have myositis specific antibodies as diagnostic biomarkers. It is important to actively involve rheumatologists in the context of multidisciplinary discussion to bridge the gap between the two medical specialties and increase awareness and expertise for both sides. Collaborative studies to determine the exact incidence of ASYS in ILD patients presenting to respiratory departments with radiological NSIP and/or OP pattern are needed. In the meantime, there should be a low threshold in ordering a myositis panel for these patients. A joint statement can serve as a valuable first step towards this goal.

## Conflicts of interest

None related to the present work.

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COMMENT

# Biologics and anti-Sars Cov2 vaccination in severe asthma riding the big wave: Unity is strength!

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In the spring of 2020, at the beginning of Covid-19 pandemic, there was a consistent medical concern raised about patients suffering from severe chronic respiratory diseases. For asthma patients, the GINA guidelines, as well as all international scientific societies, promptly provided statements strongly recommending inhalation therapy maintenance, as well as monoclonal antibodies treatment.[1-3] Indeed, at that time optimal asthma control and prevention of exacerbations represented a priority to reduce the risk of infection associated with admission to ER or hospitalization. In this regards we developed a telemedicine-based approach to monitor patients at home remotely, thus reducing access to hospital and consequently the risk of infection over the prolonged lockdown.[4,5] At the same time, we encouraged severe asthmatic patients to self-administer biologics after an appropriate face-to-face consultation or even by remote training.[4] Alternatively, home care projects were launched for the delivery and administration of biological drugs by healthcare personnel.[6]

In the pre-vaccination era, severe asthma patients treated with biologics targeting type 2 inflammation were not generally considered at increased risk for COVID-19, when compared with age- and geography-matched non-asthmatic population.[7,8] In the Severe Asthma Network in Italy (SANI), 26 cases of infections out of 1504 patients (1.73%) were reported and related mortality was 7.7%, lower than that observed in the general Italian population (14.5%).[9] Accordingly, the Dutch Severe Asthma Registry RAPSODI recorded an incidence of Sars-Cov-2 infection equal to 1.4% among severe asthma patients on biologics.[10] However, in this population the incidence of COVID-19 related hospitalization and intubation were higher, and death was 5 times higher than that observed in a comparable sample of Dutch population for age and sex.

At that time, from our experience among the 145 severe asthma patients (79/66 F/M; mean age 59±3 ys) treated with monoclonal antibodies, 12 (8%) contracted Sars- Cov-2 infection and one was admitted to ICU for respiratory failure and severe pneumonia. The remaining patients received home therapy with oral cortisone and antibiotic (azithromycin), with an average recovery time of 18±3 days.

The anti-Sars-Cov-2 vaccine became available at the beginning of 2021. Subsequently, an International Consensus produced by multidisciplinary group of international experts recommended vaccination for asthmatic subjects. However, an allergy evaluation was mandatory for patients with a history of severe allergic reaction to vaccine/excipient.[11]

At our clinic, in April 2021 we timely offered to administrate the anti-Sars-Cov-2 vaccination to severe asthmatics. No serious adverse events were recorded. Less than 20% of patients reported side effects, most of which classified as very common side effects.[12] In terms of patient reported outcomes, a significant improvement of both ACT and AQLQ was observed between the first and the second dose administration, ruling out the risk of asthma exacerbations related to the COVID-19 vaccine. During 2021 we also administered

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the third dose of Sars- Cov-2 vaccine to severe asthma patients, without observing any side effects.

In the spring 2022, on the Omicron pandemic wave, 177 severe asthma patients (99/78 F/M; mean age 56±4 ys) were on biologic treatment at our clinic: 33% were on Benralizumab 31%, on Mepolizumab, 26% on Omalizumab and 10% on Dupilumab. Among them 93 (52%) were infected by Sars-CoV-2 and one had re-infection. Nobody required hospitalization and in all cases the disease was treated at home. Most of the subjects (82%) presented a paucisymptomatic or asymptomatic infection, whereas in the remaining ones the administration of oral corticosteroids was prescribed. Anti-Sars-Cov-2 monoclonal antibody therapy was also used in 3 subject. The average recovery time was 11±2 days.

After two years of Covid-19 pandemic, the reported data provide us a glimmer of light and lead to some considerations.

According to the evidence from literature, allergic asthmatic subjects seem to be less likely to be infected by SarS-CoV-2. This could be for several reasons.[13] First, the anti-inflammatory action of inhaled corticosteroids (ICS) and their possible "turn off" effect on "cytokine storm" elicited by the virus. Second a down regulation of ACE2 and TMPRSS2 receptors, which can be related to the allergic inflammation per se or the action of ICS.[14]

On clinical ground, biologics targeting type-2 inflammation seem to decrease the risk of COVID-19 related asthma exacerbations by reducing airway inflammation and possibly through specific antiviral properties. In fact, Omalizumab, crosslinking IgE, leads to lower IFN production. Mepolizumab, Reslizumab and Benralizumab, increase the ratio of IFN γ /IL-5 mRNA, which is associated with lower viral shedding and faster disease clearance.[15]

Based on the negligible number of patients reporting side effects after vaccination and the lack of asthma exacerbations consequent to vaccine,[12] a prolonged COVID-19 vaccination campaign worldwide in patients with severe asthma is advisable.

In summary, the combination of biological treatment and anti-Sars-Cov-2 vaccination kept patients with severe asthma controlled even in the presence of the highly contagious Omicron wave causing only a disease of mild-medium severity.

These results and the above considerations undoubtedly need to be confirmed by a large number of cases and require further research. To this end, national registries of severe asthma patients and the use of international platforms become essential in order to come to more definitive conclusions.

## Author Contributions

Conceptualization: G.G., V.A.; Data curation: G.G., M. B., C. B. F.; Formal analysis: G.G., V.A.; Funding acquisition, Writing-Original draft: G.G., V.A.; Writing-Review & Editing: G. G., V.A. All authors agree to be accountable for all aspects of the work.

## Declaration of Competing Interest

No potential conflict of interest was reported by all the authors.

## Statement

The studies involving human participants were reviewed and approved by local Ethics Committee of Hospital University of Padua, Italy. The patients/participants provided their written informed consent to participate in this study.

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## Data availability statement

The data is available for reproduction of results on request from the corresponding author.

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Pulmonology 29 (2023) 276–283

PULMONOLOGY

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ORIGINAL ARTICLE

# Development and validation of a prognostic index (BODEXS90) for mortality in stable chronic obstructive pulmonary disease

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Pulmonary disease, chronic obstructive;
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**Abstract**
*Introduction:* Several multidimensional indices have been proposed to predict mortality in chronic obstructive pulmonary disease (COPD). The BODEX index is simple and easy to use for this purpose in all clinical settings. Only a few prognostic indices have integrated oxygenation variables, with measurement methods that are not practical for real life clinical practice in all settings.
*Objectives:* To develop and externally validate a new prognostic index (BODEXS90) that combines the variables included in BODEX index with rest peripheral oxygen saturation measured with finger oximetry ($SpO_2$) to predict all-cause mortality in stable COPD.
*Method:* Observational, non-intervention, multicenter historic cohort study. The BODEXS90 index was developed in a derivation cohort and externally validated in a validation cohort. Calibration of the index was carried out using Hosmer-Lemeshow test. The discrimination capacity of BODEXS90 and BODEX were compared by means of receiver-operating characteristics curves. Modelling of the index was carried out by crude and adjusted Cox regression analysis.

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*Results:* The derivation and validation cohorts included 787 and 1179 subjects, respectively. $SpO_2$ predicted all cause-mortality independently of BODEX index. Discrimination capacity of BODEXS90 to predict the outcome was significantly higher than that of BODEX, particularly for more severely affected patients, both in the derivation and in the validation cohorts.
*Conclusions:* The new index is potentially useful for designing clinical decision-making algorithms in stable COPD.


## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death in the world.[1] Therefore, predicting mortality is of paramount importance to design management strategies for this disease. Traditionally, the forced expiratory volume in one second ($FEV_1$) has been the most widely used predictor of mortality. However, it is currently clear that COPD is a complex disease, with multiple dimensions involved in its prognosis. As a consequence, several multidimensional indices have been validated, integrating assorted prognostic determinants, with the objective of improving the predictive capability of adverse outcomes provided by $FEV_1$ alone.[2] In this regard, the BODE (body mass index, airflow obstruction, dyspnea, exercise capacity) index is more effective than $FEV_1$ in predicting mortality.[3] However, the index does require performance of a 6-minute walk test, a technique that is time-consuming and requires sufficient space to perform it, making it difficult to be carried out in some settings, like primary care facilities. The BODEX index simplifies the BODE index and precludes these drawbacks by replacing the exercise capacity component with the history of COPD exacerbations that required hospitalization the year prior to patient's evaluation.[4] This index has a similar prognostic capacity to BODE.[4]

Chronic respiratory failure is associated with a higher mortality rate in COPD, and it is another dimension that is amenable to treatment, with long-term oxygen therapy.[5] For that reason, oxygenation variables might be theoretically valuable for use as a component of prognostic indices in COPD. Two previously validated indices, mBODE and DOREMI BOX have integrated these variables, but they used measurement methods (maximal oxygen consumption during exercise test and blood gas analysis, respectively) that are difficult to implement in all clinical settings and throughout the whole spectrum of disease severity.[6,7] On the other hand, measurement of peripheral oxygen saturation by means of pulse oximetry ($SpO_2$) correlates well with arterial partial pressure of oxygen,[8] it is cheap, easy and readily available in all clinical scenarios.

We hypothesized that a new index that combines rest $SpO_2$ with the BODEX index variables would increase the capacity of BODEX index to predict all-cause mortality in stable COPD patients. The objectives of this study were: 1) to determine whether rest $SpO_2$ and BODEX index are independent predictors for death, 2) to develop an index that combines the BODEX components with $SpO_2$ (BODEXS90), 3) to assess whether the prognostic capacity of BODEXS90 is higher than that of BODEX in a derivation cohort and 4) to externally validate the index in an independent cohort.

## Methods

### Study population and setting

This was an observational, non-intervention, multicenter historic cohort study. Inclusion criteria were age > 35 years, a diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] and clinical stability at the time of the first visit (i.e.: free of exacerbations in the prior 3 months). Exclusion criteria were the diagnosis of concomitant chronic respiratory diseases other than COPD (e.g: interstitial lung disease, pneumoconiosis). The derivation cohort contained consecutive patients seen at a second-level university hospital's dedicated COPD clinic (Hospital Universitario Lucus Augusti, Lugo, Spain), visited from January 2008 to October 2019. The participants were identified from a database that was set-up for clinical purposes. The validation cohort was made up of a combination of three different cohorts: two were prospective observational cohorts from third-level University hospitals (Hospital de Galdakao-Usansolo, Galdakao, Spain and Hospital Universitario Marqués de Valdecilla, Santander, Spain) recruited from April 2003 to November 2004 and from March 2018 to August 2018, respectively. The third one was a clinical cohort, formed of all consecutive patients seen at a general pulmonology clinic from a 3rd level university hospital (Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain) which was visited from January 2012 to December 2014.

### Study variables

On the first visit, the following variables were registered: age, sex, history of tobacco consumption (pack-year index, current versus former smoker), body mass index ($kg/m^2$), value of the age-adjusted Charslon comorbidity index,[9] percent-predicted forced expiratory volume in 1-second ($FEV_1$%), percent-predicted forced vital capacity (FVC%), $FEV_1$/FVC index, value of $SpO_2$ measured with the patient resting in sitting position, dyspnea measured using the modified medical research council scale (mMRC), and number of exacerbations that required hospital management during the year previous to the first visit. The BODEX index

**Table 1** Variables and score values used for the calculation of the BODEXS90 index.

| Variable | | Score 0 | 1 | 2 | 3 |
|---|---|---|---|---|---|
| B | BMI ($Kg/m^2$) | > 21 | ≤ 21 | | |
| O | $FEV_1$% | ≥ 65 | 64 − 50 | 49 -36 | ≤ 35 |
| D | MMRC dyspnea scale | 0 − 1 | 2 | 3 | 4 |
| EX | Number of COPD exacerbations[a] | 0 | 1 -2 | ≥ 3 | |
| S90 | Resting $SpO_2$ | ≥ 90% | < 90% | | |

[a] Exacerbations that required hospital management, the year before the index date. BMI: body mass index. $FEV_1$: forced expiratory volume in 1 s. COPD: chronic obstructive pulmonary disease. $SpO_2$: peripheral oxygen saturation.

was calculated as previously described.[4] Introducing $SpO_2$ in a multivariable Cox proportional hazard regression analysis did not significantly change the hazard ratios (HR) of the BODEX variables to reach the endpoint outcome (see below), and the HR associated to a $SpO_2$ below 90% was 1.6. Thus, the new BODEXS90 index was computed by adding one point to the BODEX index when $SpO_2$ was below 90% (Table 1).

## Outcome variable

All-cause mortality was the outcome variable of the study. Vital status was determined by reviewing electronic medical records and, in some cases, by telephone calls to patients or relatives. Dates of death were obtained from the medical records.

## Statistical analysis

Descriptive analyses were carried out by calculating mean and standard deviation for continuous variables and frequency and percentages for discrete variables. Comparisons between the derivation and validation cohorts were performed by means of Student's T-test or Pearson's chi-square test, as appropriate. To assess whether BODEX and $SpO_2$ had independent value as predictors of mortality, a Cox proportional hazards regression analysis was carried out in the derivation cohort, by introducing both variables simultaneously. Both BODEX index and $SpO_2$ were coded continuously, in one-unit increments. The ability of BODEX and BODEXS90 indices to predict mortality was compared by means of receiver-operating characteristics (ROC) curves. For this analysis, the indices were coded continuously, in 1-unit increments. We included a ROC analysis for the most commonly used predictor variable (FEV1%), as a comparator. The areas under the curves were compared using the method of De Long et al.[10]

Calibration of the index was performed by fitting a multivariate logistic regression model and using Hosmer-Lemeshow goodness-of-fit test. All-cause death was the dependent variable and predictors were BODEXS90 index plus age-adjusted Charlson index, pack-years index, and current smoking status. BODEXS90, Charlson and pack-years indices were coded continuously, in 1-unit increments, while current smoking status was coded dichotomously (yes/no).

We used Cox proportional hazards regression models to calculate HR for mortality and 95% confidence intervals (CI) for BODEX and BODEXS90. We calculated crude (model 1) and adjusted (model 2) HR. In model 2, we adjusted for pack-years index, current smoking status and age-adjusted Charlson index, coded as previously mentioned. To enhance the applicability of the indices for clinical practice, BODEX and BODEXS90 were divided into quartiles for this analysis[3,4] (Table 2).

**Table 2** Cut-off points for classification of BODEX and BODEXS90 into quartiles.

| | Points of indices | |
|---|---|---|
| | BODEX | BODEXS90 |
| Q1 | 0—2 | 0—2 |
| Q2 | 3—4 | 3—4 |
| Q3 | 5—6 | 5—7 |
| Q4 | 7—9 | 8—10 |

Survival curves for BODEXS90 index, divided into quartiles, were constructed using the Kaplan-Meier Method. The curves were compared by means of the log-rank test.

All the analyses were repeated in the validation cohort using the same methodology. All effects were considered significant at a p-value < 0.05. The statistical analysis was performed with MedCalc statistical software Version 13.3.3.0 (MedCalc Software bvba, Ostend, Belgium)

We did not use an *a priori* sample size calculation because this is a retrospective analysis of cohorts that recruited patients for other studies. Further, there are no overall accepted methods to estimate the sample size for derivation and validation studies of risk prediction models.[11] It has been suggested that an adequate sample size for these studies should include a number of participants ≥ 20 with the outcome event per candidate variables for derivation cohorts, and a number of at least 100 events for validation cohorts.[12] Our sample and the number of events exceeded these thresholds (see results).

## Compliance with ethical standards

The collection of clinical data from the medical records was originally authorized by the ethical committees. We obtained specific authorization to carry out the present study (Comité de Ética de Investigación Clínica del Hospital Universitario Nuestra Señora de Candelaria, Registry number: CHUNSC_2020_52). The data were de-identified for analysis. Informed consent was waived for this analysis due to the retrospective, non-interventional design of the study and the use of anonymous clinical data for the analysis.

## Results

The derivation cohort included 792 patients and the validation cohort included 1234 subjects. Five patients were lost to follow-up in the derivation cohort and 55 in the validation cohort, mainly because the patients moved to other areas or because they had withdrawn from the original prospective studies. Thus, the final sample size for the derivation and the validation cohorts were 787 and 1179, respectively. As contemplated by the Spanish COPD guidelines,[13] all the study variables are systematically registered in the participant centers, thus there were few missing data. Only 15 (1.9%) cases in the derivation cohort and 32 (2.7%) subjects in the validation cohort had missing data. Therefore, since the risk of bias was low, imputation techniques were not deemed necessary and complete case analysis was carried out.[14]

Table 3 shows the characteristics of the derivation and validation cohorts. There were significant differences in most variables and, in general, the patients from the validation cohort had less severe disease. Follow-up time was similar for both cohorts.

Table 4 shows the results of the Cox proportional hazards analysis to assess whether BODEX and $SpO_2$ had independent value as predictors of mortality. Both variables independently predicted the risk for all-cause death both in the derivation and the validation cohorts.

Area under the ROC curve (AUC) to predict mortality for BODEXS90 in the derivation cohort was 0.753 (95% CI: 0.722 − 0.783), slightly but significantly higher than the AUC for BODEX: 0.745 (95% CI: 0.713 − 0.775), difference between AUC: 0.008 (95% CI: 0.002 − 0.013), $p = 0.006$, and higher than the AUC for FEV1%: 0.687 (95% CI: 0.654 − 0.720), difference: 0.065 (95% CI: 0.037 − 0.094), $p < 0.001$.

The AUC for BODEXS90 and BODEX in the validation cohort were 0.670 (95% CI: 0.640 − 0.695) and 0.663 (95% CI: 0.636 − 0.691), respectively. The difference between AUC was small but also statistically significant: 0.007 (95% CI: 0.0001 − 0.008), $p = 0.04$. The AUC for BODEXS90 was also higher than that of FEV1% in this cohort: 0.617 (95%: 0.588 − 0.645), difference: 0.051 (95% CI: 0.026 − 0.076), $p < 0.001$.

The BODEXS90 provided an adequate match between predicted and observed mortality (Fig. 1). The value of the Hosmer-Lemeshow statistic was 5.21 in the derivation cohort and 12.8 in the validation cohort ($p = 0.73$ and 0.11 with 8 degrees of freedom, respectively).

The HR for mortality for the highest quartiles of BODEXS90 were higher than the highest quartiles of BODEX, both in crude and adjusted models, and in the derivation and validation cohorts, suggesting that BODEXS90 is a better predictor of mortality than BODEX (Table 5).

Fig. 2 shows the Kaplan-Meier survival curves for the BODEXS90 quartiles in the derivation and validation cohorts. The differences between curves were significant for both cohorts ($p < 0.0001$ for both samples).

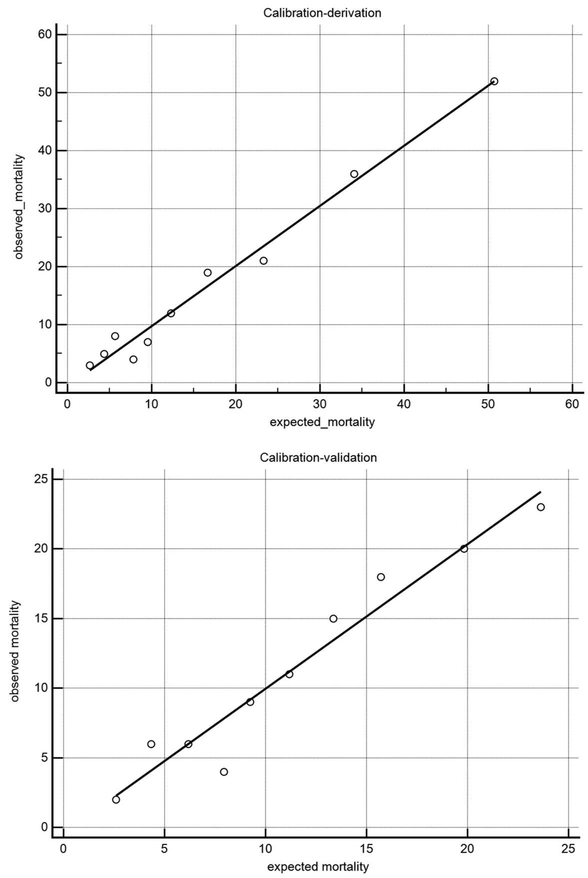


**Fig. 1** Calibration plot of the BODEXS90 score adjusted by pack-years index, current smoking status and age-adjusted Charlson index in the derivation and validation cohorts.

## Discussion

The present study has shown that $SpO_2$ has additional prognostic value to predict mortality in stable COPD patients, independent of BODEX index, and that combining oximetry results with the BODEX index components, in a new composite BODEXS90 index, increases the ability to predict all-cause mortality in this population, particularly in the most severe cases.

COPD is a major health problem worldwide. Predicting mortality in this disease is an important element to design follow-up and treatment strategies. COPD is a heterogenous, multi-component disease, and using a single dimension, like lung function variables, to predict mortality does not take into account the complexity of the factors that can influence the prognosis of patients. The GOLD initiative acknowledges the value of composite scores to predict disease outcomes and recognizes that the BODE composite score is a better predictor of survival than individual components of the index.[1] GOLD also admits that simpler composite indices that do not include exercise test might be suitable alternatives. These indices might be easier to use in non-specialized settings, but validation studies are needed before they can be used in clinical practice.[1]

Many prognostic models have been studied in COPD, although only a minority has been externally validated.[15] Some of these, like the ADO index include non-modifiable

**Table 3** Characteristics of the derivation and validation cohorts.

| | Derivation cohort (N = 787) | Validation cohort (N = 1179) | P |
|---|---|---|---|
| Age, years | 67.8 ± 9.5 | 68.0 ± 8.8 | 0.63 |
| Male sex, n (%) | 697 (88.5) | 826 (70.0) | < 0.0001 |
| Packs-year | 58.6 ± 30.0 | 49.1 ± 24.4 | < 0.0001 |
| Current smokers, n (%) | 212 (26.9) | 139 (11.7) | < 0.0001 |
| SpO2, % | 93.1 ± 4.4 | 94.3 ± 2.7 | < 0.0001 |
| Subjects with SpO2 < 90%, n (%) | 128 (16.2) | 66 (5.5) | < 0.0001 |
| $FEV_1$, % | 50.4 ± 17.2 | 55.5 ± 17.2 | < 0.0001 |
| FVC, % | 74.8 ± 17.5 | 81.9 ± 19.5 | < 0.0001 |
| $FEV_1$/FVC, % | 48.8 ± 12.5 | 52.4 ± 11.2 | < 0.0001 |
| GOLD 1, n (%) | 44 (5.5) | 88 (7.4) | 0.11 |
| GOLD 2, n (%) | 351 (44.5) | 643 (54.5) | < 0.0001 |
| GOLD 3, n (%) | 283 (35.9) | 379 (32.1) | 0.08 |
| GOLD 4, n (%) | 109 (13.8) | 69 (5.8) | < 0.0001 |
| BMI, kg/$m^2$ | 28.2 ± 5.9 | 28.1 ± 4.9 | 0.68 |
| BODEX index | 2.5 ± 1.9 | 2.5 ± 1.7 | 1.00 |
| Charlson index[a] | 5.3 ± 1.9 | 4.9 ± 2.0 | < 0.0001 |
| Follow-up time, months | 56.0 ± 30.1 | 56.3 ± 32.5 | 0.83 |
| Deaths, n (%) | 217 (27.5) | 321 (27.2) | 0.92 |

[a] Age-adjusted. FVC: forced vital capacity. GOLD: global initiative for chronic obstructive lung disease. For further definitions see legend to Table 1.

**Table 4** Results of the Cox proportional hazards regression model to assess the independent value of BODEX and SpO2 to predict mortality in the derivation and validation cohorts.

| | Derivation cohort | | Validation cohort | |
|---|---|---|---|---|
| Covariate | HR (95% CI) | P | HR (95% CI) | P |
| BODEX | 1.28 (1.19–1.38) | < 0.0001 | 1.23 (1.15–1.32) | < 0.0001 |
| $SpO_2$ | 0.93 (0.91 – 0.96) | < 0.0001 | 0.93 (0.90 – 0.97) | 0.0009 |

HR: hazard ratio. CI: confidence interval. For further definitions see legend to Table 1.

**Table 5** Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality, for BODEX and BODEXS90 indices coded in quartiles, in derivation and validation cohorts. Model 1: crude HR. Model 2: HR adjusted for pack-year index, current smoking status and age-adjusted Charlson index.

| | BODEX | | BODEXS90 | |
|---|---|---|---|---|
| | Model 1 | Model 2 | Model 1 | Model 2 |
| **Derivation cohort** | | | | |
| Q1 | Reference | Reference | Reference | Reference |
| Q2 | 3.07 (2.19–4.31) | 2.84 (1.93–4.16) | 2.86 (2.00–4.08) | 2.57 (1.72–3.86) |
| Q3 | 4.44 (3.05–6.46) | 4.24 (2.79–6.45) | 4.95 (3.47–7.06) | 4.95 (3.32–7.37) |
| Q4 | 10.02 (6.22–16.16) | 8.02 (4.34–14.79) | 11.6 (7.07–19.11) | 8.48 (4.42–16.24) |
| **Validation cohort** | | | | |
| Q1 | Reference | Reference | Reference | Reference |
| Q2 | 1.74 (1.35–2.24) | 1.63 (1.25–2.12) | 1.68 (1.30–2.17) | 1.59 (1.22–2.08) |
| Q3 | 2.61 (1.95–3.50) | 2.38 (1.75–3.24) | 2.65 (2.00–3.50) | 2.38 (1.78–3.19) |
| Q4 | 4.72 (2.61–8.55) | 3.88 (2.14–7.05) | 7.29 (3.21–16.53) | 6.69 (2.93–15.29) |

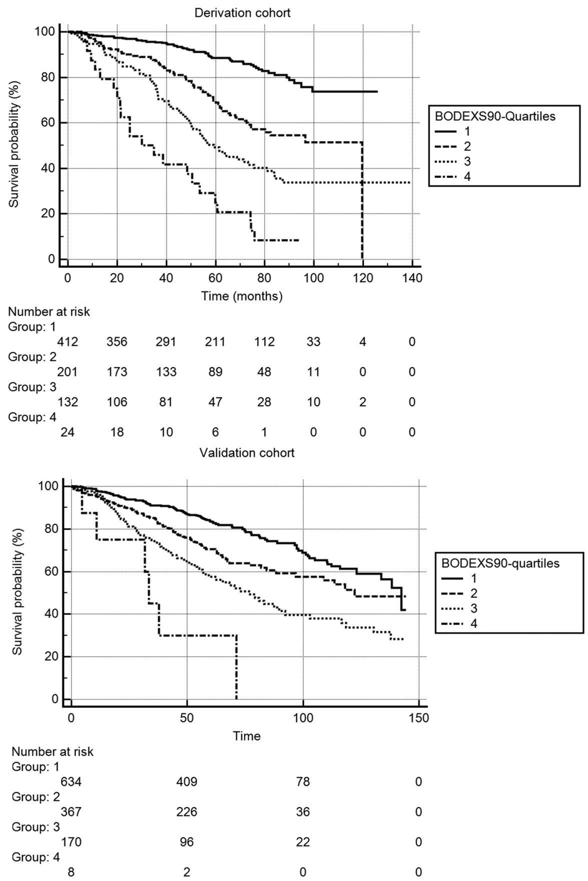


**Fig. 2** Kaplan-Meier survival curves for BODEXS90 divided in quartiles for the derivation and validation cohorts.

variables, like age, that are not directly related to the disease in itself.[11,16] The value of age and similar, non-modifiable variables in the clinical stratification of specific diseases has been questioned.[17] Although such variables, integrated into multidimensional indices are useful to inform patients and relatives about prognosis, and to help regulatory agencies to manage health resources, their utility to tailor individual treatments is less evident. On the other hand, prognostic indices integrated by components that are susceptible to modification with treatments should be more useful when designing therapeutic strategies. They could be used to measure the impact of interventions and, ideally, the improvement of index scores with treatments should correlate with better clinical outcomes. Actually, the BODE index has been found to improve with therapeutic interventions, like pulmonary rehabilitation, and to correlate in this context with better outcomes.[18] However, general implementation of BODE index is hampered by the need to carry out an exercise test. Also, patients with some comorbidities, like orthopedic or peripheral vascular diseases might not be able to perform the test, limiting its widespread availability. The simpler BODEX index, which does not require a 6-minute walk test, and replaces it by the history of severe exacerbations is advantageous in this regard.[4] This index has been externally validated by indepent teams since its development, and the value of the c-statistic to predict adverse outcomes for this model was between 0.63 and 0.73 in a recent meta-analysis.[15]

Low $SpO_2$ identifies COPD cases with more severe disease, and correlates with poorer survival.[19] Long-term oxygen therapy is one of the few interventions that have demonstrated an impact on survival of COPD patients with respiratory failure. Hence, oxygenation variables are attractive candidates for becoming part of prognostic indices, particularly in those aimed to measure the impact of therapeutic interventions. A previous paper evaluated the ability of a modified BODE (mBODE) index, that used oxygen uptake measured at peak exercise during cardiopulmonary exercise test, to predict mortality in COPD.[6] Surprisingly, the conventional BODE index performed equally well, if not even slightly better than mBODE to predict mortality. The authors speculated that some patients might have stopped the exercise test because of dyspnea or leg fatigue before reaching a true peak oxygen uptake, and concluded that simpler tests might be more practical to evaluate the multidimensional deterioration of COPD patients.[6] Our proposed BODEXS90 index is simple and easy to obtain. Global discrimination of the index, assessed with the c-statistic values, was only marginally higher than that of BODEX, and of uncertain clinical significance.[20] However, modeling of the index showed that it might be more useful than BODEX to predict mortality, particularly for those patients at higher risk (i.e: those in the highest quartiles of both indices). Therefore, the index might be particularly helpful for outcome prediction in more severe cases. It must be noted that BODEXS90 conserved its predictive value after adjusting for two important confounders, age and comorbidity, quantified with the age-adjusted Charlson index. There are two possible reasons that might explain the small increase of the c-statistic values of BODEXS90 over BODEX: the number of patients with $SpO_2 < 90\%$ was low, particularly in the validation cohort. Thus, the study might lack power to adequately assess the discrimination ability of the index. Second, it is plausible that most patients with low oxygen saturation might have been treated with supplementary oxygen, and this might have reduced the impact of this variable on the study outcome. Due to the design of the study, this possibility cannot be reliably ruled out.

The new index proposed in this study is potentially useful for future research. Comorbidities are common in COPD patients[21] and they can have an adverse effect on survival in this disease. Combining COPD-specific prognostic indices (e.g: BODEX or BODE) with comorbidity indices (e.g: Charlson or COTE) into new, combined indices, increases the ability to predict all-cause mortality.[22,23] Therefore, combining BODEXS90 with a comorbidity index might also prove advantageous in this respect. Also, COPD is a complex disease[24] and it has been found that mortality risk is different for distinct clinical phenotypes.[25] It is plausible that patients with emphysema are at a higher risk of suffering oxygen desaturation than subjects with other phenotypes. Thus, the performance of BODEXS90 may vary based on patients' phenotype.

The present study has some strengths: it incorporated a relatively high number of patients with a long follow-up, and it included an external validation cohort. Because the study variables are systematically registered by the investigators in their clinical practice, missing values were few and the risk of bias is low. The outcome variable (all-cause mortality) is robust and easy to measure in our public health system, which covers virtually the whole population, and uses electronic medical records. There were significant differences in the characteristics of patients in the derivation and validation cohorts. This can be considered a strength of the study, because it is recommended that validation studies should be performed in populations with a different case mix than the derivation cohorts.[26] Conversely, some limitations must be acknowledged: the study was performed in pneumology services, and the number of patients with less severe ventilatory obstruction (i.e. GOLD-1) was low. This is a significant limitation, particularly for an index that purports to be useful in all clinical settings. Additional studies should be carried out including patients followed-up in a primary care setting. As mentioned previously, the number of patients with $SpO_2$ < 90% was low, and the sample size might not be large enough to adequately assess the differences in the discriminative ability of BODEXS90 and BODEX indices. There were even fewer patients with $SpO_2$ < 85% and, as a consequence, we could not evaluate whether using other cut-off values for $SpO_2$ might increase the discrimination capability of BODEXS90. Besides, the outcome variable was measured over a long follow-up period. If the index is to be useful for planning ahead therapeutic strategies, its ability to predict outcomes should be ideally demonstrated within a shorter time frame (i.e: 12 months), and a larger sample size would be needed to demonstrate this.

Despite these limitations, the study shows that $SpO_2$ has additional prognostic value over the previously validated multi-component BODEX index and that a simple, easy to obtain multidimensional BODEXS90 index that includes oxygenation variables can improve the ability of the former to predict long-term all-cause mortality. These results provide the basis for future validation studies from independent investigators teams and to design impact studies to evaluate the effect of using such index in direct decision-making algorithms.

## Declaration of conflicts of interest

None.

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ORIGINAL ARTICLE

# Severe exacerbations and mortality in COPD patients: A retrospective analysis of the database of the Hungarian National Health Insurance Fund

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**KEYWORDS**
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**Abstract**
*Introduction:* COPD is one of the most common pulmonary diseases and one of the leading causes of death worldwide. Exacerbations of COPD include acute worsening that could lead to hospitalization and death. In this study, our objective was to investigate the natural course of moderate and severe exacerbations (SAE) and mortality in the Hungarian population in the past decade.
*Methods:* A retrospective financial database analysis was performed to examine the risk of additional SAEs and death after the first ever SAE in COPD patients, using the financial database of the Hungarian National Health Insurance Fund (NHIF). Patients were enrolled between 2009.01.01. and 2019.12.31. if they had received at least one inhaled drug (LABA, LAMA, ICS or SABA/SAMA) and had been hospitalized for a COPD exacerbation (ICD-10 code J44).
*Results:* A total of 63,037 patients with COPD were enrolled after their first SAE. Of them, 27,095 patients suffered at least one subsequent SAE, and 32,120 patients died during the 10-year follow-up. The median survival was 4.7 years. The risk of subsequent hospitalizations increased significantly after each SAE, with hazard ratios ranging from 1.65 to 5.01. The risk for mortality was increased after each SAE, but did not increase further with the number of SAEs. Moreover, the risk for subsequent SAE and death increased with moderate exacerbations; however, this risk did not increase further with each event.
*Conclusions:* Despite a relevant improvement in COPD treatment, the natural course of exacerbations remained unchanged. This result highlights the importance of preventing exacerbations and the need for more research to better predict them.


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## Introduction

Chronic obstructive pulmonary disease (COPD) is an irreversible, long-term respiratory syndrome that, in most cases, is the result of years of cigarette smoking. The disease is characterised by a slow but progressive worsening of respiratory function and symptoms, such as cough, sputum production and dyspnoea. The slow disease progression is often interrupted by acute exacerbations (AE).[1]

The exact definition of AE has varied over time and between studies and working groups, but all the definitions include the basic characteristics of the event: an acute worsening of symptoms, leading to the need for a change in patient care (e.g. medication, hospitalization or even assisted ventilation).[1−4] The long-term consequences of AEs are well known: worsening of respiratory symptoms, a decrease in lung function and quality of life (QoL) and an increase in the risk of hospitalization and mortality.[1−5] Furthermore, it is well established that the occurrence of one AE increases the risk of another AE, especially if the first AE required hospital admission.[6−8] For all the above reasons, the GOLD guidelines state that one of the key goals of COPD therapy is the prevention and appropriate treatment of AEs.[1]

Among the first to show the above results, Suissa et al. in their publication from 2012 reported that severe AEs (SAEs) significantly increase the risk of further SAEs and mortality. They performed a financial database analysis including patients treated with COPD from 1990 to 2005.[9] However, since then general awareness of the disease has increased, and the number of available therapies for COPD has increased substantially. The past decades have marked the introduction of combined therapies of inhaled corticosteroids (ICS), long-acting beta agonists and muscarinic antagonists (LABA and LAMA) in dual and, recently, even triple combinations. Dual combinations have repeatedly been proven superior to single therapies for improving symptoms, lung function and quality of life and preventing AEs,[1,10−12] and triple combinations are considered even more effective, with some studies even showing an increase in overall survival.[1,13,14]

In Hungary, COPD is the second most prevalent lung disease, with almost 200,000 registered patients.[15] Although all novel therapies are available to patients, COPD is still considered an underdiagnosed and undertreated disease. Furthermore, there is a lack of data on exacerbation and mortality rates in Hungarian patients with COPD; thus, a comparison of our health system to international trends had not been possible so far. Finally, since the update of the GOLD guidelines in 2015, COPD treatment has been guided by symptoms and exacerbation risk. Two or more moderate exacerbations in one year increase the risk for further exacerbations, thus warranting treatment escalation. However, we do not currently know how moderate exacerbations fit into the model of successive SAEs described by Suissa et al.

Considering all these findings, we decided to implement and expand the methodology of Suissa et al. using the database of the Hungarian National Health Insurance Fund (NHIF), analysing the data on all COPD patients from 2009 to the end of 2019, incorporating the effect of moderate exacerbations into our model.

## Methods

### Data source

A longitudinal, retrospective analysis using the NHIF database was performed. This is a complex database that encompasses almost the entire population of Hungary, collecting certain healthcare data, including all reimbursement for drug prescriptions, inpatient and outpatient visits, laboratory and imaging examinations and the International Classification of Diseases (ICD-10) codes for all these events. All these data are linked to individual patients by their insurance number. The NHIF has a legal right to handle patients' data (Act No. 80/1997 on mandatory health insurance coverage) and has a right to share it on a claim basis (based on Act 63/2012 on the reuse of public data). Due to the contract terms, it is not possible to obtain data on individual patients or results that come from aggregating the data of less than 10 individuals from the database. Permission to conduct the study was provided by the National Institution of Pharmacy and Nutrition of Hungary, based on the beneficial assessment by the National Scientific and Research Ethics Committee of Hungary (docket number: IV/8716- 3 /2021/EKU).

This database had been used in previous studies in multiple fields of medicine (oncology,[16,17] psychiatry,[18,19] diabetology[20] etc.); however, to the best of our knowledge, this is the first study in the field of obstructive pulmonary diseases.

### Patients

First, all patients who received at least one inhalation drug (ICS, LABA, LAMA or any fixed combination of these or SABA or SAMA) between 2010-01-01 and 2019-12-31 (906,461 patients) were identified. After the first respiratory medication, at least one hospital admission (inpatient hospital or ambulatory emergency care) with the J44 ICD-10 code was required (referred to as the index hospitalization event in the following sections) (82,542 patients − 100%). The baseline period was defined as one year before the index hospitalization event. Patients who were under 18 years of age (60 patients − 0.07%) or had been hospitalized with the J44 ICD-10 code one year prior to the first COPD drug dispensation or had lung cancer (C34 ICD-10 code) in the baseline period were excluded from the study (18,442 patients − 22.34%). Lung cancer can present with specific symptoms and can cause repeated hospitalizations in patients with COPD before its diagnosis; these events could be mistaken for SAE. Therefore, the follow-up of patients with lung cancer (code C34 ICD-10) was censored one year prior to the first discharge diagnosis of lung cancer. Therefore, patients who had lung cancer in the first year after the index hospitalization event were also excluded from the study, resulting in a final population of 63 037 (74.5%) patients. Follow-up of all patients continued until the end of the study (2019.12.31.), the date of death, or one year before the occurrence of lung cancer. During the follow-up time, all SAEs were recorded. The steps of cohort formation are shown in Fig. 1.

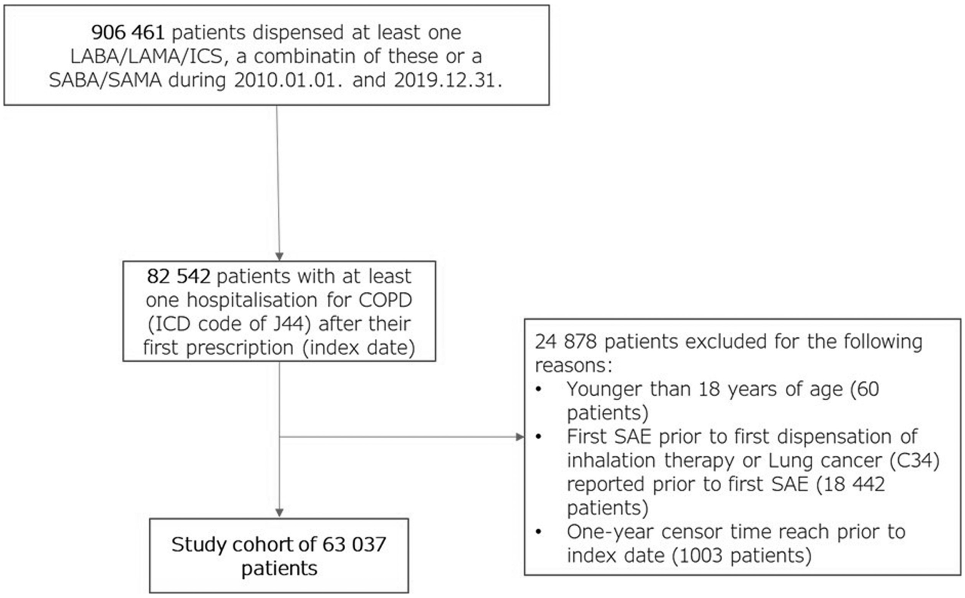


**Fig. 1** Flow chart of cohort formation.
COPD — Chronic Obstructive Pulmonary Disease; ICD-10 — 10th edition of International Classification of Diseases; LABA — Long-acting beta agonist; LAMA — Long-acting muscarinic antagonist; SABA — Short-acting beta agonist; SAE — Severe acute exacerbation; SAMA — Short-acting muscarinic antagonist.

## Data analysis

Descriptive parameters such as gender, age (calculated at the first event of exacerbation), and length and type (acute inpatient care/rehabilitation) of the first hospitalization were collected on the index date. One year before the first severe exacerbation, a baseline period was applied, which was used to collect information on comorbidities and dispensed treatments. The Charlson comorbidity index was also calculated based on the definition of Quan.[21]

The main outcomes of the study were subsequent exacerbations and death. As in the method of Suissa et al., the start of follow-up differed for the two types of outcomes. In the case of a subsequent exacerbation, the start was defined as the date of live discharge from the hospital, while in the case of death, it was defined as the date of the index hospitalization event. The survival function of mortality was estimated using the Kaplan-Meier technique. The overall hazard function of successive severe exacerbations was estimated using the additional approach of Suissa et al., where the event was defined as the next severe COPD exacerbation or death, whichever occurred first, and with a competing risk model against death. To graphically analyse the effect of successive severe exacerbations, the hazard function of each successive severe exacerbation was combined in the same figure in such a way that two consecutive hazard functions were bound together when the previous one reached the median value of the survival probability function. Finally, competing risk models were used to estimate the effect of each successive severe exacerbation on the subsequent one and on mortality. The number of previous severe and moderate exacerbations was included in both models as a time-dependent covariate, maximized at a value of 10, with sex, age, and Charlson's comorbidity index as time-independent covariates. The values of the Charlson index were classified in the model as mild (values of 1—2), moderate (3—4) or severe (5), according to the appropriate methodology.[22] In the case of the exacerbation model, the duration of the index hospitalization was also included as a covariate.[9] Prescription of oral corticosteroids under J44 ICD-10 code (or 1430 diagnosis related group code DRG) OR prescription of any antibiotic under J44 ICD-10 were considered to be a moderate exacerbation. Subsequent prescriptions within 7 days were counted as the same moderate exacerbation event. This definition was similar to those used in previous trials.[23,24] If an OCS prescription was followed by an SAE within 7 days, we only considered it as an SAE.

# Results

## Descriptive results

Following the application of all exclusion criteria, a final cohort of 63,037 patients was formed. In all, 32,227 patients were women (51.1%), and the average age was 67.4 years. Most of the patients had at least one comorbidity, with an average Charlson comorbidity index of 2.76. Most of the patients had received therapeutic regimens containing LABA (67.9%), ICS (54.9%) and LAMA (54.5%) one year before their index hospitalization. Almost two-thirds of all patients had used at least one reliever therapy (61.8%), and 37.0% had been administered more than three containers in the baseline year. Less than 1% of all patients received no therapy prior to their first SAE (0.7%). There were significant and clinically relevant differences between the general population, patients who suffered subsequent SAE and patients who died during follow-up. Members of the latter group were older and had more comorbidities (especially

**Table 1** Characteristics of the entire patient population, patients who had suffered at least one subsequent SAE and patients who died during follow-up. For age, data on the Charlson index and sex are shown as mean and standard deviation. For all other variables, data are shown as the number of patients and percentages. ICS – Inhaled corticosteroid; LABA – Long-acting beta agonist; LAMA – Long-acting muscarinic antagonist; SABA – Short-acting beta agonist; SAE – Severe acute exacerbation; SAMA – Short-acting muscarinic antagonist; SD – Standard deviation.

| | | Entire cohort | At least one subsequent exacerbation | Death |
|---|---|---|---|---|
| At the time of the index hospitalization | Number of patients | 63 037 | 27 095 | 32 120 |
| | Age at cohort entry (years) | 67.44 (11.22) | 66.18 (10.55) | 70.53 (10.57) |
| | Charlson comorbidity index) | 2.76 (1.85) | 2.63 (1.74) | 3.03 (1.94) |
| | Female (%) | 32 227 (51.1) | 13 807 (51.0) | 14 663 (45.7) |
| One year prior to the index hospitalization (%) | SABA/SAMA therapy | 38 950 (61.8) | 18 214 (67.2) | 20 101 (62.6) |
| | LABA therapy | 42 779 (67.9) | 19 604 (72.4) | 22 207 (69.1) |
| | LAMA therapy | 34 363 (54.5) | 16 297 (60.1) | 18 099 (56.3) |
| | SABA therapy without ICS therapy | 12 967 (20.6) | 5 370 (19.8) | 5 945 (18.5) |
| | More than 3 SABA/SAMA therapy | 23 331 (37.0) | 11 653 (43.0) | 12 915 (40.2) |
| | Any therapy but ICS therapy | 27 964 (44.4) | 10 549 (38.9) | 13 307 (41.4) |
| | Any therapy AND ICS therapy | 34 610 (54.9) | 16 380 (60.5) | 18 602 (57.9) |
| | No therapy at all | 463 (0.7) | 166 (0.6) | 211 (0.7) |
| Comorbidity in year prior to the index hospitalization (%) | Myocardial infarction | 3 260 (5.2) | 1 347 (5.0) | 1 945 (6.1) |
| | Heart failure | 16 939 (26.9) | 6 861 (25.3) | 10 834 (33.7) |
| | Peripheral vascular disease | 9 483 (15.0) | 3 866 (14.3) | 5 443 (16.9) |
| | Cerebrovascular disease | 12 966 (20.6) | 5 225 (19.3) | 7 008 (21.8) |
| | Diabetes | 12 586 (20.0) | 4 955 (18.3) | 6 713 (20.9) |
| | Renal disease | 2 742 (4.3) | 861 (3.2) | 1 862 (5.8) |
| | Cancer (not lung) | 5 652 (9.0) | 2 021 (7.5) | 3 521 (11.0) |
| | Metastatic cancer | 561 (0.9) | 156 (0.6) | 435 (1.4) |
| | Dementia | 1 207 (1.9) | 377 (1.4) | 828 (2.6) |
| | Rheumatoid disease | 1 189 (1.9) | 494 (1.8) | 602 (1.9) |
| | Peptic ulcer | 317 (0.5) | 133 (0.5) | 159 (0.5) |
| | Liver disease | 1 671 (2.7) | 671 (2.5) | 815 (2.5) |
| | Hemiplegia or paraplegia | 417 (0.7) | 141 (0.5) | 245 (0.8) |
| | Cardiovascular diseases | 37 834 (60.0) | 15 865 (58.6) | 21 393 (66.6) |
| | Schizophrenia | 1 824 (2.9) | 732 (2.7) | 950 (3.0) |
| | Depressive episode | 9 275 (14.7) | 4 133 (15.3) | 4 369 (13.6) |
| | Anxiety | 14390 (22.8) | 6209 (22.9) | 6832 (21.3) |

cardiovascular diseases), and a higher proportion of them were men. All other baseline details are shown in Table 1.

The mean follow-up was 1,209 days (3.31 years). At the index hospitalization, most patients (83.0%) had been treated in active inpatient care, with more than half of these patients (52%) spending 4–8 days hospitalized (average 8.51 days). However, about 17.0% of the patients had been treated in rehabilitation wards, where most of them spent 21 days. The distribution of patients according to the length of hospital stay (in days) is shown in Fig. 2.

In all, 27,095 patients (43.0%) suffered at least one subsequent AE. As in Suissa et al., the median times between exacerbations decreased significantly with each subsequent SAE, and there was a parallel increase in the risk for the next SAE, from a median of 3.2 years between the first and second SAE to 0.3 years between the ninth and tenth SAE. The hazard function of all subsequent SAEs (A) and death (B), created by the same methods as Suissa et al, is shown on Fig. 3.

A total of 32,120 patients died during the follow-up period. The median survival was 4.77 years. The Kaplan-Meier survival curve for the whole cohort is shown in Fig. 4.

## Model results

In the case of the exacerbation model, the risk of the next SAE increased from 1.636 (95% confidence interval – 95% CI:

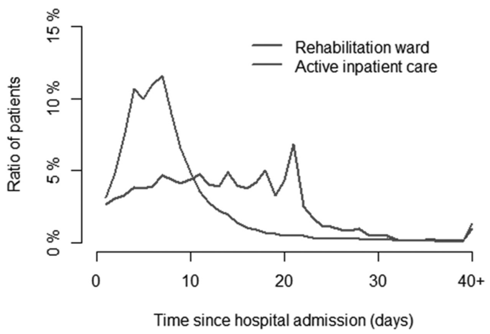


**Fig. 2** Distribution of patients according to the length of their index hospital stay (number of days) in active inpatient care and on rehabilitation wards.

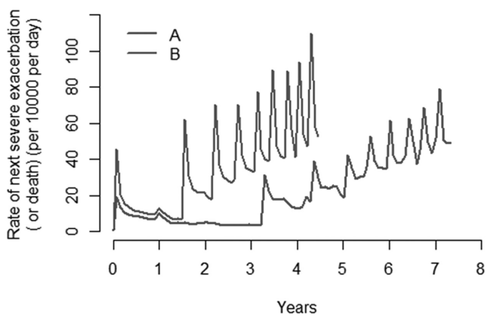


**Fig. 3** Hazard function of all subsequent SAEs (per 10,000 per day) from the time of the first SAE over the follow-up period, with the time between successive exacerbations estimated using (A) the median interexacerbation times, conditional on survival with death as a censor event, and (B) the median interexacerbation times as time to the next exacerbation or death, whichever occurred first.

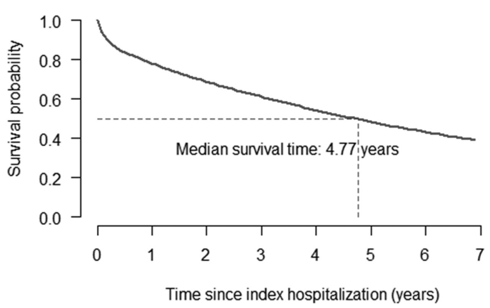


**Fig. 4** Kaplan-Meier survival function of all included patients, from their index hospitalization event throughout the follow-up period.

1.602—1.669) to 5.017 (95% CI: 4.797—5.248) between the same SAEs. In the model, the effect of moderate exacerbations, the length of the index hospitalization and the Charlson comorbidity index on the risk for the next SAEs were also examined. Interestingly, moderate exacerbations increased the risk for the next exacerbation; however, this increase was not dependent on the number of moderate exacerbations (HR of 1.183 to 1.288 for the first and tenth or more moderate exacerbation). Female patients had a significantly lower risk of subsequent exacerbations (HR = 0.925). Although age did not have a significant effect, patients with a higher Charlson index score had a lower risk of subsequent SAEs. The longer the index hospitalization, the higher the risk of a subsequent SAE event. All HR values and 95% confidence intervals are shown in Fig. 5.

The trend in mortality risk after each subsequent SAE was different from that reported by Suissa et al. With the use of a competing risk model, the effect of SAEs on the risk of mortality did not increase with the number of the SAEs: HR = 1.211 (95% CI 1.175; 1.247) after the second SAE and 1.067 (0.983; 1.159) after nine or more SAE in the adjusted model. Moderate exacerbations increased the risk of mortality only after the second moderate exacerbation event (HR values of 1.077 and 1.324 for the second and tenth or more moderate exacerbations). Female patients had a markedly lower risk of death (HR = 0.755), while advancing age is associated with an increased risk of mortality. Finally, higher values of the Charlson index conferred a significant excess risk of death (HR = 1.180 and 1.475 for moderate and severe categories, respectively). All HR values and 95% confidence intervals are also shown in Fig. 5.

## Discussion

In this retrospective analysis based on the Hungarian NHIF financial database, we showed that each exacerbation requiring hospitalization (SAE) significantly increases the risk of the next SAE event and death. The result on SAEs, based on a 10-year follow-up of more than 63,000 COPD patients, is in line with the work of Suissa et al. from 2012, who first showed important and severe worsening of the disease after each SAE. In our analysis, the risk of mortality did not increase with the number of SAEs — a result of the competing risk model that was used. Patients are more likely to suffer a subsequent SAE after a previous one than they are to die. This results in a consistently elevated risk for mortality compared to baseline, without an increase after each subsequent event. When a competing risk model was not used, the risk for death increased with each subsequent SAE.

It is important to note that the increase in risk was far greater in their study (HR of 23.5 vs. 4.491 for the next SAE after the 10$^{th}$ exacerbation). Furthermore, the median survival was longer in our study (4.7 years vs. 3.6 years in Suissa et al.[9]); however, there was a difference in the average age of the included populations (67.4 years vs. 75.4 years[9]). Nonetheless, in our study, almost 50% of all patients had died within 5 years after their first SAE — an alarming number considering the high prevalence of COPD and its exacerbations. These results highlight the importance of exacerbation prevention and the need for further research seeking markers that could help physicians identify patients with an increased susceptibility to exacerbations. Moreover, the wider use of influenza and pneumococcal vaccination and non-pharmacological approaches such as pulmonary rehabilitation, physiotherapy and smoking cessation should be advocated for every COPD patient.

We could also demonstrate that moderate exacerbations increase the risk of a subsequent SAE and mortality. This is an important addition to earlier findings because it shows that moderate exacerbations are also pivotal events that

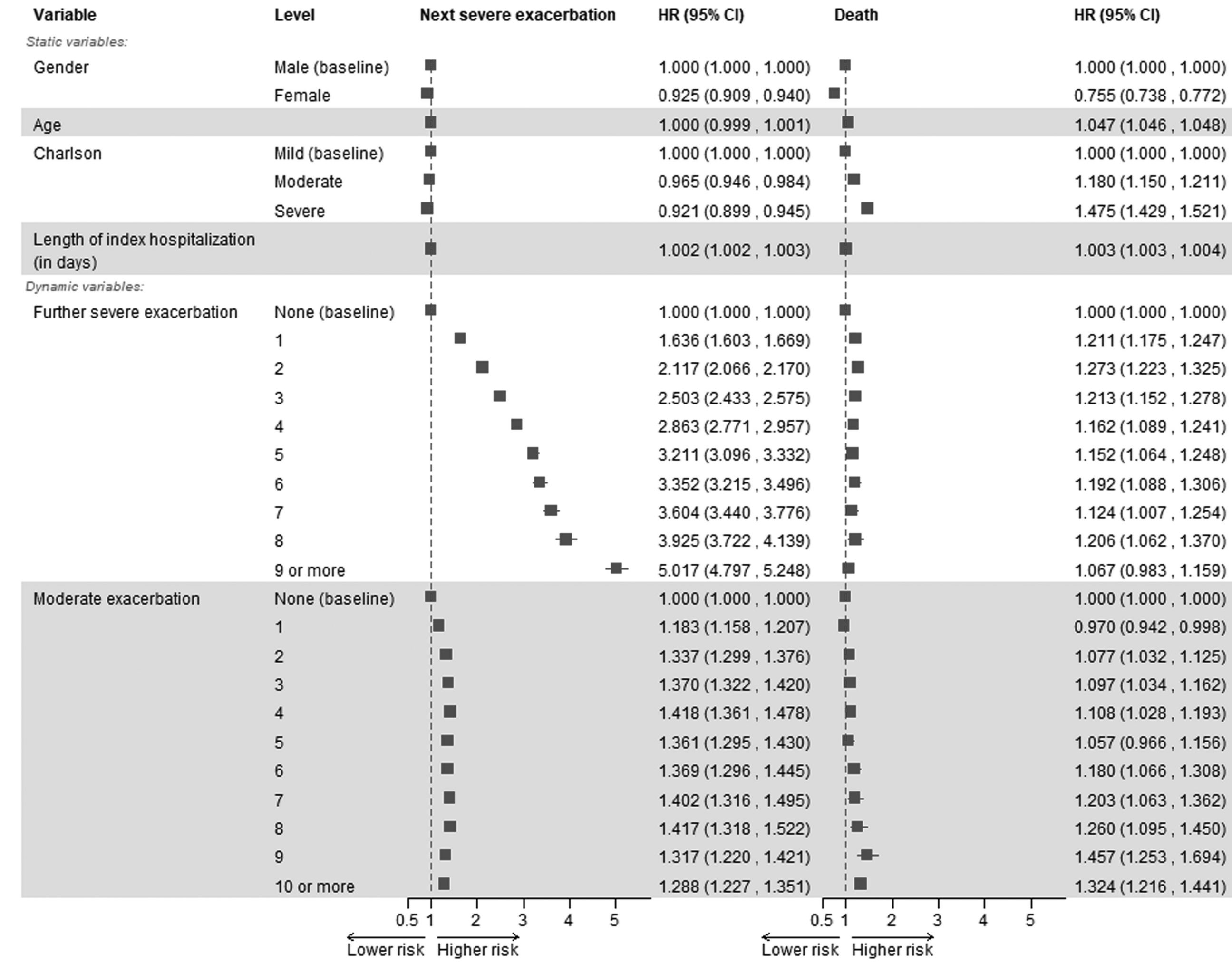


**Fig. 5** Model-estimated hazard ratios and respective 95% confidence intervals for the risk of the next severe exacerbation and death.

could significantly alter the disease course. A more thorough assessment of all exacerbations is necessary for further improvement in their treatment — an idea that has been evoked more and more frequently in recent years.[25]

Moderate exacerbations can be treated with OCS and/or antibiotics in routine clinical care; however, in most financial database analyses, the prescription of only an oral corticosteroid is considered as a moderate AE. We believe that the main reason for this exclusion is that clinicians tend to prescribe antibiotics with ICD-10 codes other than J44, even if they aim to treat a moderate exacerbation. But the inclusion of ICD-10 codes other than J44 in the definition might mistakenly label other events (such as upper respiratory tract infections) as moderate exacerbations. For these reasons, we believe that the inclusion of an antibiotic prescription with a J44 code in the definition of moderate events will result in the inclusion of a higher number of moderate exacerbations, without the possibility of misidentification of events.

To explore the treatment prescription habits of the past decade, an analysis of therapies received after each SAE was also performed. Compared to baseline, there was an increase in the use of ICS-containing medications after the first two severe exacerbations (index hospitalization and first subsequent SAE). In all, 55% of all patients used ICS at baseline and 59% and 67% after index hospitalization and first subsequent SAE, respectively, but there was no further increase in the prevalence of ICS use after subsequent events. The GOLD guidelines have recommended ICS use after one severe or two (or more) moderate exacerbations for many years now.[1] However, it was quite clear from our data that a high proportion of patients (almost one third) do not receive or do not take ICS-containing medications even after multiple SAE events. Without proper treatment, the prevention of further SAEs is impossible, as highlighted by a recent study by Tkacz et al., who showed that even a delay in appropriate treatment could also result in a large increase in the risk of exacerbation.[25]

The proportion of women among COPD patients has increased significantly in the past few decades. In our study, as in the study by Suissa et al., women also had a lower risk of subsequent SAEs and mortality. Based on our descriptive data, there were very few medically relevant differences between the enrolled women and men. While a higher proportion of men suffer from heart failure, prior myocardial infarction and peripheral vascular disease, many more women are reported to have depressive disorder or anxiety — both diseases could affect adherence to therapy, which could increase the risk of SAEs. In addition, more detailed research is needed to explain the reason for the lower risk of SAE among women.

The most important strength of our study is the large number of enrolled patients and a length of follow-up that could be difficult to match in prospective studies. Another advantage is that we could assess a population from the last decade, whose treatment had been much more uniform than that of patients in earlier studies. Finally, Hungary's health financing system is a single-payer system that includes almost the entire population of the country, resulting in a decrease in territorial or societal differences between the people included in the database and the entire population.

The most important limitation is the lack of data on the severity of COPD symptoms and lung function. Furthermore, it is impossible to verify the diagnosis of each patient based on spirometry data; inclusion was based solely on prescription medication use, and ICD-10 codes for prescriptions and discharge diagnoses. A further limitation is the lack of data on smoking history, obesity and possible exposure to high ambient air pollution.

Nonetheless, the results of our study and the conclusions drawn are of significance: despite the improvement in COPD management, the natural course of the disease cannot be altered, and exacerbations are still dominant effectors of the prognosis. Furthermore, these results highlight the huge importance of prevention of exacerbations and the need for further research on clinical parameters predicting exacerbations.

## Conclusions

We performed a retrospective financial database analysis of more than 63 000 patients followed over a 10-year period and concluded that moderate and severe exacerbations of COPD significantly increase the risk of further exacerbations and mortality. This effect increases with the number of events in the event of severe exacerbations. These results emphasize the importance of prevention of these events and the prompt initiation of appropriate treatment.

## Conflict of interest

The authors report that they have no conflicts of interest related to the submitted work.

G. Gálffy has accepted consulting fees from AstraZeneca, Chiesi, BMS, MSD, Berlin Chemie, Boehringer Ingelheim, Roche, Novartis, Pfizer, Ipsen, Mylen and Orion outside the submitted work. B. Santa, G. Tomisa and A. Horváth are all employees of Chiesi Hungary Ltd. T. Balázs and L. Németh are employees of Healthware Consulting Ltd.

## CRediT authorship contribution statement

**B. Sánta:** Conceptualization, Visualization, Funding acquisition, Formal analysis, Methodology, Writing — original draft, Writing — review & editing. **G. Tomisa:** Conceptualization, Visualization, Funding acquisition, Formal analysis, Methodology. **A. Horváth:** Conceptualization, Visualization, Funding acquisition, Formal analysis, Methodology. **T. Balázs:** Conceptualization, Visualization, Formal analysis, Methodology, Writing — original draft, Writing — review & editing. **L. Németh:** Conceptualization, Visualization, Formal analysis, Methodology, Writing — original draft, Writing — review & editing. **G. Gálffy:** Conceptualization, Visualization, Funding acquisition, Formal analysis, Methodology.

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## Ethics approval

Permission to conduct the study was provided by the National Institution of Pharmacy and Nutrition of Hungary, based on the beneficial assessment by the National Scientific and Research Ethics Committee of Hungary (docket number: IV/8716- 3 /2021/EKU). All procedures were performed in accordance with the ethical standards of the aforementioned institutions and with the Declaration of Helsinki of 1964 and its subsequent amendments or comparable ethical standards.

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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.2022.11.001.

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ORIGINAL ARTICLE

# Identification by cluster analysis of patients with asthma and nasal symptoms using the MASK-air® mHealth app

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**Abstract**

*Background:* The self-reporting of asthma frequently leads to patient misidentification in epidemiological studies. Strategies combining the triangulation of data sources may help to improve the identification of people with asthma. We aimed to combine information from the self-reporting of asthma, medication use and symptoms to identify asthma patterns in the users of an mHealth app.

*Methods:* We studied MASK-air® users who reported their daily asthma symptoms (assessed by a 0-100 visual analogue scale — "VAS Asthma") at least three times (either in three different months or in any period). K-means cluster analysis methods were applied to identify asthma patterns based on: (i) whether the user self-reported asthma; (ii) whether the user reported asthma medication use and (iii) VAS asthma. Clusters were compared by the number of medications used, VAS asthma levels and Control of Asthma and Allergic Rhinitis Test (CARAT) levels.

*Findings:* We assessed a total of 8,075 MASK-air® users. The main clustering approach resulted in the identification of seven groups. These groups were interpreted as probable: (i) severe/uncontrolled asthma despite treatment (11.9-16.1% of MASK-air® users); (ii) treated and partly-controlled asthma (6.3-9.7%); (iii) treated and controlled asthma (4.6-5.5%); (iv) untreated uncontrolled asthma (18.2-20.5%); (v) untreated partly-controlled asthma (10.1-10.7%); (vi) untreated controlled asthma (6.7-8.5%) and (vii) no evidence of asthma (33.0-40.2%). This classification was validated in a study of 192 patients enrolled by physicians.

*Interpretation:* We identified seven profiles based on the probability of having asthma and on its level of control. mHealth tools are hypothesis-generating and complement classical epidemiological approaches in identifying patients with asthma.


## Introduction

Self-reporting is a common method for gathering data in medical research. While self-reported data may be prone to information bias,[1] they can help to complement other data collection approaches.[2] Relying on the self-reporting of asthma may be problematic, as patients self-report bronchoconstriction variably,[3] may not have been diagnosed (asthma under-diagnosis ranges between 19-73%[4,5]) or believe they do not have asthma despite being symptomatic.[6,7]

Cluster analysis, combining information from different variables, may help to overcome undue reliance on self-reported asthma, improving the identification and characterisation of patients with asthma. This approach has been used to understand the heterogeneity of asthma[8-10] or to test different hypotheses in adult patients with asthma.[8,11,12] The application of clustering approaches to asthma real-world data (RWD) may also be valuable. As an example, RWD obtained with MASK-air® (Mobile Airways Sentinel networK), a validated mobile app for rhinitis and asthma, have enabled the definition of new phenotypes of allergic rhinitis[13] and the assessment of adherence to treatment.[14] MASK-air® may result in similar advances in asthma, but the correct identification of asthmatic patients is required.

In this study, we used cluster analysis to identify and characterise asthma patterns amongst MASK-air® users in a non-supervised way. We aimed to understand whether RWD from mobile apps can be informative for the identification of asthma, hinting at the frequency of misdiagnosis and, potentially, mistreatment.

## Methods

### Study design

We performed a cross-sectional analysis using the MASK-air® database to identify asthma patterns, assessing three different samples (Supplementary Figure 1). We performed cluster analysis to identify asthma patterns based on the self-reporting of asthma, asthma medication use and VAS asthma, adopting a stepwise approach to check for consistency of results. We compared the characteristics of the obtained clusters and we validated them in a sample of patients in whom asthma diagnosis had been assessed by a physician during a transfer of innovation (Twinning) of the European Innovation Partnership on Active and Healthy Ageing.[15]

### Setting and participants

MASK-air®, available since 2015, can be downloaded via the Apple App and Google Play Stores. We assessed three samples of MASK-air® users from May 2015 to December 2020. The users were aged 16-90 years and had self-reported allergic rhinitis. Samples 1 and 2 consisted of all MASK-air® users reporting VAS asthma in at least three different months - to limit the possibility of having "false-positives" (e.g., patients with high values of VAS asthma or those using asthma medication inappropriately within short periods of time as a result of respiratory infections or other non-asthma-related causes). In Sample 1, only users who answered to the Control of Allergic Rhinitis and Asthma Test (CARAT)[16] at least once were included. In Sample 2, all users were included irrespective of having answered to CARAT or not. Sample 3 consisted of all MASK-air® users reporting at least three VAS asthma, irrespective of the timing.

In the Twinning project, patients were enrolled during a medical consultation with an asthma specialist (14 centres from Germany, Italy, Lithuania, Poland, Portugal and Spain) and were instructed to use MASK-air®.[15] Asthma was diagnosed according to the Global Initiative for Asthma (GINA),[17] with patients having a pulmonary function test. Participants were classified as having "current asthma", "past asthma" or "no current or past asthma".

## Ethics

MASK-air® follows the GDPR regulations.[18] All data are anonymised using k-anonymity. An independent Review Board (Bohn-Köln; 11.05.2017; N°17-069) approval was obtained for the MASK-air studies.[15] For the Twinning project, additional local review board approvals were obtained (Mannheim − reference: 2018-527N-MA, 29.03.2018 for Germany; Coimbra − reference: CHUC-022-18, 14.09.2018 for Portugal; Warsaw − reference: AKBE/213/2019, 13.05.2019 for Poland; Vilnius 2021 for Lithuania; Bari − reference: 7287, 30.03.2022 for Italy). For patients who did not participate in the Twinning, individual boards in different countries were not required since users agree to the analysis of their data in the terms of use.

## Data sources and variables

MASK-air® comprises a daily monitoring questionnaire assessing (i) the daily impact of asthma and rhinitis symptoms by means of 0-100 VASs and (ii) users' asthma and rhinitis daily medications (available from country-specific lists with prescribed and over-the-counter medications).

MASK-air® also allows users to answer to CARAT, a 10-item questionnaire assessing rhinitis and asthma control in the previous four weeks.[19] We considered "CARAT asthma" to correspond to questions 5-7 ("Shortness of breath/dyspnoea", "Wheezing in the chest" and "Chest tightness upon physical exercise"), with a score of ≤6 out of 9 indicating symptoms suggestive of asthma.

## Size of the study

Data from all users meeting the inclusion criteria were analysed.

## Biases

There are potential information biases related to the self-reported nature of the data collection. There may be an over-representation of users suffering from moderate-to-severe asthma[20] and of younger individuals. Additionally, it is not known whether users fill in the MASK-air® daily questionnaire before or after treatment for a given day.

## Data analysis

A full description of the data analysis methods is available in the Supplement. In brief, in each sample, we applied k-means cluster analysis methods to identify patterns of MASK-air® users according to self-reported asthma, use of asthma medication and VAS asthma (supplementary Figure 2). Obtained clusters were assessed and compared regarding asthma- and rhinitis-related variables as well as patients' demographic characteristics. To check for consistency of results, we compared clusters obtained by the main clustering approach with those obtained using alternative approaches, and in a sample of patients with physician-diagnosed asthma (Twinning participants).

# Results

## Demographic and clinical characteristics

Among the 17,780 patients of the MASK-air® database, 8,075 provided data on VAS asthma at least three different times (Sample 3). Of those, 3,797 provided VAS asthma in at least three different months (Sample 2), including 466 patients who answered to CARAT at least once (Sample 1) (Supplementary Figure 3). The demographic characteristics of patients are available in Supplementary Table 1.

## Cluster analysis results

### Main analysis approach

An optimal number of four clusters (A-D) was identified in the patients of Sample 1 (Table 1A):

- Cluster A: 96% of the patients self-reported asthma and 91% reported ≥3 days of asthma medication. VAS asthma values were high (median maximum value=85/100). Asthma symptoms identified by "CARAT-asthma" were observed in 67% of the patients.
- Cluster B: 93% of the patients self-reported asthma and 87% reported ≥3 days of asthma medication. Maximum VAS asthma values were moderate (median=45). Asthma symptoms identified by "CARAT-asthma" were observed in 32% of the patients.
- Cluster C: 50% of the patients self-reported asthma and most never reported any asthma medication. High maximum VAS asthma values were reported (median=74). Asthma symptoms identified by "CARAT-asthma" were observed in 58% of the patients.
- Cluster D: Few patients self-reported asthma (15%), most never reported any asthma medication (97%) and VAS maximum asthma values were low (median=11). Asthma symptoms identified by "CARAT-asthma" were observed in 15% of the patients.

The same optimal number of clusters was identified in Samples 2 and 3. The characteristics of the four clusters were highly consistent across all samples (Tables 1B and 1C).

We subsequently identified two subgroups within Cluster B and three subgroups within Cluster D. The two subgroups of Cluster B differed on VAS asthma (Table 2; Supplementary Table 2). The three subgroups of Cluster D included (i) one subgroup with a low frequency of asthma self-reporting (<20%) and moderate maximum VAS asthma values; (ii) one subgroup with all participants self-reporting asthma and

**Table 1** Description of the four asthma-related clusters using the k-means approach.

A. Sample 1: Patients with at least 3 VAS asthma in 3 different months who answered at least once to CARAT

| | Cluster A | Cluster B | Cluster C | Cluster D | *p*-value |
|---|---|---|---|---|---|
| *N* (%) | 75 (16.1) | 69 (14.8) | 90 (19.3) | 232 (49.8) | |
| Reported days − *N* (average days per user) | 8888 (118.5) | 9066 (131.4) | 7646 (85.0) | 21,730 (93.7) | |
| Females* | 62 (82.7) | 46 (66.7) | 58 (64.4) | 147 (63.4) | 0.019[a] |
| Age‖ | 41.1 (11.2) | 40.7 (11.4) | 39.2 (14.0) | 37.5 (13.6) | 0.104 |
| Self-reported asthma* | 72 (96.0) | 64 (92.8) | 45 (50.0) | 35 (15.1) | <0.001 |
| Asthma medication reporting* | | | | | <0.001 |
| 0 days | 0 | 0 | 79 (87.8) | 226 (97.4) | |
| 1 day | 0 | 0 | 11 (12.2) | 6 (2.6) | |
| 2 days | 7 (9.3) | 9 (13.0) | 0 | 0 | |
| 3 or more days | 68 (90.7) | 60 (87.0) | 0 | 0 | |
| Total days reporting asthma medication* | | | | | |
| SABA | 1379 (15.5) | 578 (6.4) | 9 (0.1) | 7 (0.03) | <0.001 |
| LABA+ICS | 3916 (44.1) | 3369 (37.2) | 8 (0.1) | 2 (0.01) | <0.001 |
| ICS | 1168 (13.1) | 1443 (15.9) | 3 (0.04) | 0 | <0.001 |
| OCS[b] | 507 (5.7) | 41 (0.5) | 61 (0.8) | 31 (0.1) | |
| LAMA | 651 (7.3) | 456 (5.1) | 0 | 0 | |
| Omalizumab | 7 (0.1) | 6 (0.1) | 0 | 0 | |
| VAS asthma | | | | | |
| Maximum value† | 85 (76-94) | 45 (30-55) | 74 (61-86) | 11 (3-26) | <0.001 |
| Three highest values† | 73 (64-83) | 35 (23-45) | 61 (48-75) | 6 (1-14) | <0.001 |
| Days with VAS asthma >50* | 1392 (15.7) | 35 (0.4) | 1057 (13.8) | 17 (0.1) | <0.001 |
| Maximum VAS dyspnea† | 68 (56-83) | 20 (4-41) | 59 (34-74) | 20 (7-36) | <0.001 |
| CARAT asthma (questions 5-7)† | 5 (2−7) | 7 (6−9) | 6 (4−8) | 9 (7−9) | <0.001 |
| Presence of asthma symptoms[c] * | 50 (66.7) | 22 (31.9) | 52 (57.8) | 36 (15.5) | <0.001 |
| CARAT (questions 1−10)† | 13 (8−16) | 19 (17−23) | 15 (11−19) | 20 (16−24) | <0.001 |
| Uncontrolled[d] * | 73 (97.3) | 53 (76.8) | 81 (90.0) | 174 (75.0) | <0.001 |
| Maximum CSMS† | 68 (59−78) | 36 (30−46) | 63 (46−69) | 39 (20−54) | <0.001 |
| Maximum VAS global† | 84 (74−96) | 49 (41−65) | 87 (71−100) | 65 (44−84) | <0.001 |
| Maximum VAS eyes† | 78 (60−92) | 40 (19−59) | 76 (64−97) | 50 (27−76) | <0.001 |
| Maximum VAS nose† | 86 (70−98) | 58 (42−75) | 88 (75−100) | 69 (44−89) | <0.001 |
| Maximum VAS work† | 61 (43−73) | 27 (10−46) | 62 (44−83) | 31 (10−54) | <0.001 |
| Maximum VAS sleep† | 87 (71−98) | 67 (44−84) | 86 (70−100) | 66 (41−86) | <0.001 |
| Total days reporting rhinitis medication* | | | | | |
| Oral antihistamines monotherapy | 1199 (13.5) | 934 (10.3) | 710 (9.3) | 2440 (11.2) | <0.001 |
| Intranasal steroids monotherapy | 361 (4.1) | 768 (8.5) | 378 (4.9) | 776 (3.6) | <0.001 |
| Azelastine−fluticasone monotherapy | 346 (3.9) | 543 (6.0) | 107 (1.4) | 1009 (4.6) | <0.001 |
| Oral antihistamines + intranasal steroids | 2087 (23.5) | 1721 (19.0) | 454 (5.9) | 1009 (4.6) | <0.001 |
| Azelastine−fluticasone + other rhinitis medication | 878 (9.9) | 850 (9.4) | 125 (1.6) | 520 (2.4) | <0.001 |
| Conjunctivitis* | 68 (90.7) | 49 (71.0) | 66 (73.3) | 183 (78.9) | 0.016[a] |
| Sensitisation[e] * | | | | | 0.181 |
| Monosensitisation[e] | 8 (11.4) | 6 (8.8) | 8 (9.1) | 31 (13.7) | |
| Polysensitisation[e] | 51 (72.9) | 40 (58.8) | 51 (58.0) | 132 (58.1) | |

B. Sample 2: All patients with at least 3 VAS asthma in 3 different months

| | Cluster A | Cluster B | Cluster C | Cluster D | *p*−value |
|---|---|---|---|---|---|
| *N* (%) | 451 (11.9) | 414 (10.9) | 780 (20.5) | 2152 (56.7) | |
| Reported days − *N* (average days per user) | 38,823 (86.1) | 35,723 (86.3) | 47,352 (60.7) | 134,941 (62.7) | |
| Females* | 310 (68.7) | 234 (56.5) | 460 (59.0) | 1138 (52.9) | <0.001 |
| Age‖ | 41.1 (14.3) | 40.1 (14.1) | 38.3 (13.8) | 35.5 (13.2) | <0.001 |
| Self−reported asthma* | 432 (95.8) | 389 (94.0) | 391 (50.1) | 341 (15.8) | <0.001 |
| Asthma medication reporting* | | | | | <0.001 |
| 0 days | 0 | 0 | 698 (89.5) | 2102 (97.7) | |
| 1 day | 4 (0.9) | 10 (2.4) | 82 (10.5) | 50 (2.3) | |
| 2 days | 68 (15.1) | 64 (15.5) | 0 | 0 | |
| 3 or more days | 379 (84.0) | 340 (82.1) | 0 | 0 | |
| Total days reporting asthma medication* | | | | | |
| SABA | 4285 (11.0) | 1586 (4.4) | 66 (0.1) | 37 (0.03) | <0.001 |
| LABA+ICS | 16,275 (41.9) | 15,038 (42.1) | 74 (0.2) | 23 (0.02) | <0.001 |
| ICS | 4658 (12.0) | 5722 (16.0) | 25 (0.1) | 22 (0.02) | <0.001 |
| OCS[b] | 1331 (3.4) | 243 (0.7) | 244 (0.5) | 141 (0.1) | |
| LAMA | 1453 (3.7) | 534 (1.5) | 0 | 0 | |
| Biologics | 112 (0.3) | 86 (0.2) | 0 | 0 | |
| VAS asthma | | | | | |
| Maximum value† | 81 (69−92) | 38 (25−49) | 72 (58−85) | 8 (2−22) | <0.001 |
| Three highest values† | 69 (58−82) | 27 (15−37) | 56 (44−72) | 4 (0−12) | <0.001 |
| Days with VAS asthma >50* | 5610 (14.5) | 91 (0.3) | 4799 (10.1) | 94 (0.1) | <0.001 |
| Maximum VAS dyspnea† | 69 (54−82) | 31 (18−45) | 61 (42−75) | 19 (7−34) | <0.001 |
| Maximum CSMS† | 63 (52−72) | 36 (25−47) | 62 (50−71) | 37 (26−53) | <0.001 |
| Maximum VAS global† | 80 (69−93) | 49 (34−67) | 81 (68−95) | 61 (39−81) | <0.001 |
| Maximum VAS eyes† | 71 (51−89) | 34 (20−60) | 75 (57−90) | 44 (21−71) | <0.001 |
| Maximum VAS nose† | 82 (67−95) | 53 (34−75) | 85 (70−100) | 66 (41−85) | <0.001 |
| Maximum VAS work† | 57 (37−71) | 26 (9−43) | 58 (40−74) | 29 (10−52) | <0.001 |
| Maximum VAS sleep† | 72 (26−90) | 52 (33−77) | 79 (60−94) | 56 (34−79) | <0.001 |
| Total days reporting rhinitis medication* | | | | | |
| Oral antihistamines monotherapy | 4594 (11.8) | 3852 (10.8) | 4984 (10.5) | 16,971 (12.6) | <0.001 |
| Intranasal steroids monotherapy | 1787 (4.6) | 3864 (10.8) | 2290 (4.8) | 7290 (5.4) | <0.001 |
| Azelastine−fluticasone monotherapy | 1465 (3.8) | 1217 (3.4) | 1288 (2.7) | 5270 (3.9) | <0.001 |
| Oral antihistamines + intranasal steroids | 5949 (15.3) | 3362 (9.4) | 2982 (6.3) | 8158 (6.0) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| Azelastine−fluticasone + other rhinitis medication | 2568 (6.6) | 1804 (5.0) | 1601 (3.4) | 3244 (2.4) | <0.001 |
| Conjunctivitis* | 341 (75.6) | 293 (70.8) | 590 (75.6) | 1581 (73.5) | 0.239 |
| Sensitisation[f] * | | | | | 0.149 |
| Monosensitisation[f] | 18 (6.3) | 20 (7.4) | 36 (7.8) | 97 (7.6) | |
| Polysensitisation[f] | 136 (47.7) | 113 (41.7) | 181 (39.3) | 486 (38.1) | |
| **C. Sample 3: All patients with at least 3 VAS asthma** | | | | | |
| | Cluster A | Cluster B | Cluster C | Cluster D | *p*−value |
| *N* (%) | 957 (11.9) | 937 (11.6) | 1468 (18.2) | 4713 (58.4) | |
| Reported days − *N* (average days per user) | 52,649 (55.0) | 44,468 (47.5) | 54,438 (37.1) | 145,614 (30.9) | |
| Females* | 675 (70.5) | 562 (60.0) | 907 (61.8) | 2554 (54.2) | <0.001 |
| Age‖ | 39.5 (13.5) | 38.3 (13.8) | 37.1 (13.6) | 34.6 (12.9) | <0.001 |
| Self−reported asthma* | 875 (91.4) | 754 (80.5) | 680 (46.3) | 763 (16.2) | <0.001 |
| Asthma medication reporting* | | | | | <0.001 |
| 0 days | 0 | 0 | 1316 (89.6) | 4604 (97.7) | |
| 1 day | 6 (0.6) | 0 | 152 (10.4) | 109 (2.3) | |
| 2 days | 82 (8.6) | 117 (12.5) | 0 | 0 | |
| 3 or more days | 869 (90.8) | 820 (87.5) | 0 | 0 | |
| Total days reporting asthma medication* | | | | | |
| SABA | 5531 (10.5) | 1581 (3.6) | 65 (0.1) | 39 (0.03) | <0.001 |
| LABA+ICS | 20,320 (38.6) | 14,135 (31.8) | 54 (0.1) | 28 (0.02) | <0.001 |
| ICS | 5471 (10.4) | 5853 (13.2) | 25 (0.1) | 13 (0.01) | <0.001 |
| OCS[b] | 1480 (2.8) | 264 (0.6) | 355 (0.7) | 231 (0.2) | |
| LAMA | 1901 (3.6) | 307 (0.7) | 1 (0.002) | 0 | |
| Biologics | 116 (0.2) | 88 (0.2) | 1 (0.002) | 0 | |
| VAS asthma | | | | | |
| Maximum value† | 78 (65−92) | 30 (13−45) | 69 (54−84) | 6 (0−18) | <0.001 |
| Three highest values† | 65 (53−79) | 18 (6−30) | 52 (39−68) | 2 (0−9) | <0.001 |
| Days with VAS asthma >50* | 7677 (14.6) | 154 (0.3) | 6001 (11.0) | 154 (0.1) | <0.001 |
| Maximum VAS dyspnea† | 67 (53−83) | 29 (16−41) | 61 (46−76) | 17 (7−32) | <0.001 |
| CARAT asthma (questions 5−7)[g] † | 6 (3−8) | 7 (6−9) | 6 (5−8) | 9 (7−9) | <0.001 |
| Presence of asthma symptoms [c,g] * | 125 (74.9) | 55 (44.7) | 90 (61.6) | 78 (19.6) | <0.001 |
| CARAT (questions 1−10)[g] † | 15 (10−18) | 19 (15−24) | 15 (12−20) | 20 (15−23) | <0.001 |
| Uncontrolled[d,g] * | 159 (95.2) | 107 (87.0) | 138 (94.5) | 333 (83.7) | <0.001 |
| Maximum CSMS† | 61 (50−70) | 34 (23−47) | 60 (49−71) | 35 (25−51) | <0.001 |
| Maximum VAS global† | 78 (66−92) | 49 (32−69) | 78 (66−92) | 58 (36−78) | <0.001 |
| Maximum VAS eyes† | 66 (43−84) | 32 (13−59) | 72 (51−88) | 40 (16−68) | <0.001 |
| Maximum VAS nose† | 78 (64−93) | 52 (32−75) | 81 (66−97) | 62 (37−82) | <0.001 |
| Maximum VAS work† | 52 (24−67) | 21 (4−40) | 53 (27−70) | 25 (4−49) | <0.001 |
| Maximum VAS sleep† | 79 (63−95) | 54 (32−78) | 77 (58−92) | 55 (33−77) | <0.001 |
| Total days reporting rhinitis medication* | | | | | |
| Oral antihistamines monotherapy | 5880 (11.2) | 4243 (9.5) | 6431 (11.8) | 19,395 (13.3) | <0.001 |
| Intranasal steroids monotherapy | 3060 (5.8) | 4039 (9.1) | 2976 (5.5) | 8405 (5.8) | <0.001 |
| Azelastine−fluticasone monotherapy | 1963 (3.7) | 1028 (2.3) | 1476 (2.7) | 6145 (4.2) | <0.001 |
| Oral antihistamines + intranasal steroids | 7600 (14.4) | 4693 (10.6) | 3542 (6.5) | 7967 (5.5) | <0.001 |
| Azelastine−fluticasone + other rhinitis medication | 3773 (7.2) | 1766 (4.0) | 1487 (2.7) | 3414 (2.3) | <0.001 |
| Conjunctivitis* | 717 (74.9) | 660 (70.4) | 1136 (77.4) | 3487 (74.0) | 0.002[a] |
| Sensitisation[h] * | | | | | 0.021[a] |
| Monosensitisation[h] | 33 (10.5) | 28 (10.1) | 38 (10.4) | 121 (12.0) | |
| Polysensitisation[h] | 195 (62.3) | 185 (66.5) | 209 (57.4) | 657 (65.4) | |

CARAT: Control of Allergic Rhinitis and Asthma Test; CSMS: Combined symptom-medication score; ICS: Inhaled corticosteroid; IQR: Interquartile range; LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist; OCS: Oral corticosteroid; SABA: Short-acting beta-agonist; VAS: Visual Analogue Scale.

* Results presented as *N*(%).

‖ Results presented as mean (SD).

† Results presented as median (percentile 25-percentile 75).

[a] Non-significant after applying the Bonferroni correction.

[b] It is not possible to differentiate OCS used for asthma or for allergic rhinitis.

[c] Score ≤6.

[d] Score ≤24.

[e] Number of patients for whom sensitisation data are available: 70 for cluster A, 68 for cluster B, 88 for cluster C, and 227 for cluster D.

[f] Number of patients for whom sensitisation data are available: 285 for cluster A, 271 for cluster B, 460 for cluster C, and 1275 for cluster D.

[g] Number of days reporting CARAT: 167 for cluster A, 123 for cluster B, 146 for cluster C, and 398 for cluster D.

[h] Number of patients for whom sensitisation data are available: 313 for cluster A, 278 for cluster B, 364 for cluster C, and 1005 for cluster D.

with low maximum VAS asthma values and (iii) one subgroup with no participants self-reporting asthma and with very low VAS asthma values. For Clusters A and C, the silhouette score was <0.5, suggesting that clustering may not be adequate. Nevertheless, since there were around 50% of patients self-reporting asthma in Cluster C, we performed an ancillary analysis comparing Cluster C patients with self-reported asthma (C') versus those with no self-reported asthma (C''). Overall, patients of the two subgroups were similar (Supplementary Table 3).

Since selecting patients reporting VAS asthma in at least three different months could be interpreted as having some degree of arbitrariness, we performed sensitivity analyses applying the same methods in patients reporting VAS asthma

**Table 2** Asthma-related clusters and respective subgroups obtained using a two-step k-means (Sample 2).

| | Cluster A ("Treated uncontrolled asthma") | Cluster B1 ("Treated partly-controlled asthma") | Cluster B2 ("Treated controlled asthma") | Cluster C ("Untreated uncontrolled asthma") | Cluster D1 ("Untreated partly- controlled asthma") | Cluster D2 ("Untreated controlled asthma") | Cluster D3 ("No evidence of asthma") |
|---|---|---|---|---|---|---|---|
| *N* (%) | 451 (11.9) | 239 (6.3) | 175 (4.6) | 780 (20.5) | 406 (10.7) | 323 (8.5) | 1423 (37.5) |
| Reported days − *N* | 38,823 | 23,953 | 11,770 | 47,352 | 30,907 | 16,287 | 87,747 |
| Average days per user - *N* | 86.1 | 100.2 | 67.3 | 60.7 | 76.1 | 50.4 | 61.7 |
| Females* | 310 (68.7) | 138 (57.7) | 96 (54.9) | 460 (59.0) | 209 (51.5) | 176 (54.5) | 753 (52.9) |
| Age[‖] | 41.1 (14.3) | 40.8 (14.5) | 39.2 (13.6) | 38.3 (13.8) | 37.1 (13.0) | 36.3 (13.9) | 34.8 (13.1) |
| Self-reported asthma* | 432 (95.8) | 228 (95.4) | 161 (92.0) | 391 (50.1) | 18 (4.4) | 323 (100) | 0 |
| Asthma medication reporting* | | | | | | | |
| 0 days | 0 | 0 | 0 | 698 (89.5) | 401 (98.8) | 284 (87.9) | 1417 (99.6) |
| 1 day | 4 (0.9) | 10 (4.2) | 0 | 82 (10.5) | 5 (1.2) | 39 (12.1) | 6 (0.4) |
| 2 days | 68 (15.1) | 31 (13.0) | 33 (18.9) | 0 | 0 | 0 | 0 |
| 3 days or more | 379 (84.0) | 198 (82.8) | 142 (81.1) | 0 | 0 | 0 | 0 |
| Total days reporting asthma medication* | | | | | | | |
| SABA | 4285 (11.0) | 1180 (4.9) | 406 (3.4) | 66 (0.1) | 4 (0.01) | 29 (0.2) | 4 (0.01) |
| LABA+ICS | 16,275 (41.9) | 9508 (39.7) | 5530 (47.0) | 74 (0.2) | 0 | 22 (0.1) | 1 (0.001) |
| ICS | 4658 (12.0) | 3194 (13.3) | 2528 (21.5) | 25 (0.1) | 4 (0.01) | 16 (0.1) | 2 (0.002) |
| OCS [a] | 1331 (3.4) | 206 (0.9) | 37 (0.3) | 244 (0.5) | 9 (0.03) | 8 (0.1) | 124 (0.1) |
| LAMA | 1453 (3.7) | 465 (1.9) | 69 (0.6) | 0 | 0 | 0 | 0 |
| Biologics | 112 (0.3) | 81 (0.3) | 5 (0.04) | 0 | 0 | 0 | 0 |
| VAS asthma | | | | | | | |
| Maximum value[†] | 81 (69−92) | 47 (41−54) | 21 (12−29) | 72 (58−85) | 36 (26−49) | 20 (7-31) | 4 (1−9) |
| Three highest values[†] | 69 (58−82) | 35 (30−43) | 13 (6-20) | 56 (44−72) | 19 (13−25) | 12 (3-20) | 1 (0−5) |
| Days with VAS asthma >50 * | 5610 (14.5) | 90 (0.4) | 1 (0.01) | 4799 (10.1) | 89 (0.3) | 5 (0.03) | 0 |
| Maximum VAS dyspnea [†] | 69 (54−82) | 38 (26−49) | 17 (12−27) | 61 (42−75) | 29 (16−40) | 20 (13−33) | 10 (5-23) |
| CARAT asthma (questions 5-7)[b †] | 5 (2−7) | 8 (7−9) | 7 (6−8) | 6 (4−8) | 9 (7−9) | 9 (7−9) | 9 (8−9) |
| Presence of asthma symptoms[b,c,d,*] | 50 (66.7) | 19 (42.2) | 8 (33.3) | 52 (57.8) | 9 (19.1) | 7 (22.6) | 20 (13.0) |
| CARAT (questions1-10) [b,†] | 13 (8-16) | 20 (16−25) | 21 (19−23) | 15 (11−19) | 20 (16−25) | 20 (17−25) | 20 (16−25) |
| Uncontrolled [b,d,*] | 73 (97.3) | 36 (80.0) | 21 (87.5) | 81 (90.0) | 34 (72.3) | 23 (74.2) | 117 (76.0) |
| Maximum CSMS[†] | 63 (52−72) | 42 (20) | 28 (20) | 62 (50−71) | 46 (35−60) | 29 (22−46) | 35 (24−51) |
| Maximum VAS global[†] | 80 (69−93) | 53 (42−71) | 40 (21−60) | 81 (68−95) | 72 (51−86) | 47 (29−68) | 61 (38−81) |
| Maximum VAS eyes[†] | 71 (51−89) | 42 (28−66) | 29 (12−50) | 75 (57−90) | 57 (38−78) | 34 (14−55) | 42 (19−70) |
| Maximum VAS nose[†] | 82 (67−95) | 59 (42−79) | 46 (27−66) | 85 (70-100) | 76 (55−91) | 51 (32−75) | 66 (40−85) |
| Maximum VAS work[†] | 57 (37−71) | 31 (14−48) | 16 (5-31) | 58 (40−74) | 42 (21−60) | 21 (6-40) | 28 (9-52) |
| Maximum VAS sleep[†] | 72 (26.90) | 61 (40−82) | 45 (18−64) | 79 (60−94) | 53 (14−76) | 50 (26−75) | 56 (33−78) |
| Total days reporting rhinitis medication* | | | | | | | |
| Oral antihistamines monotherapy | 4594 (11.8) | 2864 (12.0) | 988 (8.4) | 4984 (10.5) | 4780 (15.5) | 1165 (7.2) | 11,026 (12.6) |
| Intranasal steroids monotherapy | 1787 (4.6) | 2291 (9.6) | 1573 (13.4) | 2290 (4.8) | 1999 (6.5) | 681 (4.2) | 4610 (5.3) |
| Azelastine-fluticasone monotherapy | 1465 (3.8) | 908 (3.8) | 309 (2.6) | 1288 (2.7) | 1220 (3.9) | 346 (2.1) | 3704 (4.2) |

**Table 2** (*Continued*)

| | Cluster A ("Treated uncontrolled asthma") | Cluster B1 ("Treated partly-controlled asthma") | Cluster B2 ("Treated controlled asthma") | Cluster C ("Untreated uncontrolled asthma") | Cluster D1 ("Untreated partly- controlled asthma") | Cluster D2 ("Untreated controlled asthma") | Cluster D3 ("No evidence of asthma") |
|---|---|---|---|---|---|---|---|
| Oral antihistamines + intranasal steroids | 5949 (15.3) | 2263 (9.4) | 1099 (9.3) | 2982 (6.3) | 1637 (5.3) | 1165 (7.2) | 5356 (6.1) |
| Azelastine-fluticasone + other rhinitis medication | 2568 (6.6) | 1448 (6.0) | 356 (3.0) | 1601 (3.4) | 1280 (4.1) | 348 (2.1) | 1616 (1.8) |
| Conjunctivitis * | 341 (75.6) | 171 (71.5) | 122 (69.7) | 590 (75.6) | 300 (73.9) | 235 (72.8) | 1046 (73.5) |
| Sensitisation [e,*] | | | | | | | |
| Monosensitisation [e] | 18 (6.3) | 13 (8.3) | 7 (6.1) | 36 (7.8) | 14 (5.5) | 10 (5.1) | 73 (8.9) |
| Polysensitisation [e] | 136 (47.7) | 65 (41.7) | 48 (41.7) | 181 (39.3) | 101 (39.6) | 72 (36.4) | 313 (38.1) |

CARAT: Control of Allergic Rhinitis and Asthma Test; CSMS: Combined symptom-medication score; ICS: Inhaled corticosteroid; IQR: Interquartile range; LABA: Long-acting beta-agonist; SABA: Short-acting beta-agonist; VAS: Visual Analogue Scale.

* Results presented as *N*(%).

‖ Results presented as mean (SD).

† Results presented as median (percentile 25-percentile 75).

a It is not possible to differentiate OCS used for asthma or for allergic rhinitis.

b Number of patients reporting CARAT: 75 for cluster A, 45 for cluster B1, 24 for cluster B2, 90 for cluster C, 47 for cluster D1, 31 for cluster D2, and 154 for cluster D3.

c Score $\leq 6$.

d Score $\leq 24$.

e Number of patients for whom sensitisation data are available: 285 for cluster A, 156 for cluster B1, 115 for cluster B2, 460 for cluster C, 255 for cluster D1, 198 for cluster D2, and 822 for cluster D3.

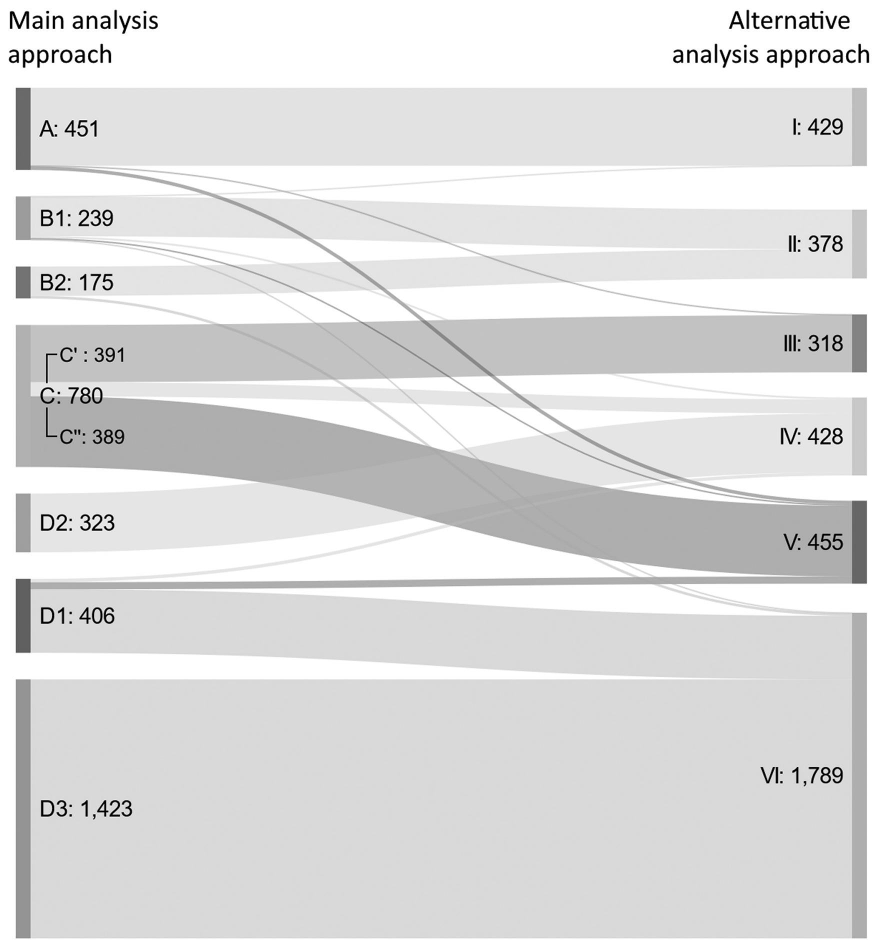


**Fig. 1** Classification of patients who reported VAS asthma in at least three different months (Sample 2) with clustering based on the main analysis approach and on the alternative analysis approach of this study.

in at least four and five different months. Similar results were obtained.

**Alternative analysis approach**

Four clusters were identified among patients self-reporting asthma, while two clusters were identified among those not self-reporting asthma (Supplementary Tables 5-6). Using a Sankey diagram, the two approaches showed consistent results (Fig. 1).

## Phenotypic characteristics of the clusters

Median VAS asthma maximal levels were over 50/100 for Clusters A and C, indicating "uncontrolled asthma". VAS asthma levels ranged from 20 to 49/100 in Clusters B1 and D1 (indicating "partly-controlled asthma") and were under 20/100 in Clusters B2 and D2 (indicating "controlled asthma"). The lowest levels were in Cluster D3 (Supplementary Figure 4).

Patients were mostly undertreated in Clusters C, D1, D2 and D3. In Cluster C, only half of the patients self-reported asthma. Therefore, Clusters C and D1 may include patients with under-diagnosed asthma. A possible clinical interpretation of the seven clusters observed with the main approach is available in Table 3.

Throughout the different months of the year, the order of VAS asthma levels was found to be consistent, with the highest levels being observed in Cluster A, followed by C, B1 and the remaining groups (Supplementary Figure 5).

Besides differences in asthma features, the seven clusters differed in the participants' demographics, in the VASs on allergy symptoms and in rhinitis treatment (Table 2, Supplementary Figures 4 and 6). The reported rhinitis treatments varied between clusters, ranging from 22.8-42.1% of days. Co-medication was reported in 21.9% of days for Cluster A, 15.4% for Cluster B1, 12.3% for Cluster B2 and around 9-10% of days in untreated asthma clusters.

## Validation of the cluster classification

We analysed 192 Twinning participants, comparing the cluster classification obtained by the main analysis approach with physician-diagnosed asthma (Supplementary Table 7).

Patients clustered as having "probable asthma" (clusters A, D and C') had a physician diagnosis of current or past asthma in 92.3% of cases. Patients with "no evidence of current asthma" (cluster D3) had a diagnosis of "no current

**Table 3** Clinical interpretation of the clusters obtained following clustering approaches.

| Asthma | | | Main clustering approach | | Alternative clustering approach | | Clinical interpretation |
|---|---|---|---|---|---|---|---|
| Treatment | Control | Majority of self-report | Cluster | % of users[a] | Cluster | % of users[a] | |
| Treated | Uncontrolled | Yes | A | 11.9-16.1 | I | 10.5-15.5 | • Probable asthma: Treated uncontrolled asthma |
| | Partly- controlled | | B1 | 6.3-9.7 | II | 9.6-13.7 | • Probable asthma: Treated partly-controlled asthma |
| | Controlled | | B2 | 4.6-5.5 | | | • Probable asthma: Treated and controlled asthma |
| Untreated | Uncontrolled | Yes | C’[b] | 9.7-10.2 | III | 7.0-8.6 | • Probable asthma: Untreated and uncontrolled asthma with self-reported asthma (possible undertreated asthma) |
| | | No | C” [b] | 8.4-10.3 | V | 11.7-12.9 | • Possible asthma: Untreated uncontrolled asthma with no self-reported asthma (possible underdiagnosed asthma) |
| | Partly- controlled | | D1 | 10.1-10.7 | VI | *40.8-50.3* [c] | • Possible asthma: Untreated partly-controlled asthma (possible under-diagnosed asthma) |
| | Controlled | Yes | D2 | 6.7-8.5 | IV | 8.6-11.3 | • Possible asthma: Untreated controlled asthma (possible over-diagnosed asthma or asthma in clinical remission) |
| | | No | D3 | 33.0-40.2 | VI | *40.8-50.3* [c] | • No evidence of current asthma |

[a] Range of percentages across the three samples.
[b] Cluster C was divided by design (not by unsupervised learning approach).
[c] Range of percentages of cluster VI as a whole.

asthma" in 90.4% of cases. Patients with "uncontrolled underdiagnosed asthma" (cluster C") had an infrequent physician diagnosis of asthma, supporting the label of underdiagnosis.

A patient with current asthma displayed an 85.5% probability of being classified in a cluster of probable asthma (sensitivity) and a 93.4% probability of being in a cluster of probable or possible asthma. A patient with no history of asthma displayed a 52.6% probability of being classified as having no asthma (specificity) and 79.3% as having current asthma.

The classification of probable *versus* possible or no asthma for the identification of current asthma *versus* past or no asthma displays an agreement of 81% and a kappa coefficient of 0.610.

## Discussion

Cluster analysis approaches were used to identify asthma control patterns in MASK-air® users combining information from self-reported asthma status, reported asthma medication use and VAS asthma. We identified seven profiles of asthma control and treatment patterns. These profiles were replicated in three samples and were validated in a sub-sample of physician-assessed patients.

### Limitations and strengths

This study has some limitations. First, clustering was not performed based on patients from asthma clinics with a confirmed diagnosis of asthma. This type of study (i) would have a limited number of patients and (ii) would have mostly included severe patients and patients under treatment. However, we validated the results of the cluster classification in a sample of participants with a physician-diagnosis of asthma. Further information biases may occur, resulting from incorrect information on self-reported asthma or medication use. However, the consistency of the results suggests that this is unlikely.

All assessed patients displayed self-reported rhinitis, and the results are only valid for those with nasal symptoms. These patients do however represent a very large proportion of patients with asthma. Furthermore, there may be an over-representation of users suffering from moderate-to-severe asthma[20] and of younger individuals.

This study also has important strengths. MASK-air® has been developed for patients with rhinitis or asthma and has been assessed in patients with both diseases. VAS asthma — which was the main assessed VAS — has been shown to have high reliability, concurrent validity (with strong correlation with VAS dyspnea,[21] significant correlation with the Asthma Control Test[22] and moderate correlation with CARAT[23]) and moderate responsiveness.[24] We also assessed a sample of participants enrolled by a physician to validate our main results. In addition, this study was conducted in 25 countries (indicating a generalisability of results).

Results were highly consistent when using two clustering methodologies or when assessing different sets of patients. Furthermore, the average number of days reported by patients was longer than in previous MASK-air studies.[20] This longer period of reporting will enable future studies to assess medication adherence.

### Interpretation

We classified approximately 70% of the MASK-air® users as having probable asthma or no current asthma (Clusters A, B, C' and D3). In addition, we identified a set of patients who would benefit from further clinical assessment, including users who present high values of VAS Asthma despite not reporting asthma or asthma medications (Clusters C" and D1). This suggests an under-diagnosis of asthma. Using the Twinning data, most patients of these clusters were classified by their physician as having no asthma. Patients of Cluster A ("uncontrolled treated asthma") may also benefit from clinical assessment for treatment adjustment. It is possible that patients of this cluster may comprise an extreme asthma phenotype, which may be poorly responsive to asthma treatment. Interestingly, this asthma phenotype also tends to display poorer rhinitis control.

Only one-third of the patients with probable asthma reported information that was at least partly compatible with proper treatment/control. This may mirror the clinical challenges related to diagnosing asthma, assessing its severity and tailoring medication. It may also enable patients to understand the importance of self-management.

Some interesting hypothesis-generating results have been observed: (i) There may be an extreme asthma phenotype with a high level of multimorbidity and a relatively poor response to treatment, both for rhinitis and asthma. If this group is confirmed in epidemiologic studies, it may be predictive of the need for biologicals and may allow patient stratification for these treatments. (ii) Better asthma control associated with lower and upper airways as well as eye symptoms. Patients had a similar control for all morbidities, whether or not they received treatment. Ocular symptoms are seldom considered in asthma, although epidemiologic studies have stated their importance.[10] (iii) Among the seven identified clusters, six were associated with asthma and one - rhinitis without current asthma - was strikingly different, suggesting that rhinitis alone and rhinitis and asthma are different diseases.[25]

Taken together, these results suggest that RWD collected under pragmatic circumstances - and particularly when combining information from different variables - can be used to investigate asthma and to identify patients who would benefit from further clinical assessment for diagnostic or therapeutic reasons. This may allow for future studies to be conducted in order to develop CSMSs for the assessment of asthma control based on MASK-air® data.

## Conclusion

This study allowed a consistent identification of seven profiles based on the probability of having asthma and on its control. It resulted in a classification supported by physician-diagnosed asthma and in the identification of a substantial percentage of patients potentially benefiting from clinical assessment for diagnosis or treatment adjustment purposes. The use of an mHealth app can help to complement classical epidemiological approaches with RWD. This can potentially support the identification of patients with asthma and reduce biases of epidemiologic studies solely relying on the retrospective data of self-reported asthma diagnoses.

## Data availability

Data are available upon request to Prof. J Bousquet (jean.bousquet@orange.fr).

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## Take-home message

K-means cluster analysis algorithms using real-world data obtained using a mobile app in over 8,000 patients identified patients with probable or possible asthma confirmed by a sub-study in patients with physician-diagnosed asthma.

## Conflicts of interest

Dr. Agache has nothing to disclose.

Dr. Amaral has nothing to disclose.

Dr. Antó has nothing to disclose.

Dr. Basagaña has nothing to disclose.

Ms. Bedbrook has nothing to disclose.

Dr. Bergmann has nothing to disclose.

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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.2022.10.005.

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ORIGINAL ARTICLE

# Prescribing and adjusting exercise training in chronic respiratory diseases — Expert-based practical recommendations

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**KEYWORD**
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**Abstract**
*Background:* International guidelines recommend endurance (ET) and strength training (ST) in patients with chronic respiratory diseases (CRDs), but only provide rough guidance on how to set the initial training load. This may unintentionally lead to practice variation and inadequate training load adjustments. This study aimed to develop practical recommendations on tailoring ET and ST based on practices from international experts from the field of exercise training in CRDs.
*Methods:* 35 experts were invited to address a 64-item online survey about how they prescribe and adjust exercise training.
*Results:* Cycling (97%) and walking (86%) were the most commonly implemented ET modalities. Continuous endurance training (CET, 83%) and interval endurance training (IET, 86%) were the frequently applied ET types. Criteria to prescribe IET instead of CET were: patients do not tolerate CET due to dyspnoea at the initial training session (79%), intense

*Abbreviations:* AACVPR, *American Association of Cardiovascular and Pulmonary Rehabilitation*; ACCP, *American College of Chest Physicians*; ATS, American Thoracic Society; BTS, British Thoracic Society; CET, continuous endurance training; CRD, chronic respiratory disease; ERS, European Respiratory Society; ET, endurance training; IET, interval endurance training; PR, pulmonary rehabilitation; RCT, randomized, controlled trial; ST, strength training.

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breathlessness during initial exercise assessment (76%), and/or profound exercise-induced oxygen desaturation (59%). For ST, most experts (68%) recommend 3 sets per exercise; 62% of experts set the intensity at a specific load that patients can tolerate for a range of 8 to 15 repetitions per set. Also, 56% of experts advise patients to approach local muscular exhaustion at the end of a single ST set.
*Conclusions:* The experts´ practices were summarized to develop practical recommendations in the form of flowcharts on how experts apply and adjust CET, IET, and ST in patients with CRDs. These recommendations may guide health care professionals to optimize exercise training programs in patients with CRDs.


## Introduction

Patients with chronic respiratory diseases (CRDs) perceive various limitations of exercise capacity, which go far beyond (exertional) breathlessness. Peripheral muscle weakness and associated physical inactivity accelerate physical deconditioning and amplify exercise-induced breathlessness and peripheral muscle discomfort.[1] The beneficial effects of exercise training (either as a stand-alone intervention or as part of a pulmonary rehabilitation (PR) program) have been well documented in patients with CRDs.[2-4] Thus, exercise training has been established as a key component of non-pharmacological treatment options in CRDs.[5,6] However, when it comes to practical recommendations on how to prescribe exercise training in patients with CRDs, there is only scarce information available in the international respiratory societies' official statements and guidelines (Tables 1-2).[5,7,8] This lack of information is even more noticeable regarding how exercise training should be adjusted and progressed during an ongoing exercise training program. Therefore, we collected the experiences of multiple international experts from the field of exercise training in CRDs on how they initially set and subsequently adjust exercise training workloads in patients with CRDs.

## Methods

We initially developed a 64-item online survey to understand international expert practices on the delivery of exercise training in the setting of PR in patients with CRDs like chronic obstructive pulmonary disease, asthma, or interstitial lung disease. Peers checking for plausibility and consistency proofread the survey before its dissemination. The survey consisted of mixed open-ended questions and multiple-choice questions. Most of the questions afforded multiple answers — no question was mandatory to be addressed. The survey was built by using SurveyMonkey Software.

### Dissemination of the survey

The survey was sent by email to 45 international experts from the field of exercise training in CRD patients and was available from 18 January 2022 to 18 February 2022. Participants for the survey were selected from contributor lists of previous international surveys and statements on PR[5,9] and were partly expanded by experts based on the experiences and judgment of the authors. Only one expert per center was invited to participate in the survey to avoid a center-based bias. Participation in the survey was voluntary and participants were asked if they agreed that their names would be disclosed in the section of acknowledgments.

### Data analysis

Quantitative data were reported as percentages of answers for each question of the survey.

## Results

Thirty-five out of 45 invited experts from 21 countries across 5 continents (e-Figure 1) completed the survey (response rate: 78%). The professional background of the experts was multidisciplinary, consisting of physiotherapists (66%), pulmonologists (20%), and clinical exercise physiologists (14%). Most experts provide outpatient programs (71%) of 8 to 12 weeks, including 2 to 3 training sessions per week or inpatient exercise programs (37%) for 3 to 4 weeks applying 5-7 exercise sessions per week (e-Figures 2-4). All experts (100%) provide endurance training and 94% apply strength training. The online supplement includes all survey questions and the experts´ responses.

Tables 1-2 summarise the findings from the survey relevant to CET, IET and ST recommendations reported within international respiratory society statements, and guidelines as well as evidence from the literature.

### Endurance training

Cycling (97%) and walking (ground floor 86% or treadmill 77%) were the most common endurance training modalities, and continuous endurance training (CET, 83%) or interval endurance training (IET, 86%) were the most used modes (e-Figures 8-9). Criteria to prescribe IET instead of CET were: when patients do not tolerate CET due to dyspnoea at the initial training session (79%), intense breathlessness during the initial exercise assessment (76%), or profound exercise-induced oxygen desaturation (59%). The following measurements are usually performed during CET and IET: 10-point Borg scale rating of breathlessness (94%) and leg discomfort (86%), oxygen saturation (87%), and heart rate (80%) (e-Figures 20 and 33).

**Table 1** Overview of recommendations to prescribe and adjust continuous and interval endurance training in patients with chronic respiratory diseases including experts' practices from the current survey.

| Continuous endurance training (CET) | ACCP/AACVPR 2007 [8] | BTS 2013 [7] | ATS/ERS 2013 [5] | Evidence from the literature (n=13 studies) 1 Meta-analysis [10] | Expert-based practices from the current survey 2022 |
|---|---|---|---|---|---|
| **Modality** | Walking or cycling | Walking or cycling | Walking (treadmill or ground-based) or cycling (cycle ergometer) | Stationary cycling | Walking (treadmill or ground-based) or cycling (cycle ergometer) |
| **Frequency** | Not stated | 2-3 days per week (minimum) | 3-5 days per week | 2-6 days per week | 2-3 days per week (outpatient)<br>5-7 days per week (inpatient) |
| **Intensity** | 60-80% of peak work rate | >60% of peak work rate | >60% of peak work rate | 50-80% of peak work rate | 60-70% of peak work rate |
| **Duration** | Not stated | 30-60 minutes per session | 20-60 minutes per session | 20-47 minutes per session | 30-40 minutes per session |
| **Dyspnoea/Leg discomfort (10-point Borg scale)** | Not stated | Not stated | 4-6 | 4-5 | 4-6 |
| **Criteria for work-load progression** | Not stated | Not stated | Not stated | - Mainly when symptoms on the Borg scale are <3-4<br>- increase the intensity by 5-10% of baseline workload<br>- total workload increments weekly or monthly | **When symptoms on the Borg scale are ≤3:**<br>1) Increase intensity and<br>2) Increase duration, both according to symptoms<br>**When symptoms on the Borg scale are >4:**<br>Increase duration up to 30-40 minutes, if tolerated<br>Increase intensity, according to symptoms<br>*See the flowchart for detailed information (Figure 1)* |

| Interval endurance training (IET) | ACCP/ AACVPR 2007 [8] | BTS 2013 [7] | ATS/ERS 2013 [5] | Evidence from the literature (n=13 studies) 1 Meta-analysis [10] | Expert-based practices from the current survey 2022 |
|---|---|---|---|---|---|
| **Modality** | Not stated | Walking or cycling | Typically stationary cycle based | Stationary cycling | Typically cycle based |
| **Frequency** | Not stated | 2-3 days per week (minimum) | 3-5 days per week | 2-6 days per week | 2-3 days per week (outpatient)<br>5-7 days per week (inpatient) |
| **Intensity** | Not stated | Not stated | Not stated | 80-100% of peak work rate for the active period and typically complete rest in the passive period | 80-100% of peak work rate |
| **Duration** | Not stated | 30-60 minutes per session, interval duration not stated | 20-60 minutes per session; interval duration not stated | 20-45 minutes per session, most common rate 1:1 with 30 seconds per interval | 20-40 minutes per session;<br>The most common mode is 1:1 with 30-60 seconds per interval |
| **When to apply interval instead of continuous endurance training (CET)** | Not stated | The choice of interval or continuous training will be down to the patient and/or therapist's preference | Not stated | When CET is not tolerated due to dyspnoea | - CET is not tolerated due to dyspnoea<br>- intense breathlessness during the initial exercise assessment<br>- profound exercise-induced oxygen desaturation during CET |
| **Criteria for work-load progression** | Not stated | Not stated | Not stated | - Mainly when symptoms for the BORG scale are <3-4<br>- increase the intensity by 10-20% from the baseline workload<br>- total workload increment weekly | **When symptoms on the Borg scale are ≤3:**Increase intensityReduce the duration of the recovery period**When symptoms on the Borg scale are >4:**<br>Increase total duration up to 20-40 minutes, if tolerated<br>- Increase intensity, according to symptoms |

Abbreviations: ACCP — American College of Chest Physicians, AACVPR — American Association of Cardiovascular and Pulmonary Rehabilitation, BTS — British Thoracic Society, ATS — American Thoracic Society, ERS — European Respiratory Society, CET — continuous endurance training.

**Table 2** Overview of recommendations to prescribe and adjust strength training in patients with chronic respiratory diseases including experts' practices from the current survey.

| Strength Training (ST) | ACCP/AACVPR 2007 [8] | BTS 2013 [7] | ATS/ERS 2013 [5] | Evidence from the literature (n=11 RCTs) 2 Meta-Analyses [11,12] | Expert-based recommendations from the current survey 2022 |
|---|---|---|---|---|---|
| **Modality** | Machine weights, free weights, elastic resistance bands, and lifting the body against gravity | Not stated | Not stated | Strength training machines, dumbbells, elastic tubes, or bodyweight | Strength training machines, dumbbells, elastic tubes, or bodyweight |
| **Frequency** | 2-3 days per week | 2 days per week (minimum) | 2-3 days per week | 2-3 days per week | 2-3 days per week (outpatient)<br>5-7 days per week (inpatient) |
| **Load** | Not stated | Not stated | 60-70%1RM or 8-12 RM | 40-90% 1RM | 8-15 RM at an intensity that evolves `local muscular exhaustion´ |
| **Duration** | Not stated | 2-4 sets of 10-15 repetitions | 1-3 sets of 8-12 repetitions | 2-4 sets of 5-15 repetitions | 3 sets à 8-15 repetitions |
| **Criteria for workload progression** | Not stated | The load chosen should be individualized and progressed once all sets can be completed with the selected weight | When an individual can perform the current workload for 1 or 2 sets over the desired number of 6 to 12 repetitions, on 2 consecutive training sessions the load should be increased | - Reassessment with 1RM test when required sets and/or repetitions are achieved without difficulty or<br>- improvements based on 1RM tests every 2 weeks or<br>- based on Borg scale when scores <4 for muscle discomfort at a given fixed number of repetitions or can increase number of repetitions for a given set | **When patient discontinued strength training exercise <8 repetitions:**<br>1) Decrease the load until patients reach `momentary muscular failure´ between 8 to 15 repetitions<br>2) Decrease the number of total sets according to the patient's tolerance<br>**When patient completed strength training exercise >15 repetitions:**<br>1) Increase the load until patients reach `momentary muscular failure´ between 8 to 15 repetitions<br>2) Increase the number of total sets according to the patient's tolerance |

Abbreviations: ACCP − American College of Chest Physicians, AACVPR − American Association of Cardiovascular and Pulmonary Rehabilitation, BTS − British Thoracic Society, ATS − American Thoracic Society, ERS − European Respiratory Society, RM − repetition maximum, RCT − randomized controlled trial.

## Setting initial CET load

To set initial training intensity, 82% of experts start CET at 60-70% of peak work rate and 77% use the 10-point Borg scale to set exercise intensity aiming for a dyspnoea score between 4 and 6. Seventy-four percent prescribe a total duration of 10 to 20 minutes during the first training session (Table 1).

## Adjusting CET load during an ongoing training program

To advance the training load, 57% of experts initially increase the duration of exercise, aiming for a total CET duration of 30 to 40 minutes per session (71% of experts, e-Figure 21). As a second step, the intensity is increased. The rate of intensity progression is variable, as 71% increase the intensity depending on the patients´ symptoms (breathlessness and/or leg discomfort, e-Figure 25). Fig. 1 provides an overview on experts´ practices, when patients need to interrupt a CET session due to various reasons.

## Setting initial IET load

Most experts (59%) use a ratio of 1 to 1 alternating exercise with active or complete recovery periods. Work to recovery ratios of 1 to 2 (29%) or 2 to 1 (26%) are also used (e-Figure 35). Periods of 30 to 60 seconds are usually (69%) implemented as the length of time for the interval (exercise or recovery) phases (e-Figure 36). The initial intensity for the work interval is mostly (78%) set between 80% to 100% of baseline peak work rate with an initial total exercise duration of 10 to 20 minutes (61%) during the first training session (e-Figures 37 and 41).

## Adjusting IET load during an ongoing training program

All experts (100%) agreed that it is necessary to progressively adjust the load during IET (e-Figure 43) with 76% allowing a total IET duration ranging between 20 and 40 minutes per session based on the patients´ tolerance (e-Figure 42). Also,

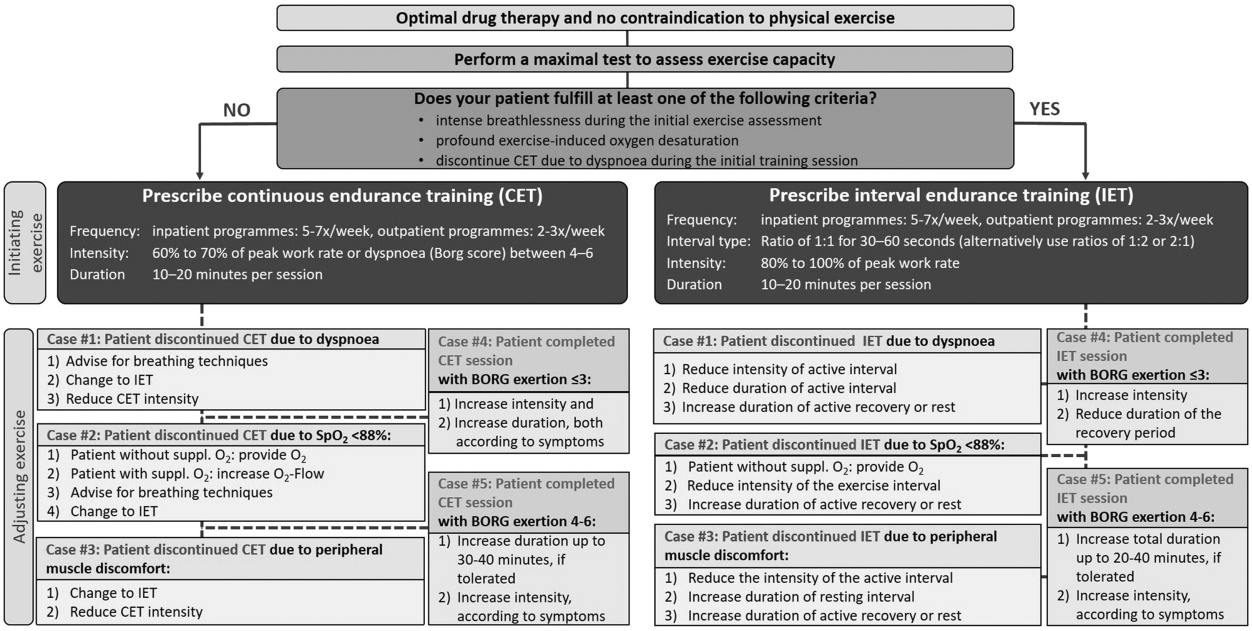


**Fig. 1** Summary of expert-based practices for prescribing and adjusting continuous and interval endurance training in patients with chronic respiratory diseases.

76% of experts progressively increase the intensity of exercise during IET based on the patients´ symptoms (e-Figure 45). Fig. 1 provides an overview on experts´ practices when patients discontinue a IET session due to various reasons.

## Strength training (ST)

Experts used various ST apparatus, such as regular weight training machines (79%), elastic tubes (56%), dumbbells (53%), or bodyweight only (53%) (e-Figure 52). The following muscle groups were seen as a minimum standard for ST: knee extensors (91%), chest muscles (59%), arm flexors (59%), arm elevator muscles (56%), hip extensors (56%), and upper back muscles (50%) (e-Figure 53). Fifty-one percent of experts do not perform a 1-repetition maximum test at the beginning of a ST program (e-Figure 54).

## Setting initial load for ST

Most experts (68%) perform 3 sets per exercise (e-Figure 58). 62% of experts set the intensity at a specific load that patients can tolerate for a range of 8 to 15 repetitions per set, whereas 56% of experts use a range of around 60% to 70% from the 1-repetition maximum test to determine the initial ST intensity (e-Figure 55). Also, 56% of experts advise patients to reach local muscular exhaustion (or close to it) at the end of a single ST set (e-Figure 59).

## Adjusting ST load during an ongoing training program

When patients can complete all sets during an exercise workout without significant exhaustion, experts increase the load to the next higher tolerated workload (41%), increase the weight by 5 to 10% of the 1-repetition maximum (35%) or increase the training load until patients reach local muscular exhaustion (or close to it) at the end of a single set (35%) (e-Figure 63). 53% of experts also extend the total number of exercises, according to the patients´ tolerance to further progress training volume (e-Figure 64).

## Exercise prescription flowcharts

Exercise flowcharts were developed (Figs. 1 and 2) to facilitate tailoring of exercise training prescription to the individual patient's needs and capabilities. The expert practices on adjusting exercise training for the presented cases, were derived on the basis of the most prevalent responses to the survey questions (see online supplement).

# Discussion

We conducted a survey to capture the practices of international experts in delivering exercise training for patients with CRDs. Based on the expert clinical practice, exercise flowcharts were developed including suggestions on prescribing and adjusting continuous, interval, and strength training in patients with CRDs. International experts from 35 different centres across 21 countries completed the survey. This reflects the largest collection of multiple expertise within this field and provides an update and extension of previously published practical recommendations on exercise training in patients with COPD.[13] Interestingly, there was considerable heterogeneity amongst experts on how they apply and adjust exercise training. This shows that there are several ways to reach the same aim for improving physical performance.

International guidelines and statements on PR provide recommendations on how exercise training in patients with CRDs should be prescribed (Tables 1–2). Our survey indicates that exercise training practices closely align with these guidelines. However, guidance on how to further adjust exercise training

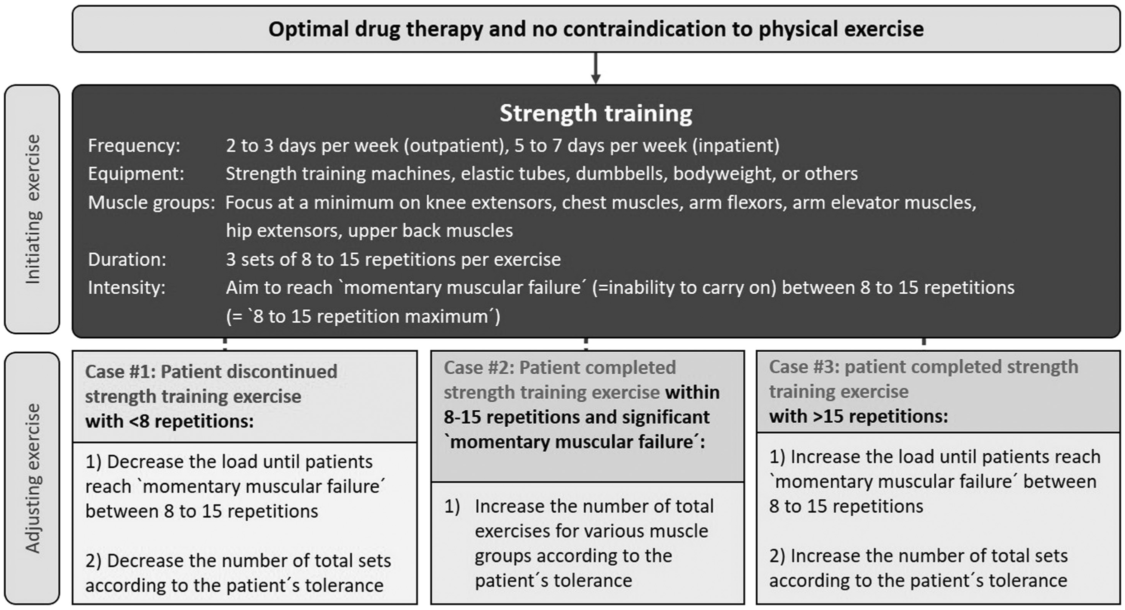


**Fig. 2** Summary of expert-based practices for prescribing and adjusting strength training in patients with chronic respiratory diseases.

workload during an ongoing exercise training program and how to deal with situations when patients need to discontinue a session of exercise training due to various limitations, is scarce. Former surveys about exercise prescription also focussed more on exercise programme structures and modalities rather than on practical advice on tailoring exercise training workload.[14,15] However, these aspects are highly relevant to the delivery of exercise training, and as such our flowcharts may provide further practical guidance on prescribing and adjusting exercise training according to the individual patient's needs and capabilities.

Endurance training (CET or IET) is consistently considered a fundamental component of exercise training in patients with CRDs.[5,16-18] Most endurance training programmes are based on the CET method, in which exercise is performed at a constant intensity for an extended period without interruption. However, patients with severe CRDs are usually unable to sustain CET at relatively high intensities for an extended period due to increased respiratory distress.[19,20] IET, which consists of repeated bouts of maximal/high-intensity exercise, alternated with short intervals of rest or low-intensity exercise, is a suitable alternative to CET.[21] Several systematic reviews have consistently concluded that CET and IET demonstrate comparable efficacy in improving exercise capacity, exercise-induced dyspnoea sensations, muscle fiber structure and function, and quality of life.[10,22] However, there is also some evidence, that especially patients with advanced CRDs perceive less dyspnoea during IET compared to CET.[20,23] Underlying physiological reasons include a lower reliance on anaerobic glycolysis associated with lower ventilatory requirement and degrees of dynamic hyperinflation during IET.[24,25] This explains the greater tolerance to IET compared to CET in patients with advanced CRDs. In our flowchart we presented practical indications from the experts´ experiences on when to consider IET instead of CET. Furthermore, practical cases are presented, that show how experts proceed, when patients need to interrupt CET or IET due to various reasons.

Studies have shown, that endurance training combined with strength training results in significantly greater improvements in muscle strength, muscle hypertrophy, and quality of life compared to endurance training alone in patients with COPD.[11,12,26,27] Therefore, when patients with COPD have the capacity to perform a combined endurance and strength training program, this may provide the optimal exercise prescription.

One of the most important considerations concerning strength training is intensity. The general use of the term `intensity´ in the strength training literature, including the ACSM statement,[28] refers to the load used (i.e. the fraction of 1 repetition maximum, %1RM). However, the expression of %1RM only represents the training load given as a fraction of maximal effort. The %1RM does not explicitly imply how hard an individual is working *during* a set of strength exercises. Therefore, Fisher and colleagues proposed that `intensity´ in its truest sense is the level of a subject´s effort applied to a given load.[29] The inability to perform additional concentric contractions at a given load without significant changes in posture or movement speed was defined as `momentary muscular failure´.[29] It has been shown that training to `momentary muscular failure´, maximizes muscle fibre recruitment (especially to the higher threshold fast-twitch muscle fibres), and increases the secretion of growth-promoting hormones compared to not reaching `momentary muscular failure´.[30] Both are important factors for the capability of producing the greatest increases in muscle strength and hypertrophy.

To date, many studies have investigated the benefits of strength training and the different approaches to determine the optimal strength training intensity/load. Several systematic reviews have consistently concluded that muscle hypertrophy can be equally achieved across a wide spectrum of loads (30%1RM to 90%1RM).[29,31,32] This evidence suggests that reaching `momentary muscular failure´ at the end of a strength training set (i.e. within a range of 8 to 15 repetitions) is the most important aspect for maximizing muscle hypertrophy. Therefore, it is not necessary to perform a 1RM effort for prescribing strength training intensity at a certain fraction of 1RM, because the fraction of 1RM alone is not relevant for improving muscle hypertrophy.[29] Instead, it is the effort that a subject perceives as strenuous.

We are aware that the requirements for exercise training programmes in patients with CRDs vary widely across the world within different healthcare systems and local infrastructure. However, different types of exercise training apparatus (e.g. regular strength training machines, free weights, elastic tubes, etc.) can potentially increase exercise performance, when appropriate exercise training principles and intensity progression to reach `momentary muscular failure´are applied.[33,34] Recent studies have shown that an exercise training program using minimal equipment can be equally effective in increasing muscle strength and exercise performance compared to using sophisticated exercise apparatus.[33,34] Therefore, what is much more relevant is *how* adequately patients exercise and not what kind of apparatus they use. Hence, our flowchart suggestions are also transferable to different exercise training settings.

Some limitations need also to be addressed. First, there is no direct proof of the benefits of the training recommendations included in our flowcharts. A clinical validation is needed. However, we suggest that the meaningful benefits shown in numerous exercise training studies might also apply to our expert-based recommendations since there is a substantial overlap in several basic training principles between the experts´practices and scientific evidence.

Second, there was no official panel discussion involving all experts like a Delphi consensus process. Third, we did not ask for safety issues related to the experts´experiences with exercise training. However, exercise training is usually accepted as a safe intervention for patients with CRDs following a baseline patient assessment to rule out any contraindications for physical exercise.[5] Fourth, we provided general recommendations for a range of CRDs and did not take disease-specific considerations into account (i.e. an interval warm-up phase of 10-15 minutes in patients with asthma to prevent exercise-induced bronchoconstriction during a subsequent endurance training).[35]

Finally, the current flowcharts do not take into account non-invasive ventilation during exercise training,[36] or other types of lower-limb muscle training, such as neuromuscular electrical stimulation,[37] single-leg cycling,[38] and whole-body vibration.[39]

A strength of this survey is the large collection and consolidation of international experts´experiences for adjusting exercise training in patients with CRDs during an ongoing training program.

During the process of this survey, we have also identified important questions for future research like what patient/modality combinations are the best to safely achieve the largest training effects? What are the underlying changes in exercise performance, including intramuscular changes[40] and oxygen uptake kinetics.[41] Furthermore, is there a valid approach to optimise walking speed during ground-based walking training? Future studies should include a larger number of rehabilitation experts and should collect more data with a more detailed description of the expert responses, in order to standardize procedures at a world level in the area of exercise training in CRDs.

In conclusion, based on these experts´ experiences, exercise prescription flowcharts were developed. These flowcharts are meant to guide healthcare professionals in prescribing and adjusting continuous, interval, and strength training in patients with chronic respiratory diseases.


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### Guarantor

RG had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

### Other contributions

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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.2022.09.004.

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ORIGINAL ARTICLE

# Utility of solar-powered oxygen delivery in a resource-constrained setting

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**Abstract**
*Background:* Pneumonia is a leading cause of childhood mortality globally. Children with severe pneumonia associated with hypoxaemia require oxygen ($O_2$) therapy, which is scarce across resource-constrained countries. Solar-powered oxygen (SPO2) is a novel technology developed for delivering therapeutic $O_2$ in resource-constrained environments.
*Research question:* Is the introduction of SPO2 associated with a reduction in mortality, relative to the existing practice?
*Study design:* This was a pragmatic, quasi-experimental study comparing mortality amongst children $<$ 5 years of age with hypoxaemic respiratory illness before and after the installation of SPO2 in two resource-constrained hospitals.
*Methods:* Participants were children $<$ 5 years old admitted with acute hypoxaemic respiratory illness. The intervention was SPO2, installed at two resource-constrained hospitals. The primary outcome was 30-day mortality. Secondary outcomes included in-hospital mortality (time to death), length of hospital stay among survivors, duration of $O_2$ therapy (time to wean $O_2$), and $O_2$ delivery system failure(s).
*Results:* Mortality amongst children admitted with acute hypoxaemic respiratory illness decreased from 30/50 (60%) pre-SPO2 to 15/50 (30%) post-SPO2 (relative risk reduction 50%, 95%CI 19 – 69, $p$ = 0.0049). The post-SPO2 period was consistently associated with decreased mortality in statistical models adjusting for potential confounding factors. Likewise, survival curves pre- and post- SPO2 differed significantly (hazard ratio 0.39, 95% CI 0.20 – 0.74,

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$p = 0.0043$). A reduction in the frequency of $O_2$ delivery interruptions due to fuel shortages and multiple patients needing the concentrator at once was observed, explaining the mortality reduction.

*Interpretation:* Solar-powered oxygen installation was associated with decreased mortality in resource-constrained settings.



## Introduction

Pneumonia is a leading cause of mortality among children under 5 years of age, accounting for more than 800,000 deaths annually.[1] Oxygen ($O_2$) is an essential therapy for hypoxaemic illnesses, including pneumonia; however, $O_2$ is often not available on paediatric wards in resource-constrained hospitals.[2,3] In the current COVID-19 pandemic, $O_2$ demand is expected to increase dramatically in low- and middle-income countries, exacerbating this pre-existing shortage.

In resource-constrained settings, methods of delivering $O_2$ include $O_2$ cylinders and grid-powered $O_2$ concentrators,[4,5] both of which are limited by cost and logistical issues.[2,6] Studies conducted in Uganda and Kenya reported that < 20% of paediatric wards in district hospitals have access to functional $O_2$ delivery systems,[2] with facilities experiencing power outages 7% of the time.[7]

Improved $O_2$ delivery systems can lead to significant improvements in mortality from childhood pneumonia.[8] We have previously detailed the design and implementation of a novel method of $O_2$ delivery capable of implementation in remote locations with limited access to consistent electrical supplies: solar powered oxygen (SPO2).[9,10] Solar powered $O_2$ involves photovoltaic cells to collect solar energy, which is then stored in a battery bank and used to power an $O_2$ concentrator for the production of medical grade $O_2$. The feasibility, safety, and efficacy of SPO2 has been demonstrated through a proof-of-concept study and a randomized controlled trial, showing non-inferiority compared to cylinder $O_2$ in terms of hospital length of stay, duration of $O_2$ therapy, and recovery time.[9,10] An evaluation of the impact of SPO2 on mortality is warranted.

The objective of this study was to compare the mortality among infants and children admitted with acute hypoxaemic respiratory illness at two resource-constrained hospitals in the Democratic Republic of the Congo (DRC) before and after installation of SPO2. We hypothesized that the introduction of a reliable source of $O_2$ would be associated with a reduction in mortality, relative to the existing practice, in which the $O_2$ supply was scarce and inconsistent.

## Methods

### Study design

This was a pragmatic, quasi-experimental study comparing the mortality amongst children under 5 years of age admitted with acute hypoxaemic respiratory illness before (pre-SPO2) and after (post-SPO2) the installation of SPO2 in two resource-constrained hospitals. Before-after designs have been used in several recent trials evaluating $O_2$ systems in resource-constrained settings,[11] novel $O_2$ delivery methods,[12] other respiratory therapies,[13-15] and childhood infections.[16,17] Although subject to limitations such as temporal trends, before-after study designs are effective research tools that, in some cases, have changed practice.[18] To mitigate potential biases inherent in this study design, we used prospective data collection with consistent reporting criteria and multivariable statistical methods to correct for potential confounding factors.

### Setting

The DRC ranks 179th out of 188 countries in terms of the human development index and 88% of the population lives on less than US $1.25 per day.[19] The mortality under five years of age is 300,000/year, with 45,000 deaths/year due to pneumonia.[20] The delivery of health services is complicated by ongoing armed conflicts and security concerns, which contribute to the elevated mortality rates in these regions.[21] The DRC has also experienced outbreaks of Ebola virus, with the most recent outbreak in North Kivu beginning in August 2018, during this study's implementation. Availability of $O_2$ remains poor across rural parts of the DRC.[22]

The study enrolled hypoxaemic children admitted to two hospitals in Butembo, DRC. Matanda Hospital is a 260-bed facility, with a 6-bed intensive care unit. The solar powered $O_2$ concentrator was installed in the intensive care unit during the present study. The Centre Hospitalier Universitaire du Graben is a 178-bed facility, with dedicated pediatric and neonatal wards. The solar powered $O_2$ concentrator was installed in the neonatal ward during the present study. Of note, the solar powered $O_2$ concentrators were not present during the pre-SPO2 period at either site. The two hospitals have a high ratio of patients to healthcare providers (approximately one nurse for every 20 patients). Each site was staffed by one general practitioner and one pediatrician. Fingertip pulse oximeters (ChoiceMMmed brand, 2018Beijing Choice Electronic Tech Co., Beijing, China) were used for spot checks of $O_2$ saturation. Use of pulse oximetry was individualized and guided by the individual clinicians, according to clinical judgement.

### Participants

Patients presenting to selected sites meeting the following criteria were included: (1) age < 5 years; (2) hypoxaemia

($O_2$ saturation < 90%); (3) warranted hospital admission based on clinical judgement.

## Intervention and Study procedures

The solar powered $O_2$ system has been previously described.[10] In brief, the system consisted of locally sourced solar panels, charge controller, battery bank, DC/AC current inverter, and a 300 W $O_2$ concentrator (model 525 KS, DeVilbiss, Healthcare LLC, Somerset, PA, USA).[10] The system components were purchased from and installed by a Congolese non-profit association providing essential medicines and equipment throughout the DRC (Association Régionale D'Approvisionnement en Médicaments Essentiels, ASRAMES, Goma, DRC).

Eligible participants' parents or legal guardians were approached for written informed consent to participate in the study. The study's purpose, benefits, risks, confidentiality, and alternatives were explained to parents or legal guardians in the appropriate language. Patients received standard care for their underlying illness. Fifty patients were recruited in both in the pre- and post- implementation periods, a sample size similar to previous before-after designs in the field.[12]

Demographic information and clinical data were collected from the medical records. After discharge, follow-up was done by telephone to determine vital status 30 days after admission (primary outcome). The need for $O_2$ therapy was evaluated daily using standard operating procedures for weaning $O_2$. The final disposition of the patients was recorded (discharged with or without disability, transferred to another facility, absconded, death), and the length of stay was calculated amongst survivors.

## Outcome measures

Our primary endpoint was mortality at 30 days post-admission. Secondary outcomes were in-hospital mortality (time to death), length of hospital stay among survivors, duration of $O_2$ therapy (time to wean $O_2$), and $O_2$ delivery system failure(s).

## Statistical considerations

Descriptive statistics used number and percentage for binary variables and median with interquartile range for continuous variables. Comparative statistics used chi-squared or Fisher's exact test, as appropriate, for binary variables and Mann-Whitney U-test for continuous variables. Kaplan-Meier survival analysis was used to compare the time to death pre- and post-SPO2. We used stratified analysis to examine mortality across strata that could confound the association of SPO2 and mortality. There was no missing data pertaining to the primary outcome. We used logistic regression models to examine the effect of SPO2 on mortality while adjusting for clinical and statistical co-variates (R version 4.0.0, R Computing, Vienna, Austria). Model selection was guided by both biological and statistical considerations. Models were restricted to a maximum of five independent variables for parsimony and to avoid overfitting (limited sample size with 45 deaths).

## Ethics approval

The study was approved by the Comité d'Éthique du Nord Kivu (Centre Hospitalier Universitaire du Graben, Butembo, DRC, Protocol number 005/TEN/2017) and by the Research Ethics Board of the University of Alberta (Study ID Pro00061203).

# Results

Fifty patients were recruited between 1 September 2017 and 19 March 2018 (pre-SPO2). Solar-powered oxygen systems were installed in both hospitals from 5-8 October, 2018. Fifty patients were then recruited between 10 October 2018 and 1 August 2019 (post-SPO2). Table 1 shows the demographic and clinical features of the pre-SPO2 and post-SPO2 groups. Most differences between the pre-SPO2 and post-SPO2 groups were not statistically significant, with key data presented in Table 1. Table 2 shows the treatment and outcome for patients enrolled pre- and post-SPO2.

The 30-day mortality among hypoxaemic infants and children was 30/50 (60%) pre-SPO2 and 15/50 (30%) post- SPO2 ($p$ = 0.0049). This represents a relative risk reduction of 50% (95% CI 19 – 69%) and a number needed to treat of 3.3 (95% CI 2.1 – 8.8). The survival curves pre- and post-SPO2 differed significantly (hazard ratio 0.39 [95%CI 0.20-0.74], $p$ = 0.0043, Fig. 1).

There was a significant reduction in the number of patients experiencing interruptions to their $O_2$ therapy from 26/50 (52%) pre-SPO2 and 1/50 (2%) post-SPO2 ($p < 0.0001$). More specifically, there were fewer interruptions due to fuel shortages (12/50 [24%] to 0/50 [0%], $p$ = 0.00023) and decreased need to share $O_2$ therapy among multiple patients (14/50 [28%] to 1/50 [2%], $p$ = 0.00039). The duration of $O_2$ therapy and the total volume of $O_2$ administered increased significantly from pre-SPO2 to post-SPO2 (Table 2)

Because of the quasi-experimental design, several potential confounding factors were identified to be different in the pre-SPO2 and post-SPO2 periods including site, markers of disease severity (presence of cough, tachycardia, deep breathing), primary diagnosis (malaria *versus* pneumonia, sepsis and other conditions), and co-treatments (intravenous glucose, third-generation cephalosporin, ampicillin, metronidazole, and antipyretics) (Table 2). We performed a stratified analysis, examining the difference in mortality pre- and post- SPO2 in these subgroups (Fig. 2). We found a consistent reduction in mortality across multiple subgroups, suggesting that there was no confounding that would have affected the observed mortality difference pre- and post-SPO2.

We next constructed multivariable logistic regression models to adjust for potential effects of co-variates (Supplemental e-Table 1). Model 1 adjusted for disease severity (RISC, coded as a continuous variable) and diagnosis (categorical variable with four levels, pneumonia, sepsis, malaria, and other), and showed that the association between lower mortality post-SPO2 remained statistically significant (adjusted odds ratio 0.31 [95%CI 0.12-0.77], $p$ = 0.013). Model 2 adjusted for potential factors affecting mortality based on statistical considerations. Cough and malaria were both statistically significantly associated with reduced mortality and were more frequent post-SPO2. In

**Table 1** Characteristics at admission of 100 children under 5 years of age hospitalized with hypoxaemia.

| | Overall (*N* = 100) | Pre-SPO2 (*N* = 50) | Post-SPO2 (*N* = 50) | *p*-Value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age [months] median (IQR) | 2 (0-8.2) | 2.2 (0-10) | 2 (0-4.8) | 0.18 |
| <2 months | 42 (42) | 19 (38) | 23 (46) | 0.54 |
| 2-59 months | 58 (58) | 31 (62) | 27 (54) | |
| Female sex | 48 (48) | 22 (44) | 26 (52) | 0.55 |
| Site | | | | 0.0088 |
| CHU Graben | 44 (44) | 15 (30) | 29 (58) | |
| Matanda Hospital | 55 (55) | 35 (70) | 21 (42) | |
| **Clinical features** | | | | |
| Cough | 72 (72) | 26 (52) | 46 (92) | <0.0001 |
| Fever prior to admission | 68 (68) | 29 (58) | 39 (78) | 0.054 |
| Unable to feed or drink | 70 (70) | 36 (72) | 34 (68) | 0.83 |
| Vomiting everything | 10 (10) | 6 (12) | 4 (8) | 0.74 |
| Lethargic | 79 (79) | 40 (80) | 39 (78) | >0.99 |
| Convulsions | 28 (28) | 14 (28) | 14 (28) | >0.99 |
| **Physical findings** | | | | |
| Severely underweight[1] | 33 (33) | 19 (38) | 14 (28) | 0.39 |
| Mid-upper arm circumference [mm], median (IQR) | 110 (100-130) | 110 (100-130) | 120 (100-130) | 0.72 |
| $SpO_2$ [%], median (IQR) | 70 (60-78) | 70 (60-77) | 71 (60-80) | 0.45 |
| Temperature [°C], median (IQR) | 38 (36-38) | 38 (36-38) | 38 (36-38) | 0.63 |
| Tachycardia[2] | 24 (24) | 17 (34) | 7 (14) | 0.035 |
| Tachypnea[2] | 28 (28) | 12 (24) | 16 (32) | 0.50 |
| Chest indrawing | 80 (80) | 37 (74) | 43 (86) | 0.21 |
| Deep breathing | 69 (69) | 27 (54) | 42 (84) | 0.0025 |
| **Composite clinical severity score** | | | | |
| RISC, median (IQR)[3] | 6 (5-6) | 6 (5-6) | 6 (5-6) | 0.94 |
| **Laboratory** | | | | |
| Haemoglobin [g/L], median (IQR)[4] | 110 (90-130) | 110 (90-120) | 110 (90-130) | 0.38 |
| Glucose [mmol/L], median (IQR)[5] | 4.4 (3-7.2) | 6.7 (3.4-9.9) | 3.2 (3-4.5) | 0.037 |
| **Primary diagnosis** | | | | |
| Pneumonia | 33 (66) | 16 (32) | 17 (34) | >0.99 |
| Sepsis | 29 (29) | 18 (36) | 11 (22) | 0.19 |
| Malaria | 20 (20) | 5 (10) | 15 (30) | 0.023 |
| Neonatal respiratory distress syndrome | 9 (18) | 4 (8) | 5 (10) | >0.99 |
| Bronchiolitis | 3 (3) | 2 (4) | 1 (2) | >0.99 |
| Congenital heart disease | 3 (3) | 3 (6) | 0 (0) | 0.24 |
| Ebola virus disease | 1 (1) | 0 (0) | 1 (2) | >0.99 |
| Other[6] | 2 (2) | 2 (4) | 0 | >0.99 |

Values represent n (%) unless otherwise specified
[1] Less than 3 standard deviations below the mean weight for age[28]
[2] Less than 99th percentile of the vital sign for age
[3] Respiratory Index of Severity in Children[29]
[4] Hemoglobin was measured in 89 (89%) of children
[5] Glucose was measured in 40 (40%) of children
[6] Other primary diagnoses: malformation, meningitis

addition, although not statistically significant, treatment with cefotaxime/ceftriaxone and intravenous glucose were associated with reduced mortality and were more frequent post-SPO2. Model 2, adjusting for cough, malaria, cefotaxime/ceftriaxone, and intravenous glucose treatment, showed that the association between lower mortality post-SPO2 remained statistically significant (adjusted odds ratio 0.30 [95%CI 0.095-0.89], $p$ = 0.033). In summary, the post-SPO2 period was consistently and robustly associated with decreased mortality in statistical models adjusting for potential factors associated with mortality that were different pre- and post-SPO2 (Supplemental e-Table 2).

## Discussion

This study found that implementation of SPO2 systems was associated with a 50% decrease in 30-day mortality in children with hypoxaemic respiratory illness. Installation of SPO2 systems was associated with a reduced frequency of

**Table 2** Clinical management and outcomes of 100 children under 5 years of age hospitalized with hypoxaemia.

| | Overall (*N* = 100) | Pre-SPO2 (*N* = 50) | Post-SPO2 (*N* = 50) | *p*-Value |
|---|---|---|---|---|
| **Oxygen treatment** | | | | |
| Duration of $O_2$ therapy [hours], median (IQR)[1] | 16 (9.7-48) | 6.5 (4.0-24) | 20 (12-57) | 0.0049 |
| Total volume of $O_2$ delivered [× 1000 L], median (IQR)[1] | 39 (22-110) | 15 (9.0-68) | 50 (31-120) | 0.0049 |
| $SpO_2$ at last encounter [%], median (IQR) | 91 (52-95) | 81 (55-96) | 94 (42-95) | 0.56 |
| Interruptions to $O_2$ therapy | 27 (27) | 26 (52) | 1 (2) | <0.0001 |
| Fuel shortages | 12 (12) | 12 (24) | 0 (0) | 0.00023 |
| Multiple patients | 15 (15) | 14 (28) | 1 (2) | 0.00039 |
| **Antibiotic Use** | | | | |
| Ampicillin | 9 (9) | 8 (16) | 1 (2) | 0.031 |
| Gentamicin | 59 (59) | 29 (58) | 30 (60) | >0.99 |
| Cefotaxime or Ceftriaxone[2] | 93 (93) | 43 (86) | 50 (100) | 0.012 |
| Metronidazole | 10 (10) | 9 (18) | 1 (2) | 0.016 |
| Other[3] | 9 (9) | 7 (14) | 2 (4) | 0.16 |
| **Other Treatments** | | | | |
| Intravenous glucose | 73 (73) | 26 (52) | 47 (94) | <0.0001 |
| Antipyretics | 60 (60) | 24 (48) | 36 (72) | 0.025 |
| **Length of Stay, median (IQR)**[1] | 7 (5-9) | 6 (5-7) | 8 (5-10) | 0.054 |
| **Mortality** | | | | |
| At 48 hours after admission | 30 (30) | 18 (36) | 12 (24) | 0.28 |
| In hospital | 43 (43) | 30 (60) | 13 (26) | 0.0012 |
| At follow-up 30 days after admission | 45 (45) | 30 (60) | 15 (30) | 0.0049 |

[1] Among survivors (*N* = 55)
[2] As ceftriaxone or as combination ceftriaxone-tazobactam (brand name Tazex®)
[3] Other antibiotics included azithromycin (2), amoxicillin (1), amoxicillin-clavulanate (1), cefpodoxime (1), clindamycin (1), vancomycin (1), levofloxacin (1), and antituberculous medications (1)

interruptions to $O_2$ therapy due to fuel shortages or need to share systems among multiple patients, suggesting an improvement in the quality of care being delivered.

Oxygen availability remains a challenge in many resource-constrain settings around the world. In a survey conducted in Kenya, approximately 20% of rural healthcare facilities lacked $O_2$ equipment. Of those with equipment, a third of their patients faced interruptions lasting a median of 11 minutes, with less than 20% having access to backup $O_2$ cylinders.[7] In Uganda, only 18% of paediatric wards had access to functional $O_2$ delivery systems.[2] Similar shortages have been reported in other resource-constrained settings across Africa.[5,23] Similarly, in the current study, prior to SPO2 installation, 52% of patients experienced interruptions to their $O_2$ therapy, half of which were due to fuel shortages leading to concentrator failure. After installing SPO2, only a single patient (2%) experienced an interruption to their $O_2$ therapy, in their case due to multiple paediatric patients requiring the $O_2$ concentrator simultaneously. Among survivors, the duration of $O_2$ therapy and the total volume of $O_2$ delivered were statistically significantly greater after SPO2 installation (Table 2), reflecting fewer interruptions and greater $O_2$ availability. Overall, these findings suggest that the lack of available $O_2$ equipment together with frequent power interruptions contribute to the elevated mortality associated with hypoxaemic respiratory illnesses.

While hypoxaemia is known to be associated with an increased risk of mortality in patients with acute respiratory illnesses, the mortality rate seen in our study before the implementation of SPO2 (60%) was higher than many past reports.[24] This may reflect the remote, rural, and severely resource-constrained hospitals selected for this study (e.g., lack of reliable access to $O_2$ as well as ventilators). Danger signs (i.e., not able to drink, persistent vomiting, convulsions, lethargy, stridor at rest, or severe malnutrition)[25] were common in our cohort and were associated with subsequent mortality (Supplemental e-Table 1), consistent with previous studies. Of note, the frequency of danger signs and the RISC scores did not differ between the pre- and post-SPO2 periods, suggesting that the severity of presenting illness was comparable pre- and post-SPO2.

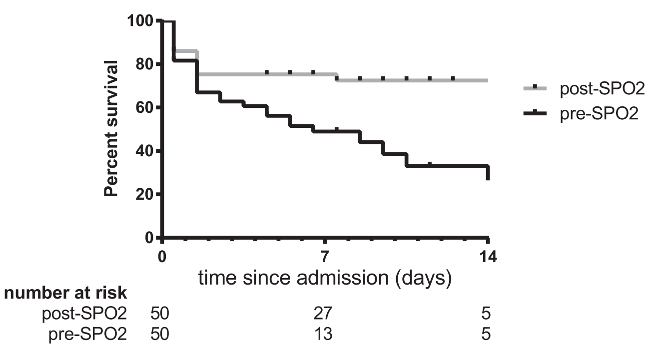


**Fig. 1** Survival analysis of 100 infants and children hospitalized with hypoxaemia. The survival curves were significantly different pre- and post-SPO2 implementation (hazard ratio 0.39 [95% CI 0.20-0.74], *p* = 0.0043).

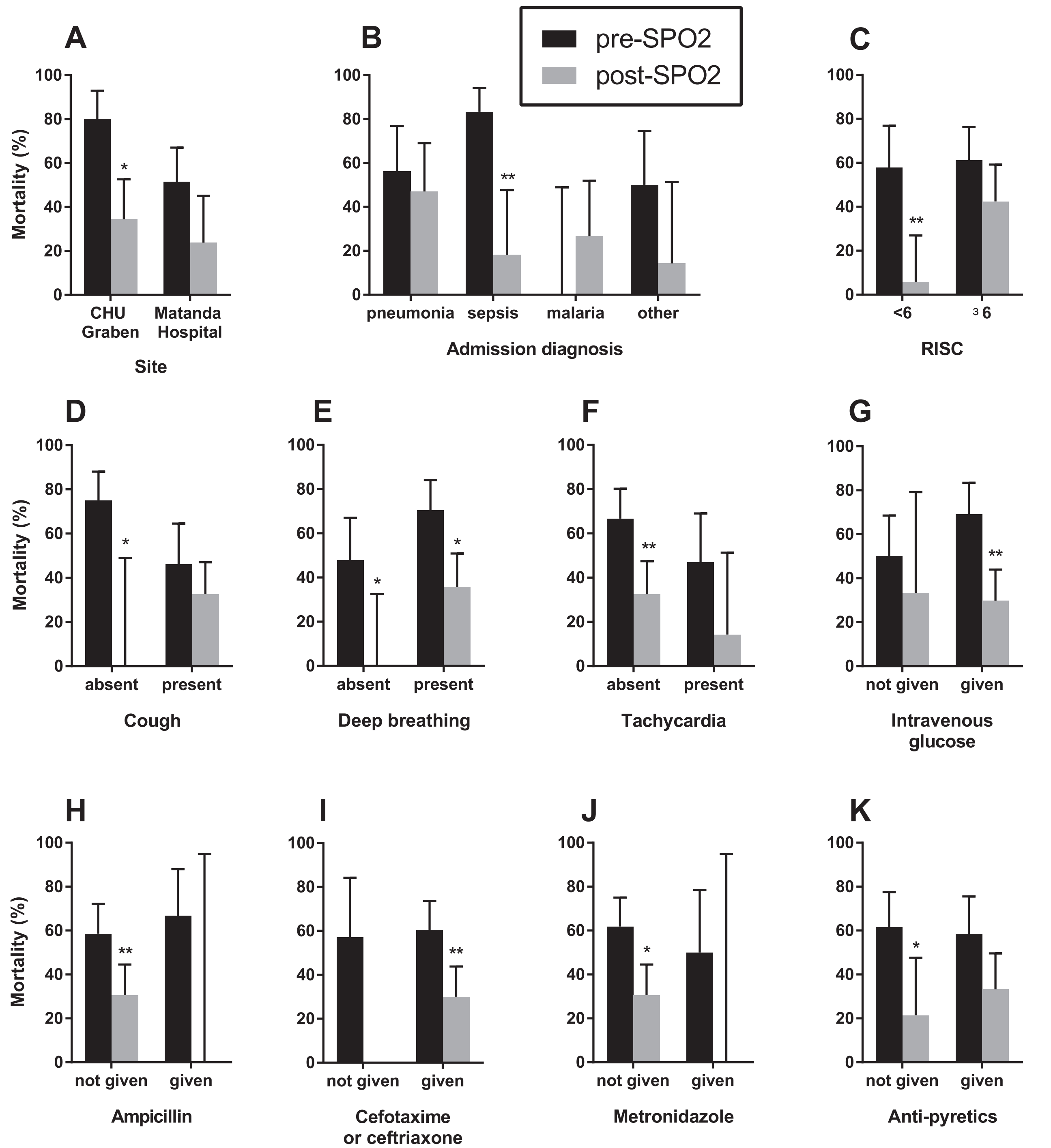


**Fig. 2** Stratified analysis of mortality differences amongst 100 infants and children hospitalized with hypoxaemia pre- and post-SP02 installation. Across all strata, there was a decrease in mortality in post-SPO2 compared to pre-SPO2. * - significantly different ($p < 0.05$); ** - significantly different ($p < 0.01$).

There were a number of differences, besides mortality, in patients enrolled in the post-SPO2 period, relative to the pre-SPO2 period: higher proportion of patients from the CHU Graben; higher frequency of cough and deep breathing; lower frequency of tachycardia; and higher proportion diagnosed with malaria (Table 1). Of these factors, only the presence of cough and a diagnosis of malaria were associated with decreased 30-day mortality (Supplemental e-Table 1). In a multivariable logistic regression model including these variables (Model 2, Supplemental e-Table 2), the association between SPO2 and decreased mortality remained statistically significant, suggesting that the higher proportion of children with cough and malaria post-SPO2 did not explain the observed mortality reduction.

This study builds on our group's previous work evaluating SPO2 in resource-constrained settings. Previously, we have demonstrated proof-of-concept,[10] non-inferiority relative to cylinder $O_2$,[9] and cost-effectiveness[26] of SPO2. The current study provides quasi-experimental evidence of mortality reduction associated with SPO2. Additional experimental evidence from cluster-randomized controlled trials will be needed to conclusively show that SPO2 reduces mortality. Currently, we are conducting a stepped-wedge cluster-randomized controlled trial of SPO2 at 20 sites across Uganda.[27]

The median length of hospital stay was 6 days (interquartile range [IQR] 5-7) pre-SPO2 and 8 days (IQR 5-10) post-SPO2, a difference that approached statistical significance ($p = 0.054$). The possible prolongation of duration of admission may be due to delay in discharge with improved recognition of clinically apparent hypoxaemia that resulted from increased use of pulse oximeters with our study. Of note, one previous randomized controlled trial demonstrated that SPO2 was not associated with prolonged length of stay, relative to cylinder $O_2$.[9]

Our study has several limitations. Quasi-experimental before-after designs are subject to the confounding effects of time and lack a distinct control group.[18] Indeed, imbalance in co-treatments (e.g., intravenous glucose) pre- and post-SPO2 were directly attributable to improvements in patient care that arose as a result of our study. Potential confounding variables were examined through stratified analyses (Fig. 2) and multivariable modelling (Supplemental e-Table 2). Nonetheless, further investigation is required to conclusively show mortality benefit of SPO2. The limited samples size (50 patients in each group) restricted the number of co-variates that could be included in multivariable models. This sample size is small relative to the burden of disease globally and relative to the patient volumes treated at the participating facilities. A larger study would be desirable to comprehensively adjust for co-variates. Moreover, replication of these findings in other resource-constrained settings would be needed to demonstrate the generalizability of these findings.

## Conclusions

SPO2 installation was associated with a marked reduction in mortality among children hospitalized with hypoxaemia in two resource-constrained hospitals. SPO2 is an innovative and simple approach to providing therapeutic $O_2$ to resource-constrained settings. Its ease-of-use, cost-effectiveness, and efficacy in decreasing childhood mortality make it an accessible and effective solution to the high burden of childhood pneumonia. $O_2$ requirements have spiked globally during the ongoing COVID-19 pandemic, and SPO2 can provide a useful countermeasure in resource-constrained settings.

## Conflict of interest

The authors have no conflicts of interest to declare.

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## Prior Abstract Publication/ Presentation

None.

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REVIEW

# The misunderstood link between SARS-CoV-2 and angiogenesis. A narrative review

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**KEYWORDS**
Cytokine storm;
Endothelialitis;
Microenvironment factors;
SARS-CoV-2 infection

**Abstract** Novel Coronavirus Disease 2019 (Covid-19) is associated with multi-systemic derangement, including circulatory dysfunction with features of endothelial dysfunction, microangiopathic thrombosis and angiocentric inflammation. Recently, intussusceptive angiogenesis has been implicated in the pathogenesis of the disease.

Herein, we conducted a narrative review according to the SANRA guidelines to review and discuss data regarding splitting angiogenesis including mechanisms, drivers, regulators and putative roles. Relevant angiogenic features in Covid-19, including their potential role in inflammation, endothelial dysfunction and permeability, as well as their use as prognostic markers and therapeutic roles are reviewed. Splitting angiogenesis in Covid-19 involve hypoxia, hypoxia-inducible factors, classic angiogenic mediators, such as the Vascular Endothelial Growth Factor (VEGF), Angiopoietins, hyperinflammation and cytokine storm, and dysregulation of the Renin-Angiotensin-Aldosterone System, which combined, interact to promote intussusception.

Data regarding the use of angiogenic mediators as prognostic tools is summarized and suggest that angiopoietins and VEGF are elevated in Covid-19 patients and predictors of adverse outcomes. Finally, we reviewed the scarce data regarding angiogenic mediators as therapeutic targets. These preliminary findings suggest a potential benefit of bevacizumab as an add-on therapy.


## Introduction

Covid-19 is a potentially life-threatening disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.[1] Since its first identification in December 2019, the disease evolved into an international public health emergency, and in March 2020, the World Health Organization declared it a pandemic.

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SARS-CoV-2 is associated with a plethora of clinical manifestations ranging from pauci-symptomatic to an invasive, severe infection with acute respiratory distress, systemic hyperinflammation and multi-organ failure.[1] SARS-CoV-2 engages the same receptor as SARS-CoV, the angiotensin-converting enzyme 2 (ACE2).[2] By expressing abundant ACE2, endothelial cells (EC) are a primordial target to SARS-CoV-2 infection. Accordingly, SARS-CoV-2-mediated endothelial damage is an important issue regarding the virus effects.[2-4]

## Methods

This narrative review was performed according to the SANRA (Scale for the quality Assessment of Narrative Review Articles) guideline.[5] A literature search was performed in PUBMED. The search strategy was focused on articles of four categories: (1) vasculopathic effects of SARS-CoV-2 infection (query used: [Endothelial OR Vasculopathic OR Endothelium] AND [COVID-19 OR SARS-CoV-2]), (2) Vascular effects of cytokine storm (query: [Cytokine OR Cytokine storm] AND [Endothelial OR Vasculopathic OR Endothelium OR Angiogenesis]), (3) Angiogenic features of Covid-19 (query used: [Angiogenesis OR Intussusceptive angiogenesis OR Splitting angiogenesis] AND [COVID-19 OR SARS-COV-2]) and (4) General features of intussusceptive angiogenesis (query used: [Intussusceptive angiogenesis OR Splitting angiogenesis]). The search included articles from a time span ranging 1986 (the year when IA was discovered) and February 2021. Furthermore, we performed an extensive search of the selected articles' bibliography to retrieve further papers of interest.

Table 1 summarizes the most significant articles evaluated with relevant data.

## Covid-19 as a vascular disease

Studies suggest that vascular disease plays a major role in Covid-19 course, influencing both susceptibility and outcomes of the infection. Classical cardiovascular risk factors such as hypertension, cardiovascular disease, diabetes, and obesity are the most prevalent comorbid conditions among Covid-19 patients.[2,3] These conditions are associated with worse outcomes and are independently associated with Covid-19 related deaths.[2,3] Furthermore, they also correlate with age, as ageing is associated with complex vascular changes that result in endothelial dysfunction. Age is the strongest predictor of Covid-19 mortality, implying that endothelial dysfunction might be responsible for part of the excess mortality in the elderly.[2,3]

SARS-CoV-2 infection results in the disruption of endothelial homeostasis with loss of Renin-angiotensin-aldosterone system (RAAS) balance, anti-thrombotic and immune functions.[6] The hyperinflammatory state potentiated by SARS-CoV-2 infection is deleterious to EC. High circulating cytokines levels (the cytokine storm context) act as endothelial activators shifting EC towards a pro-inflammatory, chemotactic phenotype with high permeability and pro-thrombotic features.[6,7] A maladaptive innate immune response is also responsible for endothelial damage as DAMPs and PAMPs-mediated TLR activation promotes oxidative stress.[8] Neutrophil extracellular traps are also associated with endothelial injury.[9]

These immune changes along with RAAS dysregulation are associated with hypercoagulability state.[10] SARS-CoV-2 infection leads to loss of ACE2 activity in ECs,[11] which reduces angiotensin II metabolism and inactivation and consequently lower levels of Angiotensin$_{1-7}$ (the byproduct of angiotensin II degradation). Higher levels of ATII associated with lower levels of $AT_{1-7}$ cause vasoconstriction, leucocyte and platelet adhesion, thus promoting thrombogenicity and suppressing fibrinolytic activity.[12] Furthermore, ATII regulates NADPH oxidase 2 and higher levels of ATII result in increased oxidative stress,[13] further amplifying vascular dysfunction.

This prothrombotic milieu has analytic repercussions. Patients with Covid-19 exhibit increased levels of fibrinogen, D-dimer and fibrin degradation products, von Willebrand factor/factor VIII and lower levels of Plasminogen Activator Inhibitor 1 (PAI-1).[10] Data suggests that these mediators

**Table 1** List of significant papers presenting the most relevant informations.

| Authors | Description | References |
|---|---|---|
| Nishiga M et al | This review summarizes the current understanding regarding the interaction between COVID-19 and the cardiovascular system and its related disorders. | 3 |
| Pons S et al | This article focused on the effects of SARS-CoV-2 infection in the endothelium, describing endothelialitis and endothelial dysfunction that arises in COVID-19. | 4 |
| Iba T et al | This article elucidates the phenomena of COVID-19 associated coagulopathy (CAC), its pathophysiology, prognostic and therapeutic implications. | 10 |
| Patel BV et al | This paper demonstrated the presence of a hypercoagulable phenotype in severe COVID- as well as impaired pulmonary perfusion likely caused by pulmonary angiopathy and thrombosis. | 14 |
| Ackermann M et al | In this study Ackermann et al examined lungs from patients who died from Covid-19 and compared them with lungs obtained from patients who died from A(H1N1) infection as well as uninfected control lungs. This paper demonstrated for the first time Intussusceptive Angiogenesis as a feature of Covid-19 infection. | 16 |
| Rovas A et al | This paper demonstrated alterations of the microcirculation and the endothelial glycocalyx in patients with COVID-19, further implicating systemic vascular alterations in COVID-19 pathogenesis | 18 |
| Burri PH et al | This review elucidates the various aspects of intussusceptive angiogenesis including the processes of pilar morphogenesis, IBR, IMR, IAR. | 26 |
| Medford A et al | This review elucidates the role of VEGF in ALI/ARDS, as well as the putative pneumotrophic roles of VEGF. | 52 |
| Smadja D et al | This paper demonstrated the prognostic role of Angiopoetin-2, as a predictor of admission in ICU and death. This reinforces that endothelial activation is likely a major contributor in COVID-19 pathology. | 58 |
| Pang J et al | This study evaluated the efficacy of Bevacizumab, an anti-angiogenic drug, as add-on therapy for COVID-19. Although the results are promising, further studies are needed to evaluate the role of IA in Bevacizumab's efficacy. | 78 |

correlate with disease severity and thrombotic risk.[10,12] This hypercoagulability state is an important part of the pathophysiological basis of cardiovascular complications in Covid-19 patients, such as myocardial injury and dysfunction, deep venous thrombosis, pulmonary thromboembolism and some obstetric complications in pregnant women with SARS-CoV-2 infection such as pre-eclampsia and HELLP syndrome.[6]

Altogether, these findings provide strong evidence that SARS-CoV-2 infection results in the development of vascular disease.

## Pulmonary vascular bed alterations in Covid-19

An important feature of COVID-19 associated coagulopathy is microcirculatory endothelial damage in pulmonary vascular beds. Although less well characterized, peripheral pulmonary vascular repercussions are an important pathogenic factor that may result in increasing perfusion-ventilation mismatch, ultimately leading to worsening hypoxemia.[14]

Covid-19 associated coagulopathy is associated with two main forms of thrombotic repercussions in the pulmonary vascular bed. As Covid-19 is associated with a pro-thrombotic phenotype, the risk of deep vein thrombosis or pulmonary thromboembolism is significantly higher and is a potential cause of acute exacerbation in patients.[10] However, the most common form of thrombosis is microangiopathic thrombosis in the pulmonary microcirculation. Studies report microthrombosis features in pulmonary capillaries.[15,16] In fact, microthrombi in the pulmonary vascular beds are 9 times more common in SARS-CoV-2 infection than in Influenza infection[16] and are associated with worsening hypoxia, shunting and increasing pulmonary vascular resistance. Changes in pulmonary microvascular resistance, more specifically in venules, is responsible for the discrepancy between the relatively preserved ventilatory mechanics and the severity of hypoxemia in Covid-19 patients, which differs from Acute Respiratory Distress Syndrome (ARDS) caused by other agents.[17] Microangiopathic thrombosis is also responsible for up to 90% reduction in capillary density in lungs of patients with Covid-19.[18]

This microangiopathic phenomenon has been demonstrated by histopathological and ultrastructural studies. Typically, pathological evidence shows thrombi in pulmonary arterioles associated with diffuse alveolar damage and hyaline membrane formation.[15] The latter are a direct repercussion of increased permeability in the microcirculation and disruption of intercellular junctions of the pulmonary endothelium. Hyaline membranes impair alveolar-capillary barriers and jeopardize gas exchange, contributing to hypoxemia and V/Q mismatch.

Besides the thrombotic manifestations in pulmonary vascular plexus, Covid-19 is associated with features of small vessel vasculitis.[16] This is not exclusive to the lung, and Kawasaki-like cases of coronary vasculitis have been described.[19] Nevertheless, in the pulmonary vascular beds, SARS-CoV-2 infection promotes angiocentric inflammation. Patients with SARS-CoV-2 infection, especially those with ARDS, exhibit features of vascular acute inflammatory infiltrates with perivascular T-lymphocytes infiltration.[16] These inflammatory infiltrates contribute to endothelial barrier disruption that leads to hyaline membrane formation and aggravate respiratory failure. Interestingly, Covid-19 patients display a feature similar to solid organ rejection characterized by a pattern of a T-lymphocyte crown surrounding a highly activated EC. This interaction between immune environment and endothelium has been termed endothelialitis.[16,20] These features are highly common in Covid-19 patients and impair the pulmonary vascular bed.

## Angiogenesis and Covid-19

Ackermann *et al* analyzed 7 lungs from people who died from Covid-19 and compared them to lungs from patients who died from Influenza and healthy controls.[16] They found significant distortion of the lung angioarchitecture with prominent variations in small vessels caliber. Surprisingly, capillaries in Covid-19 subjects lungs exhibit cylindrical microstructures in the capillary lumina, implicating, for the first time, intussusceptive angiogenesis (IA) in the pathogenesis of Covid-19. IA offers the advantage of being faster and more efficient than sprouting angiogenesis (SA) in expanding a vascular plexus,[21] promoting arborization through intussusceptive arborization (IAR), optimizing the microangioarchitecture by pruning ineffective or occluded branches (IBR). However, the findings of Ackermann *et al* must be taken with caution. As Hariri *et al* point out, sample size is too small to make any extrapolation, as ARDS and Covid-19 are too heterogenous entities.[22] But an interesting hypothesis is that these vasculocentric features represent a particular ARDS endotype. Angiogenesis has been implicated in ARDS pathology in subgroups of patients, in the pre-Covid era.[23] Nevertheless, this is the first time that IA has been described in the context of ARDS.

The populations compared in the study had major differences, as pointed out by Ackermann and his colleagues.[16] In the Covid-19 group, no single patient had been mechanically ventilated, whereas in the Influenza group, a significant proportion of the subjects had been intubated without protective lung measures. It is possible that mechanical ventilation has repercussions in microcirculatory dysfunction and angiogenesis.

The authors also suggest the possibility that differences noted between the two groups were attributable to the differences in the stages, as the Influenza subjects had more advanced and extensive diffuse alveolar damage. Contradicting this hypothesis, Ackermann and his colleagues report increasing levels of IA with increasing time of hospitalization and in Influenza it remained significantly lower and relatively constant.

We believe that IA has been overlooked in pathology reports of patients with ARDS and Covid-19. IP cannot be detected by light microscopy requiring corrosion casting or scanning electron microscopy to be identified, which are rarely used techniques. Furthermore, IA remains largely unknown and poorly studied. IP could be misidentified as artifacts or simply overlooked. Therefore, researchers should be aware of this phenomenon when conducting pathology studies in Covid-19 populations.

## Overview of IA mechanisms and role

IA was first noticed in 1986 by Caduff *et al* while studying angiogenesis in the postnatal rat lung.[24] These authors noticed small holes in sheet-like regions of the microvasculature which enlarge to constitute a microvascular network.[25] IA is a dynamic process of microvascular growth and development through the formation of IPs that span and divide capillaries lumen forming neovascular networks. Transluminal pillar morphogenesis is the hallmark of IA.[26] Pillar development starts with the protusion of diametrically opposed capillary walls into the lumen until direct contact between EC in both sides is established. The result of this protrusion is the formation of a transluminal interendothelial cellular bridge. Further reorganization of the interendothelial junction results in a perforated core within the endothelial bilayer which is occupied in a centripetal fashion by cytoplasmatic processes of fibroblasts and pericytes. Pericytes and fibroblasts then secrete collagen fibrils further dividing the initial single lumen into two.[27] Alternative morphogenic mechanisms of pillar formation has been described[27] and include pillar formation by kissing or peg-like contacts, meso-like intravascular folds, merging of adjacent capillaries or splitting of intercapillary meshes.

Mechanistically, IA can be divided into three different processes: intussusceptive microvascular growth (IMG), IAR and intussusceptive branching remodeling (IBR), which occur in tandem during embryogenesis. In post-natal organs however, they overlap in time and constitute a single process.[26,27]

IA starts with IMG, which initiates pillar morphogenesis and expansion, allowing a quick capillary plexus development. This constitutes a primordial vascular bed characterized by an increased surface area. IMG is a ubiquitous mechanism[28,29] allowing rapid expansion of capillary plexus without jeopardizing vascular and hemodynamic efficiency.[28] This quick vascular expansion is particularly useful in tissues with high metabolic demands, ischemia or hypoxia allowing nutrients and oxygen to be readily delivered and metabolites to be swiftly removed.[30] IAR then allows the establishment of the proper angioarchitecture by remodeling the capillary bed in an organized, branched.[28,29] Ultimately, IBR increases the efficiency of nutrient and gas exchange by remodeling branches in poorly oxygenated areas and pruning branches that are superfluous or inefficient.[28,29]

Evidence of IA was found during the formation and remodeling of vascular beds in many organs including: the mammary gland, the bone, the glomeruli, the skeletal muscle, the ovaries, and others.[31-37] This ubiquity of the process of IA in the human body was not exclusive of physiological mechanisms and soon, evidence of IA in pathological scenarios arose, including both non-neoplastic and neoplastic diseases.[38-44] This data proves that IA is a relevant form of angiogenesis, playing a pivotal role in a wide variety of settings. However, its stimuli, molecular mechanisms, whether it occurs in synergy with other vascularization processes, and whether it plays an advantageous role in pathological conditions remain poorly understood.

## Possible hypothesis on the occurrence of IA in Covid-19 patients

Evidence suggests that IA occurrence in Covid-19 results from the dynamic interaction between different factors:

1. Hypoxia, VEGF and angiopoietins:

In ARDS, inflammatory markers (e.g. IL-1) and neutrophilic mediators (e.g. ROS, elastasis, LPS) cause extensive damage to the alveoli capillary plexus and endothelium. Such damage leads to transudation of fluid to the interstitium and air spaces during exudative phase and, later, exudation of neutrophils and protein-rich fluid, culminating in the formation of hyaline membranes that impair gas exchange and ultimately cause hypoxemic respiratory failure with regional alveolar hypoxia.[45]

Hypoxia is a known angiogenesis promoter.[46] Local hypoxia associated with ongoing inflammatory processes results in HIF-1$\alpha$ stabilization. HIF-1$\alpha$ regulates the expression of a wide range of genes involved in vasodilation, extracellular matrix remodeling, angiogenic pathways such as the VEGF and Angiopoietin/Tie2.[47]

Viral infections (e.g HCV, EBV, HPV) *per se* induce HIF-1$\alpha$ activation.[48] This phenomenon seems to be dual as HIF-1$\alpha$ also contributes to the pathogenesis of the infection itself. Interestingly, HIF-1$\alpha$ overexpression reduces ACE2 membrane expression.[49] However, this effect is damped if AT II is inhibited, suggesting a close relationship between HIF1$\alpha$ and AT II.[48] This might explain why populations living under chronic hypoxic conditions (e.g. Himalaya and the Andes) display less severe disease features.[50] Thus, it is likely that HIF-1$\alpha$ is induced in Covid-19 associated ARDS. Nevertheless, its role in IA is unknown.

VEGF and its receptors are widely expressed in the lung (mainly in the alveolar epithelium) even in a non-pathological state, suggesting a potential physiological role of VEGF in the lung.[50] In fact, VEGF acts as a stimulant and mitogen of the alveolar epithelium[52] and primary human type 2 alveolar epithelial cells express VEGFR2[52] which implies a possible autocrine role of VEGF in the air space beside its paracrine actions in vascular bed.[52] VEGF also plays an important role in pulmonary organogenesis as VEGF antagonism during the embryonic period arrests alveolarization besides leading to impaired lung vasculogenesis.[52] Conversely, transgenic HIF-2$\alpha^{-/-}$ mice (leading to VEGF downregulation) have diminished surfactant production and die from neonatal respiratory distress syndrome (RDS). Interestingly, *in utero* administration of $VEGF_{165}$ to these mice is protective against RDS.[52] Post-natal, VEGF-R2 blockage results in emphysema and alveolar apoptosis without inflammatory features,[52] implying that VEGF pneumotrophic role is not only important during embryogenesis but also in the post-natal life.

VEGF has been implicated in the pathogenesis of ARDS before the pandemic. In fact, VEGF seems to be a key regulator of the interstitial edema that happens in ARDS. This edema occurs despite normal pulmonary capillary wedge pressure and normal oncotic pressure, which implicates endothelial permeability as the main culprit. VEGF is one of the prominent mediators of vascular permeability. VEGF/VEGFR2 interaction results in an intracellular cascade that among other factors, results in the downstream activation of nitric oxide synthase (NOS) and Rho-Rac pathway with subsequent involvement of junctional signaling proteins leading to increased vascular permeability.[53] Gene therapy delivering $VEGF_{165}$ resulted in non-cardiogenic lung edema and an increased capillary permeability, a phenotype very similar to that of ARDS.[52] Pro-inflammatory stimuli such as LPS and neutrophil-derived enzymes stimulate VEGF secretion by alveolar cells and acute lung injury (ALI)/ARDS models demonstrated increased VEGF levels in the lung, early after insult, simultaneously to increased protein levels and neutrophils in bronchoalveolar lavage.[54] This suggests a pivotal role of VEGF in exudate and hyaline membranes formation phases of ARDS. Yet, typically, there is a concentration gradient through the alveolar-capillary membrane with VEGF concentration in the air space being 500 times higher than in the capillary. In ARDS, however, there is a shift of this ratio and even though plasma VEGF levels increase, there is a marked reduction of the levels in the air space.[51] It is possible that this reduction of VEGF results in a loss of its pneumotrophic protection and aggravation of alveolar damage.

Besides its role in vascular permeability, VEGF signaling probably plays an important role in Covid-19-associated IA. VEGF family members and their pathways are the best studied angiogenic stimulating factors promoting mitogenesis, differentiation and migration of ECs. VEGF plays a critical role in both SA and IA[29] and its actions are therapeutically modulated in settings where angiogenesis is contributing to the pathogenesis of the underlying condition (e.g. retina neovascularization and tumor neoangiogenesis).[55] Its role in IA was demonstrated in models of the chorioallantoic membrane (CAM)[26] as well as in human skeletal muscle.[56,57] VEGF signaling in SA and IA depend on a multitude of factors such as experimental model, dose, location, process.[56] While high levels of VEGF promote sprouting, lower levels of VEGF may be crucial in promoting intussusception. Such dose-dependent effect explains the transient increase in intussusception in tumor neovascular beds after treatment with anti-VEGF therapies. However, in skeletal muscle, high levels of VEGF are associated with IA mainly because there is a disruption of the concentration gradient, therefore promoting a switch from SA to IA.[56,57] Reduced levels of VEGF are also associated with vascular pruning and may play a role in IBR.[28] In Covid-19 patients, high VEGF plasma levels have been reported from early stages.[57] This is consistent to previous findings in ARDS patients. It is, therefore, likely that disruption of the alveolar-plasma VEGF gradient in Covid-19 patients aggravates diffuse alveolar damage already in the early stages of disease. Although VEGF concentration gradient disruption may promote shifting from SA to IA, as IA seems to be a late feature, associated with prolonged hospitalization, it is unlikely that VEGF *per se* can cause angiogenesis by splitting. Other factors may as well contribute to IA in Covid-19 patients.

VEGF overexpression associated with Angiopoietins-1/2 overexpression results in a higher number of small holes in primordial capillary plexuses, a sign of increased IA.[29] Angiopoietins are important signaling molecules for EC-pericyte crosstalk. Ang-2 secretion by EC is stimulated by hypoxia (the hallmark of ARDS), TNF-$\alpha$ (typically elevated in Covid-19), turbulent flow and thrombin. Therefore, Ang2 is a marker of endothelial activation and associates with endothelial dysfunction.[58] In Covid-19 patients, Ang2 levels rise along with VEGF levels, probably reflecting extensive endothelial dysfunction and activation.[58] High levels of VEGF and of Ang-2 in the latter stages of Covid-19 could be the molecular drive to promote IA. While VEGF may act as a promoter of IA, Angiopoietins may play a crucial role in the subsequent phases.[29] Ang-2 acts as an Ang-1 antagonist and promotes vascular regression, disrupts vessel integrity and promotes EC death. Ang-2 also acts with PDGF to promote pericyte division, migration and recruitment, which is important in pillar morphogenesis.[29] This is corroborated by the fact that Tie2-knockout mice have impaired pillar morphogenesis.[29] Angiopoietin expression is modulated by shear stress. Accordingly, laminar shear stress down-regulates Ang-2 expression while turbulent shear stress promotes the opposite.[29]

2. Microangiopathic thrombosis, hemodynamic and platelet derived factors:

Covid-19 is associated with extensive microangiopathic thrombosis. Obstruction of pulmonary microcirculation results in significant changes in hemodynamic conditions. The MYSTIC study[18] reported significant reductions of $V_{RBC}$ associated to capillary density loss in Covid-19 patients. This loss is almost exclusive to small capillaries between 4−6 $\mu$m diameter and results in a lower area of gas exchange, contributing to worsening hypoxia. D-dimers correlate strongly with vascular density, indicating a causality between microthrombi and vascular regression. This could be explained by a mechanism of intussusceptive branching remodeling and pruning. Microthrombi result in vasooclusion and acute reductions in blood flow, shear stress together with high transmural pressures caused by the thrombi promote IBR, which optimize the disrupted angioarchitecture, reconducting blood flow to spared areas.

Local changes in hemodynamic forces remarkably impact in IA mechanisms. It has been demonstrated that IMG and IAR occur predominantly in regions with high blood flow.[59-60] Blood flow redistribution to patent branches results in areas of high blood flow with high distending forces promoting IP morphogenesis and high shear stress promoting arborization of the newly formed branches by IAR.

Apart from hemodynamic factors, platelet derived factors may also play a role in IA. PDGF-BB markedly accelerates the splitting process.[56] PDGF-BB modulates VEGFR-2, promotes pericyte survival and controls vascular circular expansion.[57] This mechanism protects against aberrant angiogenesis promoted by exacerbated VEGF.[55,56]

3. Inflammation, endothelialitis and cytokine storm:

The immune system also plays an important role in IA. Mononuclear cells stabilize IP by protruding uropod-like projections and producing collagen.[61] The role of mononuclear cells such as lymphocytes or monocytes was first described in a Notch knockout model.[61] Notch inhibition has been associated with mononuclear cell recruitment and migration as well as with increased pillar morphogenesis. While the precise mechanism is unclear, this process is known to depend on chemokines such as CXCL12 or SDF-1.[61,62] SDF-1 is responsible for the Notch-dependent mobilization of mononuclear cells acting in MMP-9.[63] Furthermore SDF-1 also acts in CXCR4 receptor in mononuclear cells to promote the formation of the uropod-like that stabilize the IP's.[63]

VEGF and bFGF promote IA by acting on the SDF-1/CXCR4 pathway.[62] In fact, a study using a mouse model of diabetic retinopathy reported increased retinal neovascularization after vitreal injection of SDF-1.[64] Hypoxia, a known angiogenic trigger, promotes SDF-1 up-regulation and SDF-1/CXCR4 pathway seems to play an important role in re-establishing blood flow to ischemic zones through IA.[61-63]

SDF-1/CXCR4 are associated with T-lymphocyte infiltrates in Covid-19.[65] It is therefore likely that a positive feedback between shear stress alterations induced by inflammation (particularly T-cell), SDF-1, hypoxia and eNOS promote angiogenesis. This represents a vascular adaptation to maintain high blood flow prominent inflammatory areas. A dynamic interaction between T-cell infiltrates and EC, a phenomenon of endotheliatis has been described in Covid-19. This further contributes to prolonged local inflammation, enhancing thus angiogenesis. In endothelialitis, T-cell infiltrates activate ECs, which overexpress TLRs and MyD88. These molecules recognize SARS-CoV-2 and promote cytokine, chemokine and adhesion molecule expression as well as angiogenic factors namely VEGF, NOS, and CD14 monocytes recruitment.[65]

One of the most prominent features of COVID-19 is an inappropriate and excessive inflammatory response with concomitant release of large amounts of pro-inflammatory (e.g. IL-6 and TNF-$\alpha$), a process termed "cytokine storm" (CS).[66] CS relates to the severity of Covid-19 and is directly correlated with lung injury, multi-organ dysfunction and adverse outcomes in Covid-19 patients.[66-67]

IL-6 is the most frequently reported cytokine elevated in Covid-19 and its levels are independently associated with higher mortality.[67] IL-6 has been implicated in pathogenic angiogenesis in different scenarios (rheumatoid arthritis, stroke and cancers). Studies in tumors have shown that IL-6 levels are directly correlated with VEGF levels and vessel density.[68] The published literature suggests that IL-6 can drive aberrant angiogenesis.[69] IL-6 promotes the formation of defective vascular beds with abnormal pericyte coverage. Loss of pericytes has been described in Covid-19,[70] however it was postulated that this was a direct effect of viral infection as pericytes express ACE2. We suggest that IL-6 might be a contributor to this shift. Loss of pericytes has been previously implicated as an angiogenic driver, promoting both SA and IA.[71] Thus, the aberrant effects of IL-6 on pericytes could be related to IA in Covid-19.[68] Furthermore, studies showed that IL-6-trans-signaling inhibits proliferation and tube formation of ECs that could also explain the shift from SA towards IA in Covid-19.[71]

Taking into account the complex etiopathogenesis of Covid-19, we anticipate that the development of IA is attributed to the intricate involvement of hypoxia, proangiogenic and platelet-derived molecules, microangiopathic thrombosis, hemodynamic forces and inflammatory factors in these patients.

## Prognostic and therapeutic implications of IA in Covid-19

Ackermann et al reported increasing density of angiogenic features with increasing duration of hospitalization, suggesting IA as a potential prognostic tool in Covid-19 patients. Angiogenic mediators have an established prognostic role in ARDS. Positive correlations between VEGF, soluble VEGFR2 (sVEGFR2), Ang2 and Ang2/Ang1 ratio and ARDS development in critical illness have been described.[54] Moreover, Ang2 and sVEGFR2 are also associated with adverse outcomes and higher risk of mortality in ARDS patients.[54,72]

Ang2 is a marker of endothelial activation.[58] Ang2 levels have been consistently reported elevated in critical Covid-19 patients. High levels of Ang2 are also associated with poor lung compliance, higher CRP and D-dimers,[58,73,74] thus reflecting CAC in Covid-19 patients. Ang2 is associated with worse outcomes in Covid-19, predicting ICU admission, mechanical ventilation, and death.[58,74] Therefore, Ang2 is a strong prognostic biomarker in critical Covid-19 patients. However, whether that reflects only endotheliopathy and EC activation or also IA is unknown. It is possible that EC activation triggers Ang2 secretion which in turn promotes angiogenesis, therefore linking endothelial dysfunction and IA. It is also unknown if Ang2 levels correlate with IA in critical Covid-19 patients, although that hypothesis seems likely.

Moreover, data also suggests that VEGF-A and Flt-1 levels are elevated in both non- and critical patients.[75] VEGF-D levels are lower in patients in mechanical ventilation than those who are not submitted to this procedure.[76] However, plasma VEGF levels must be analyzed with caution as plasma VEGF changes may not reflect local VEGF changes and VEGF may be sequestered by tissues as most VEGF isoforms are heparin binding.

Other endothelial dysfunction markers have been described in critical ICU patients such as follistatin, PAI-1, E-selectin and vWF.[73-75] These markers are also higher in patients that died than survivors, suggesting a potential prognostic role.

Biomarkers of angiogenesis are also associated with other factors such as vascular permeability and endothelial dysfunction. Further studies should focus on confirming whether IA is an independent prognostic factor in Covid-19. Direct quantification of angiogenic features would be a better way of establishing this process, than using indirect biomarkers such as Ang or VEGF because the latter are susceptible to many factors implicated in Covid-19's pathogenesis.

Therapeutic modulation of IA is a potential adjuvant therapy in Covid-19. Among the therapeutic strategies implemented in COVID-19, a few are known to inhibit angiogenesis. Glucocorticoids alone or in combination with other pharmacological agents have been largely used to treat SARS-CoV-2. Corticosteroids are well known to exert anti-angiogenic effects in many disorders including cancer and vasoproliferative ocular disorders.[77] Currently, the anti-angiogenic drug, bevacizumab is being studied in Covid-19 (NCT04344782, NCT04305106 and NCT04275414). Bevacizumab is a monoclonal antibody that targets VEGF-A and inhibits its actions, used in oncotherapy of different neoplasms with efficacy and safety.[78] A recent single-arm trial (NCT04275414) suggested beneficial results of using Bevacizumab as an add-on therapy.[79] They report improvements in oxygenation (reflected by $PaO_2/FiO_2$ ratio, oxygen support), radiologic improvement, fever and lymphocyte count. Although anti-angiogenic, IA degree was not taken into consideration in this study. The authors suggest that the

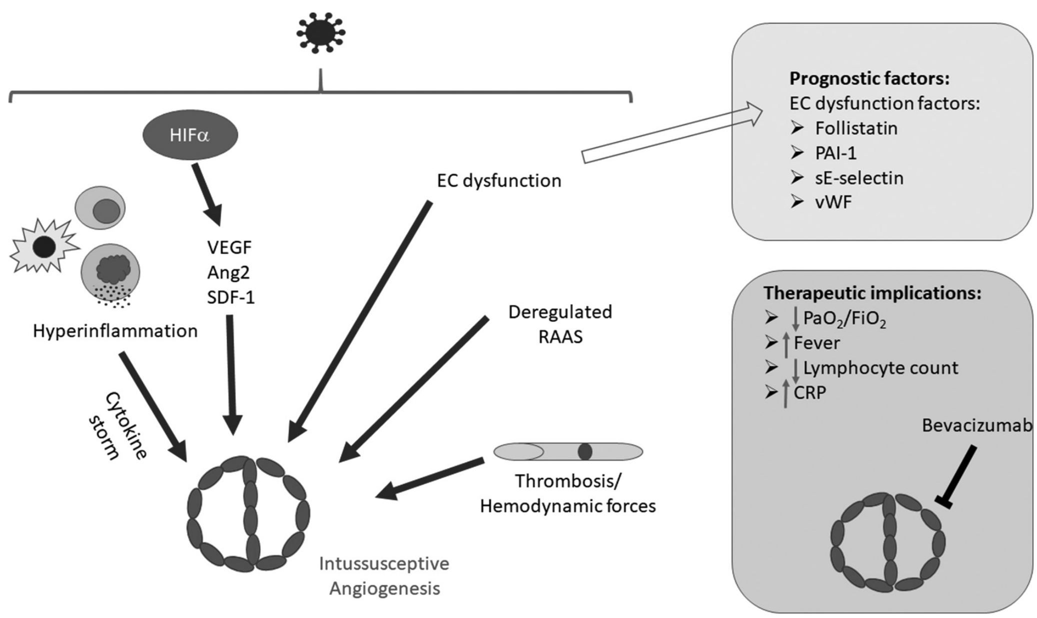


**Figure 1** Schematic diagram of the stimuli interactions that drive intussusceptive angiogenesis occurrence in COVID-19. In a synergic way, hypoxia-induced angiogenic factors, including VEGF, SDF-2 and Ang-2, hyperinflammation and cytokine storm, thrombosis and associated hemodynamic changes and RAAS dysregulation will trigger intussusceptive growth in COVID-19 patients. Factors implicated in endothelial dysfunctions may be used as prognostic factors. Splitting angiogenesis may therefore be a therapeutic target in COVID-19. EC, Endothelial cell; HIF1$\alpha$, Hypoxic-inducible factor 1$\alpha$; VEGF. Vascular endothelial growth factor; Ang2, Angiopoietin-2, SDF-1, Stromal-derived factor-1, RAAS, Renin-angiotensin-aldosterone system; PAI-1, Plasminogen activating inhibitor-1; E-selectin, Endothelial-leukocyte adhesion molecule; vWF, von Willebrand factor; CRP, C reactive protein.

beneficial effects of bevacizumab in oxygenation are related to modulation of vascular leakage and diminishing pulmonary edema (a rationale similar to the effect of bevacizumab in capillary-leakiness in age-related macular degeneration). Interestingly, they report positive outcomes of fever resolution and lymphocyte count. VEGF has a speculative role in immunopathology, promoting inflammatory cell mobilization to pathological tissues. Therefore, bevacizumab's antipyretic effect could be related to antagonism of inflammation caused by SARS-CoV-2 infection, as bevacizumab also resulted in lower CRP levels in Covid-19 patients. Another striking finding is that bevacizumab improves lymphopenia, associated with worse outcomes in Covid-19. Although the exact mechanism is unknown, it is hypothesized that bevacizumab might affect lymphocyte extravasation and redistribution. Further randomized control trials are needed to establish the use of bevacizumab in Covid-19 and to assert its effects on intussusception. Nonetheless, these findings are promising, and pave the way for the use of anti-angiogenic therapeutic agents against Covid-19.

## Conclusion

The pathogenesis of SARS-CoV-2 infection is complex and different pathogenic factors contribute to the severity of the infection. Among those, vascular repercussions of the infection are a major threat, severely worsening prognosis and significantly increasing mortality. Notwithstanding the fact that a lot of effort was put into studying these vascular repercussions (including the endothelial dysfunction), intussusceptive angiogenesis, a prominent feature of Covid-19, remains poorly understood. There are significant gaps in knowledge regarding splitting angiogenesis including molecular control and regulation, microenvironmental factors and therapeutic and prognosis implications. The current paper reviewed the main characteristics and mechanisms of IA and formulated a theoretical model that explains the occurrence of splitting angiogenesis in Covid-19 (Fig. 1). We conclude that although there is much to learn regarding this subject, IA is likely to be the product of hypoxia, classical angiogenic molecular factors (e.g. VEGF, Ang-2), hyperinflammation and cytokine storm, thrombosis and associated hemodynamic changes and RAAS dysregulation. To the best of our knowledge this is the first comprehensive review regarding this intriguing feature of Covid-19.

## Conflict of interest

The authors declare that there are no conflicts of interest.

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Pulmonology 29 (2023) 332–334

PULMONOLOGY

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LETTER TO THE EDITOR

# Effectiveness of a remote simulation training in mechanical ventilation among trainees

*Dear Editor,*

Understanding basic principles of pathophysiology, modes, patient-ventilator interaction and waveform analysis is essential for the safe delivery of mechanical ventilation.[1–3] The COVID-19 pandemic has profoundly impaired medical education, reducing the chance of in-person educational events and leading to an increasing number of physicians with little or no specific experience (i.e. trainees or physicians from other fields) being hired and managing mechanically ventilated critically ill patients. Thus, effective methods to teach competencies in mechanical ventilation to large cohorts of physicians in short periods of time were urgently needed. Simulators for training had been previously investigated[4–6] for teaching purposes, but free or open source simulators are rare, and they often have outdated technical requirements, limiting their use in current educational programs.

To address such issues, we conducted a randomized controlled trial assessing the effectiveness of a remote simulation-based training using VentSim©,[7] free, interactive,

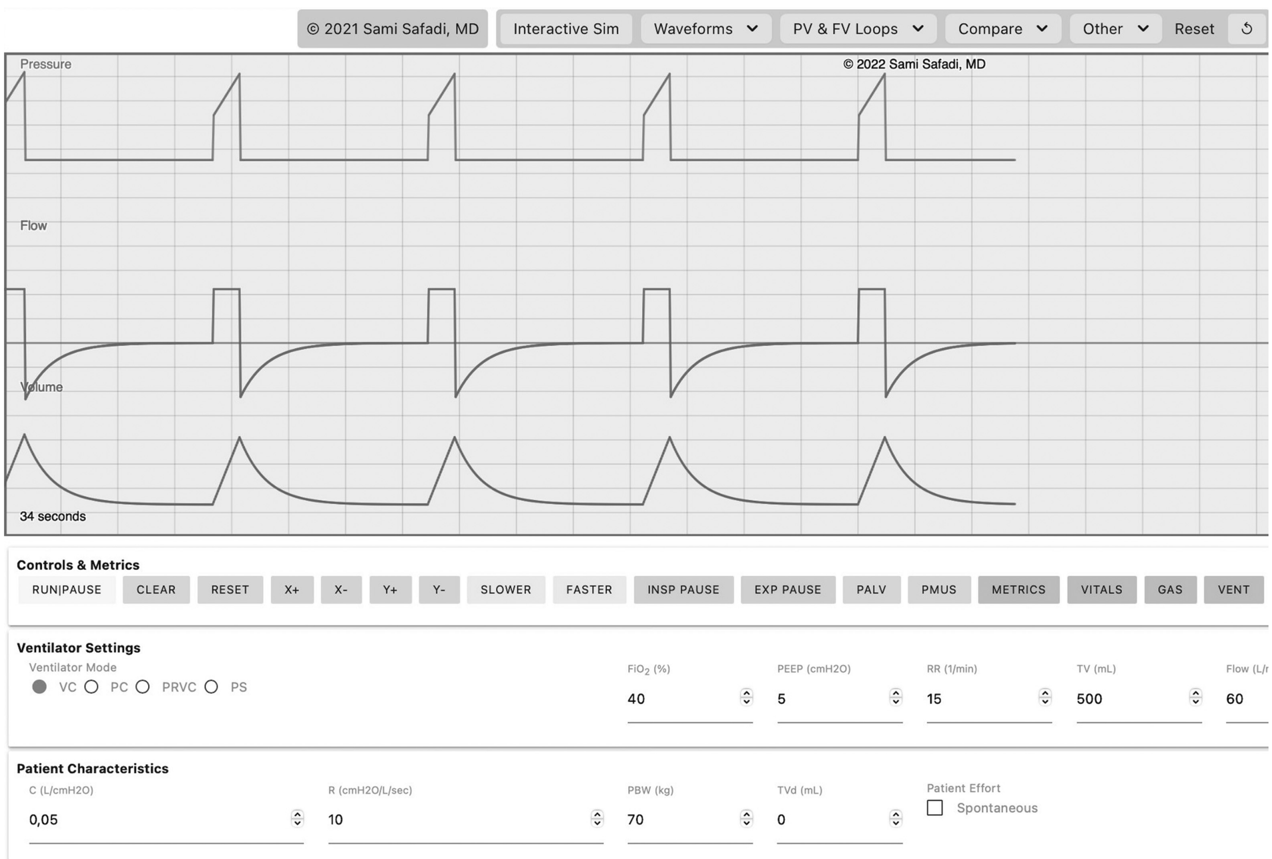


**Fig. 1** VentSim© software main features> The figure shows the simulation environment of VCV ventilation in the main modality offered by the software.

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online software with a graphic interface displaying standard ventilator curves, able to simulate basic modes of mechanical ventilation and patient-ventilator interaction (Fig. 1). The protocol of this trial was approved by the Ethics Committee Palermo 1 (ID: 11/2021, date: 15 December 2021) and followed the Helsinki Declaration. We assessed the effectiveness of providing a short educational cycle with standard teaching alongside simulation-based lessons, in comparison to standard teaching alone, to increase the knowledge and skills on mechanical ventilation of trainees in anesthesia and intensive care.

For the purpose of this study, all the trainees regularly attending the specialty training program in a single centre in Italy were officially invited to participate to the study. A total of 183 residents voluntarily joined the study and were randomized, using strata based on previous rotation in the Intensive Care Unit (ICU). The rate of lost to follow up was 19%. All the analyses were performed under the intention-to-treat principle. All the participants attended two two-hour remote lessons provided by two academics, consultants in Anesthesia and Critical Care (CG and AC) on core topics of mechanical ventilation. Participants randomized to the intervention group ("VentSim© group") also attended two remote simulation-based lessons, delivered using the simulation software VentSim©.[7] All the lessons were held in the period from 24th February and 29th March 2022. We collected baseline characteristics of the participants including age, gender and information about previous rotations in ICU.

The primary outcome of the trial was the number of correct answers to a 50 multiple choice questionnaire, composed of 21 theorical questions, 24 waveform interpretation questions, and 5 clinical scenarios. Trainees' satisfaction on the educational program was also assessed as secondary outcome, through 5 sentences on which the participants had to express agreement with a 5-points Likert scale.

The overall number of correct answers was similar between the VentSim© group and control group (28.6 ± 8.6 vs. 27.6 ± 9; $P$ = 0.49). Using a 5-points-Likert scale, the VentSim© group rated 4 [4—5] the contents, 4 [4—5] the clarity of explanation, 4 [4—5] the self-perceived comprehension of mechanical ventilation and 4 [3—4] the self-perceived ability to manage mechanically ventilated patients. No significant effect of the intervention was registered in term of satisfaction through these items. The VentSim© group rated 5 [4—5] the utility of integrating simulation in routine training of residents.

Our data showed that a remote simulation-based course on mechanical ventilation with VentSim© did not significantly improve the competencies of trainees in anaesthesia and intensive care in comparison with traditional lessons at the end of a short educational cycle (Table 1). These data

**Table 1** Characteristics of included participants and outcome measures.

| | Intervention | Control | *P value* |
|---|---|---|---|
| *Characteristics of participants* | | | |
| Age, years | 29 [28—30] | 28 [27—30] | 0.73 |
| Female, n (%) | 39 (53%) | 48 (64%) | 0.25 |
| Experience in ICU, % | 22 (30%) | 25 (33%) | 0.81 |
| Year of residency | | | 0.62 |
| I | 23 (31.5%) | 27 (36%) | |
| II | 24 (32.8%) | 16 (21%) | |
| III | 15 (20.5%) | 19 (25%) | |
| IV | 7 (1%) | 9 (1.2%) | |
| V | 4 (0.5%) | 4 (0.5%) | |
| *Outcomes* | | | *P value* |
| Correct answers, *mean ± SD (%)* | 28.6 ± 8.6 (58%) | 27.6 ± 9 (56%) | 0.49 |
| Correct answers among those with experience in ICU, *mean ± SD* (%) | 32.7 ± 7.8 (65%) | 31.3 ± 7.1 (63%) | 0.52 |
| Correct answers among those without experience in ICU, *mean ± SD* (%) | 26.8 ± 8.4 (53%) | 25.7 ± 9.4 (51.4%) | 0.54 |
| Correct waveform interpretation answers, *median [IQR] (%)* | 14 [11—18] (58%) | 14 [10.5—18] (58%) | 0.45 |
| Correct theorical answers, *median [IQR] (%)* | 12 [10—14] (57%) | 12 [9.5—13.5] (57%) | 0.15 |
| Correct answers to clinical scenarios, *median [IQR] (%)* | 3 [2—3] (60%) | 3 [2—4] (60%) | 0.74 |
| Agreement on usefulness of contents, *median 1—5Likert [IQR]* | 4 [4—5] | 4 [4—5] | 0.80 |
| Agreement on clarity of contents, *median 1-5Likert [IQR]* | 4 [4—5] | 4 [3—5] | 0.76 |
| Agreement on self-perceived improvement in knowledge, *median 1-5Likert [IQR]* | 4 [4—5] | 4 [3—5] | 0.60 |
| Agreement on self-perceived improvement in competencies, *median 1-5Likert [IQR]* | 4 [3—4] | 4 [3—4.5] | 0.94 |
| Agreement on inclusion of simulation-based lesson in the ordinary curricula of the school, *median 1-5Likert [IQR]* | 5 [4—5] | - | - |

Data are reported as mean ± SD or median [IQR] and percentages, as appropriate.
The number of correct answers (primary outcome) and overall agreement on satisfaction statements (additional outcome) were compared using $t$- test for independent means, if normal distribution confirmed through Shapiro-Wilk test. Mann Whitney U test was used in case of non-normal distribution of the data. Unbalances between of the two groups on participants' characteristics were also checked for, using Mann Whitney U test and Chi-square, as appropriate. Statistical significance was accepted at $p$-value < 0.05 and all tests were 2-tailed. A secondary analysis was conducted on the type of questions, considering only the questions related to waveforms interpretation. A subgroup analysis basing on previous clinical rotation in ICU was also conducted.

could be interpreted in favor of the potential need to resume face-to-face teaching educational programs of adequate duration during the chronic phase of pandemic. Among limitations, the single-center design and the potential bias due to assignment to intervention (e.g., residents in the control groups may have studied more to offset their assignation group) may have limited the results. Also, the external validity is limited, as the results may be different in other centers. Finally, we did not grant learners free access to the platform after the workshops, which could be an advantage of using software instead of macrosimulation, also in term of information retention. However, the high rate of satisfaction among the participants, the absence of associated costs and the readiness to be used in remote meetings, make VentSim© a potentially valuable complementary didactical tool.

Overall, our data seem to suggest that remote training may not be the best option for educational programs on mechanical ventilation, although these pandemic years made such solutions inevitable. Moreover, the results suggest that it is unlikely that a single short educational cycle can lead to full understanding of the mechanical ventilation techniques or the ability to solve clinical scenarios, independently of the methods. These considerations should be taken into account when setting educational programs for young physicians. Further studies should assess the efficacy of face-to-face simulation-based educational program on mechanical ventilation using VentSim©, also evaluating the best group size of trainees to optimize such learning experiences.

## Data availability statement

Data are available upon reasonable request to the corresponding author.

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None.

## Conflicts of interest

Sami Safadi is the owner of VentSim© software. All the other authors declare no conflicts of interest.

## CRediT authorship contribution statement

**M. Ippolito:** Conceptualization, Visualization, Formal analysis, Data curation, Writing — original draft. **B. Simone:** Data curation, Resources, Writing — review & editing. **S. Safadi:** Writing — original draft, Software, Data curation, Writing — review & editing. **E. Spinuzza:** Data curation, Writing — review & editing. **T. Catania:** Data curation, Writing — review & editing. **G. Ingoglia:** Data curation, Writing — review & editing. **M. Milazzo:** Data curation, Writing — review & editing. **S.M. Raineri:** Data curation. **A. Giarratano:** Data curation, Writing — review & editing. **C. Gregoretti:** Writing — original draft, Writing — review & editing. **A. Cortegiani:** Conceptualization, Visualization, Writing — original draft.

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PULMONOLOGY

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LETTER TO THE EDITOR

# Use of the Borg dyspnea scale to identify dynamic hyperinflation during the 6-minute walking test in individuals with moderate-severe COPD: A pilot study

In individuals with chronic obstructive pulmonary disease (COPD), dynamic hyperinflation (DH) may be a determinant of the worsening in dyspnea discomfort during exertion.[1] DH is the temporary increase of the end-expiratory lung volume above baseline values, with consecutive reduction of the inspiratory capacity (IC), which occurs when ventilatory demand is acutely increased.[2] The assessment of DH during exertion can be limited in clinical settings when there is need for expensive and specific equipment and trained assessors.[2] Therefore, this study aimed to determine whether the Borg dyspnea scale[3] (BORG-D), an easy and affordable tool to assess dyspnea, may have a cutoff point capable of identifying individuals with stable COPD who develop DH during the 6-minute walk test (6MWT). Also, it investigated if other clinical outcomes are similarly associated with dyspnea complaints in women and men with COPD.

This cross-sectional analysis was developed with data previously collected in a convenience sample of consecutive individuals with COPD at the Laboratory of Research in Respiratory Physiotherapy of the Universidade Estadual de Londrina, Brazil. Inclusion and exclusion criteria may be found in the original publication.[4] The protocol was approved by the institution's ethics committee (#151/2013) and all participants signed an informed consent form.

The 6MWT was performed according to international standardization.[5] Dyspnea was quantified using the BORG-D ranging from 0 (no dyspnea) to 10 (maximum dyspnea) and patients were properly instructed before the application of the scale. The main outcome used for analysis was dyspnea self-reported immediately after the 6MWT minus that reported immediately before the test (Δ_BORG-D). Additionally, $\Delta SpO_2$/distance index was determined as post minus pre $SpO_2$ divided by the 6MWT distance x 100.

DH during the 6MWT was quantified by serial assessments of IC using a portable spirometer (Spiropalm, Cosmed, Italy). The device's original face mask model was used for all patients. There were no complaints concerning the mask's use as tested in the original study.[4] Measures were done at rest, 2 and 4 min after the beginning of the test, 15 s before completion, and immediately at the end of the test. DH was defined by a reduction in IC over the test (delta IC nadir minus pre-test, or ΔIC) according to two criteria: at least 150 ml ($\Delta IC > 150$ ml)[2] or at least 4.5%predicted ($\Delta IC > 4.5\%$pred)[6] relative to the resting value.

Data were described as mean±standard deviation or median [interquartile range 25–75%] according to normality in data distribution (Shapiro-Wilk test). The cutoff points for Δ_BORG-D were verified by the area under the curve (AUC) of the receiver operating characteristics. Differences between sexes were analyzed through parametric, non-parametric and Chi-square tests, as indicated. The software used was SPSS 22.0 (IBM, USA) with a statistical significance level set as $P<0.05$.

Twenty-four individuals with moderate-severe COPD (13men; 67±6years) were studied. Table 1 shows all sample characteristics and sex comparisons. Out of the 24 patients, 75% (11 male and 7 female) developed DH according to the $\Delta IC > 150$ ml criterium, whereas 79% (11 male and 8 female) developed DH according to the $\Delta IC > 4.5\%$pred criterium. In addition, in comparison to men, women were younger, had less severe disease, less static hyperinflation and lower $\Delta SpO_2$.

Table 2 shows that a cutoff point for Δ_BORG-D (increase > 2.75 points in BORG_D after the 6MWT) satisfactorily identified $\Delta IC > 4.5\%$pred for the whole (general) group and especially for men. When using $\Delta IC > 150$ ml, the same cutoff point was satisfactory only for men. Regarding women, a satisfactory cutoff point could not be found with any DH criterium (Table 2).

The present results corroborate with previous literature[1] showing an association between DH and BORG-D during the 6MWT. However, it takes it further by proposing a cutoff point of an increase ≥2.75 (or 3) points in BORG-D after the 6MWT as able to identify individuals with moderate-severe stable COPD who develop DH defined as a decrease in IC >4.5%pred during exertion.[6] Thus, individuals who showed an increase in BORG-*D* > 3 points after the 6MWT are

*Abbreviation:* COPD, Chronic obstructive pulmonary disease; DH, Dynamic hyperinflation; EELV, End-expiratory lung volume; IC, Inspiratory capacity; BORG-D, Borg dyspnea scale; 6MWT, 6-minute walk test; AUC, area under the curve; $FEV_1$, Forced expiratory volume in the first second; BMI, Body mass index; RV/TLC, Residual volume/total lung capacity.

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**Table 1** Sample characteristics and comparison according to sex.

| Variable | Overall (*n* = 24) | Men (*n* = 13) | Women (*n* = 11) | *P* value (men *vs* women) |
|---|---|---|---|---|
| Age (years) | 67.00 ± 5.85 | 69.15 ± 5.14 | 64.45 ± 5.6.2 | 0.039 |
| BMI (kg/m$^2$) | 28.90 ± 4.3 | 28.74 ± 5.56 | 28.42 ± 5.73 | 0.800 |
| $FEV_1$ (L) | 1.48 ± 0.38 | 1.52 ± 0.46 | 1.45 ± 0.30 | 0.706 |
| $FEV_1$ (% predicted) | 55.52 ± 17.58 | 47.45 ± 14.11 | 6.27 ± 17.31 | 0.018 |
| FVC (L) | 2.84 ± 0.49 | 3.09 ± 0.48 | 2.59 ± 0.37 | 0.019 |
| FVC (% predicted) | 83.96 ± 16.51 | 77.85 ± 12.86 | 91.18 ± 17.96 | 0.046 |
| FEV1/FVC (%) | 52.29 ± 9.99 | 48.83 ± 11.11 | 55.75 ± 7.71 | 0.139 |
| IC pre 6MWT (L) | 2.22 ± 0.54 | 2.79 ± 0.73 | 2.51 ± 0.66 | 0.341 |
| IC 2min_6MWT (L) | 1.93 ± 0.51 | 2.11 ± 0.57 | 1.71 ± 0.34 | 0.076 |
| IC 4 min_6MWT (L) | 1.90 ± 0.48 | 2.06 ± 0.47 | 1.71 ± 0.43 | 0.086 |
| IC 5:45_6MWT (L) | 1.88 ± 0.51 | 2.13 ± 0.48 | 1.60 ± 0.38 | 0.011 |
| IC post 6MWT (L) | 1.97 ± 0.50 | 2.21 ± 0.49 | 1.69 ± 0.36 | 0.017 |
| ΔIC nadir-pre 6MWT (L) | −0.48 ± 0.40 | −0.61 ± 0.42 | −0.35 ± 0.35 | 0.107 |
| ΔIC nadir-pre 6MWT >150 ml, Yes/No (n[%]) | 18[75] / 6[25] | 11[85] / 2[15] | 7[64] / 4[36] | 0.478 |
| ΔIC nadir-pre 6MWT >4.5%pred, Yes/No (n[%]) | 19[79] / 5[21] | 11[85] / 2[15] | 8[73] / 3[27] | 0.475 |
| RV/TLC ratio (%) | 49.58 ± 7.56 | 52.69 ± 6.44 | 45.91 ± 7.38 | 0.025 |
| 6MWT (m) | 458.67 ± 46.44 | 466.69 ± 59.92 | 449.18 ± 21.65 | 0.342 |
| 6MWT (% predicted) | 88.33 ± 10.54 | 87.08 ± 12.16 | 89.82 ± 8.47 | 0.538 |
| $SpO_2$ post-6MWT (%) | 90.58 ± 5.03 | 89.38 ± 5.37 | 92.00 ± 4.42 | 0.212 |
| $\Delta SpO_2$ post-pre 6MWT(%) | −4.13 ± 3.34 | −5.54 ± 3.17 | −2.45 ± 2.80 | 0.021 |
| $\Delta SpO_2$/distance index | 0.60 ± 0.83 | 0.90 ± 0.85 | 0.25 ± 0.69 | 0.054 |
| ΔBORG D (points) | 3.37 ± 2.14 | 3.88 ± 2.22 | 2.77 ± 1.97 | 0.179 |
| ΔBORG F (points) | 2.12 ± 2.23 | 2.61 ± 2.42 | 1.53 ± 1.90 | 0.275 |
| Literate Yes/No (*n*[%]) | 23[96] / 1[4] | 13[100] / 0[0] | 10[91] / 1[9] | 0.458 |

Data presented in absolute frequency, mean ± standard deviation or median [interquartile rage 25% −75%]. BMI: body mass index; $FEV_1$: forced expiratory volume in the first second; FVC: forced vital capacity; IC: Inspiratory capacity; 6MWT: 6-minute walking test; L: liters; RV: residual volume; TLC: total lung capacity; DH: Dynamic Hyperinflation; $SpO_2$: Pulse oxygen saturation; Index Δ $SpO_2$/distance: ratio of $SpO_2$ pre-post to 6MWD x 100. BORG D: Borg dyspnea; BORG F: Borg fatigue.

possible hyperinflators, whereas this applies especially for men but not necessarily for women. Previous literature described that hyperinflation may be related to various clinical outcomes in addition to dyspnea. Abdelwahab et al.[7] found that severe hyperinflation can be predicted by the index between $\Delta SpO_2$ and the 6MWT distance presenting value ≥0.6. In the present study, only the general sample and the male group had values above this cutoff. This corroborates the finding of higher DH in men, although comparable increase in DH during exertion between men and women have been previously described.[8] The non-feasibility of finding a cutoff point for women is probably due to the fact that the female participants in this sample were younger, had less severe disease, less static hyperinflation and lower $\Delta SpO_2$ than male participants. A study with a sample of slightly older women with more severe disease and more

**Table 2** Results of different criteria to detect dynamic hyperinflation (delta inspiratory capacity nadir-pre test) in individuals with COPD performing the 6MWT.

| Criterium | AUC | Sensibility | Specificity |
|---|---|---|---|
| ΔIC nadir-pre 6MWT >150 ml, general | 0.60 | 72% | 67% |
| ΔIC nadir-pre 6MWT >4.5%pred, general | 0.72 | 74% | 80% |
| ΔIC nadir-pre 6MWT >150 ml, men | 0.84 | 81% | 100% |
| ΔIC nadir-pre 6MWT >4.5%pred, men | 0.84 | 82% | 100% |
| ΔIC nadir-pre 6MWT >150 ml, women | 0.43 | 86% | 50% |
| ΔIC nadir-pre 6MWT >4.5%pred, women | 0.60 | 88% | 67% |

Receiver operating characteristic (ROC) curve of the delta cutoff point of the Borg dyspnea scale (Δ _BORG-D nadir-pre 6MWT) to identify dynamic hyperinflation (DH) in individuals with COPD performing the 6-minute walk test (6MWT). Criterium ΔIC>150ml: reduction of inspiratory capacity of at least 150 ml during or after the 6MWT; Criterium ΔIC>4.5%pred: reduction of inspiratory capacity of at least 4.5% predicted during or after the 6MWT. The cutoff point for men and general sample was an increase >2.75 points in the BORG dyspnea scale after the 6MWT, whereas for women was >1.75 points.

pronounced static hyperinflation may be necessary to identify such a cutoff for female patients. Further, previous literature describes that it is common for women with COPD to be more symptomatic than men, even with milder disease severity, and this can be justified by the reduced ventilatory reserve that contributes to women reaching total lung capacity limit faster.[9] Therefore, a female-specific cutoff may be necessary.

Another difference found was that women showed less hyperinflation compared to men. Perhaps static hyperinflation is better related to dyspnea in women than in men; previous studies with mixed samples have shown that there is an association between these outcomes.[10] Further studies may advance understanding of the mechanisms of dyspnea in women.

Despite its novelties, the present study has limitations such as the small sample size, lack of testing of the cutoff on a larger sample and absence of the BORG-D measurements at the minutes 2, 4 and 5:45 of the 6MWT. Furthermore, a convenience sample of consecutive individuals with COPD was used in which women had different characteristics than men, and perhaps the design could have encompassed matched groups of male and female patients with similar characteristics. New studies with larger samples, similar characteristics between the sexes (including disease severity and static hyperinflation), a wider range of disease severity and with other relevant outcomes could be useful to expand the understanding of the present results.

In conclusion, when defining DH as a reduction in IC of at least 4.5%predicted, an increase $\geq$2.75 (or 3) points in the Borg dyspnea scale after the 6MWT was able to satisfactorily identify individuals with moderate/severe COPD who hyperinflate during the test. In specific analyses according to sex, it was also possible to establish the same satisfactory cutoff point for men using the same definition of DH, as well as defining DH based on a reduction in IC of at least 150 ml. However, no satisfactory cutoff point was found for women using any DH criterium.

## Authors' contribution

A.P.V.M.F. conceptualization, formal analysis, methodology, investigation, writing − original draft and writing − review & editing. L.F.B. conceptualization, formal analysis, methodology, investigation, writing − original draft and writing − review & editing. F.P. conceptualization, formal analysis, methodology, investigation, writing − original draft and writing − review & editing. L.M. conceptualization and writing − review & editing. N.A.H. conceptualization and writing − review & editing.

## Declaration of Competing Interest

None.

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LETTER TO THE EDITOR

# Changes in exercise endurance and inspiratory capacity after lumacaftor/ivacaftor therapy in cystic fibrosis

*Dear Editor,*

The long-term positive effects of the combination of the corrector lumacaftor (LUM) with the potentiator ivacaftor (IVA) on physical activity and oxygen uptake values obtained during a symptom-limited incremental cardiopulmonary exercise test (CPET) in cystic fibrosis (CF) have been described.[1] Among available exercise-testing protocols, constant work-rate exercise tests, such as a cycle endurance test, deliver a reliable assessment of changes in exercise capacity following intervention (both pharmacologic and nonpharmacologic).[2] As previously demonstrated, one-month LUM/IVA therapy did not increase exercise endurance or modify dyspnea or leg discomfort in adult CF patients[3] and no data are available on the longer-term effects of such modulator therapy on exercise endurance and symptoms of exertion. The aim of this study was to examine the potential impact of LUM/IVA therapy (400 mg/250 mg administered orally every 12 h) on exercise endurance time (EET) and symptoms of exertion during constant work-rate cycle ergometry (CWRCE) after six months treatment. This was a prospective, observational, multicenter study, involving three CF centers in Italy (Rome, Milan, Orbassano). The study (number 853/18) was approved by the ethics committee of Policlinico Umberto I Hospital, Sapienza University of Rome, Italy, and other local ethics committees. All patients provided written informed consent for this study. During the study period from April 2019 to March 2020, we recruited three stable adult CF patients ($\geq$ 18 years old, homozygous for Phe508del) who were about to initiate LUM/IVA treatment. We used a protocol consisting of two visits: 3-4 weeks prior to initiation of LUM/IVA treatment (visit 1) and 6 months afterwards (visit 2). During each visit, in the morning patients performed spirometry and a symptom-limited incremental CPET using cycle ergometry to determine peak work rate (defined as the highest work rate maintained for $>$ 30 s). In the afternoon, all subsequent symptom-limited CWRCE tests were conducted at 80% of peak work rate. Inspiratory capacity and intensity of breathing discomfort and leg discomfort (Borg scale[4]) were measured prior to exercise, every 2 min during exercise and at the point of symptom limitation (end-exercise). Minute ventilation (V'E) and oxygen uptake ($V'O_2$) were measured using a calibrated metabolic system (Cosmed K5). After completing each exercise test, patients identified the primary reason for stopping (due to leg and/or breathing discomfort or another reason). Patients were asked to continue any respiratory-related medications before the visits. Assessment was conducted at the same place and time of day for all subjects. The number of pulmonary exacerbations were prospectively collected throughout the 6- month period. For each patient we calculated the percentage of change between "pre" and "post" the start of LUM/IVA therapy for each variable.

Patient 1 is a 28 - year-old man of Caucasian origin diagnosed with CF at birth (Table 1). He commenced LUM/IVA treatment in May 2019. During six months treatment, he presented with one pulmonary exacerbation, which was treated with oral antibiotics. He reached his peak exercise at a higher oxygen uptake than that measured prior to therapy (Table 2). Patient 1 showed an improvement in oxygen pulse ($V\ O_2$/HR) following treatment, as well as slightly higher values of ventilation ($V'E_{peak}$), while mean maximal ventilation was less than the predicted MVV (208 L) and breathing reserve (BR) was reduced (Table 2). Ventilatory efficiency ($V'E/V'CO_2$ slope) and partial pressure of end-tidal $CO_2$ ($PETCO_2$) were slightly lower. After six month treatment, there was an increase in EET (344 s *vs* 644 s, 87%) and an improvement in inspiratory capacity prior to exercise of 520 mL, +17% (Table 2). The improvements in inspiratory capacity were sustained during exercise and end-exercise (160 mL, 4%, Table 2). There was a reduction in breathing discomfort and leg fatigue.

Patient 2 is a 34-year-old man of Caucasian origin diagnosed with CF at birth (Table 1). He commenced LUM/IVA treatment in July 2019. During six months treatment, the patient did not have exacerbations. He reached peak exercise at a higher oxygen uptake uptake than prior to treatment (+5%, Table 2). There was an improvement in $V\ O_2$/HR by + 6%. We observed lower values of $V'E_{peak}$, a mean maximal ventilation less than the predicted MVV (130 L) and a higher BR following treatment, suggesting that ventilation limit was not a limiting factor. $V'E/V'CO_2$ slope and $PETCO_2$ were slightly reduced. There was an increase in EET (416 s *vs* 635 s, 52%) and an improvement in inspiratory capacity prior to exercise of 350 mL, 16% (Table 2). The improvement in inspiratory capacity was sustained during exercise and end-exercise (540 mL, 23%, Table 2). There was a reduction in breathing and leg discomfort as indicated in Table 2.

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**Table 1** Anthropometric and clinical characteristics of adult CF patients.

| Characteristics | Patient 1 | | | Patient 2 | | | Patient 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre | Post | % change | Pre | Post | % change | Pre | Post | % change |
| BMI, Kg/ m2 | 24.2 | 25.1 | +4 | 23.9 | 24.6 | +3 | 21.3 | 21.1 | -0.93 |
| *Pseudomonas aeruginosa* colonization | no | no | 0 | yes | yes | 0 | yes | yes | 0 |
| *Staphylococcus aureus* colonization | yes | yes | 0 | yes | yes | 0 | yes | yes | 0 |
| *Burkholderia cepacia* colonization | no | no | 0 | no | no | 0 | no | no | 0 |
| Pancreatic insufficiency | yes | yes | 0 | yes | yes | 0 | yes | yes | 0 |
| CF-related diabetes | no | no | 0 | no | no | 0 | no | no | 0 |
| FEV1, % predicted | 106 | 109 | +3 | 75 | 82 | +10 | 72 | 65 | -9.7 |
| FVC, %predicted | 123 | 118 | -4 | 102 | 101 | -0.9 | 98 | 84 | -14.2 |

*Definition of abbreviations*: BMI = body mass index; FEV1 = Forced expiratory volume in 1 second; FVC = forced vital capacity; CF = Cystic Fibrosis.

Patient 3 is a 30-year-old man of Caucasian origin diagnosed with CF at birth (Table 1). He commenced LUM/IVA treatment in June 2019. During the following 6 months, the patient had one pulmonary exacerbation requiring IV antibiotic therapy. He reached peak exercise at a lower oxygen uptake (17% less, Table 2) and there was a marked reduction in V $O_2$/HR of 29%. He showed lower $V'E_{peak}$ and BR values, with maximal ventilation less than the predicted MVV (107 L). The $V'E/V'CO_2$ slope improved marginally. There was an increase in EET (371 s *vs* 460 s, 23%). Althought the patient showed dynamic hyperinflation both before and after treatment (IC$\Delta$ pre − 0.37 L, post − 0.3 L), there was an improvement in inspiratory capacity prior to exercise of 180 mL (+6%) and at end-exercise 250 mL (+10%; Table 2). There was a reduction in breathing and leg discomfort (Table 2).

Results from these case series demonstrate a longer EET after six months LUM/IVA treatment. Improvements in exercise endurance were accompanied by improvements in inspiratory capacity prior to exercise and additional serial

**Table 2** Measurements at peak symptom-limited incremental cycle exercise and at constant work-rate cycle ergometry (CWRCE) of adult CF patients.

| Variables at Peak CPET | Patient 1 | | | Patient 2 | | | Patient 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre | Post | % change | Pre | Post | % change | Pre | Post | % change |
| Work rate, watt | 180 | 172 | -4.4 | 180 | 210 | +16.6 | 120 | 125 | +4.1 |
| $V'O_2$, ml/min | 2084 | 2328 | +11.7 | 2650 | 2786 | +5.1 | 1699 | 1384 | -18.5 |
| $V'O_2$, ml/min/Kg | 25.41 | 27.39 | +7.8 | 38.41 | 39.24 | +2.1 | 26.97 | 22.14 | -17.9 |
| $V'O_2$, % predicted maximum | 67 | 69 | +3 | 97.6 | 102.2 | +5 | 62.2 | 51.3 | -17.5 |
| HR, beats·min−1 | 179 | 175 | -2.2 | 150 | 148 | -1.3 | 134 | 156 | +16.4 |
| V $O_2$/HR, ml $O_2$/beat | 11.6 | 13.3 | +15 | 17.7 | 18.8 | +6.2 | 12.7 | 8.9 | -29 |
| $\Delta SpO_2$ | 0 | 0 | 0 | -1 | -1 | 0 | 0 | 0 | 0 |
| $V_T$ *peak* (l) | 2.6 | 2.5 | -3.8 | 3.84 | 3.7 | -3.6 | 1.9 | 1.7 | -10.5 |
| V'E, l/min | 88.4 | 96 | +8.6 | 86.5 | 81.4 | -5.8 | 50.5 | 48.3 | -4.3 |
| BR (%) | 115 | 112 | -2.6 | 28.3 | 49 | +73 | 64.7 | 59.3 | -8 |
| V'E /V $CO_2$ slope | 36.9 | 35.4 | -4 | 30.3 | 28.9 | -4.6 | 27.5 | 30.5 | +10 |
| $PET_{CO2}$ *peak* (mmHg) | 34 | 32 | -5.8 | 42 | 41 | -2.3 | 43 | 38 | -11.6 |
| Dyspnea, Borg scale | 8 | 7 | -12.5 | 7 | 8 | +14.2 | 5 | 4 | -20 |
| Leg discomfort, Borg scale | 9 | 7 | -22.2 | 7 | 8 | +14.2 | 8 | 7 | -12.5 |
| **Variables at CWRCE** | | | | | | | | | |
| EET,s | 445 | 644 | +87 | 416 | 635 | +52 | 371 | 460 | +23 |
| IC baseline, l | 3.05 | 3.57 | +17 | 2.1 | 2.45 | +16 | 2.82 | 3 | +6 |
| IC end-exercise, l | 4.31 | 4.47 | +4 | 2.36 | 2.9 | +23 | 2.45 | 2.7 | +10 |
| Dyspnea, Borg scale | 6 | 5 | -17 | 6 | 5 | -17 | 5 | 4 | -20 |
| Leg discomfort, Borg scale | 9 | 7 | -22 | 9 | 7 | -22 | 9 | 8 | -11 |

*Definition of abbreviations*: $V'O_2$ = oxygen uptake; HR = heart rate; V $O_2$/HR = oxygen pulse; $\Delta SpO_2$ = arterial oxygen saturation delta from rest to peak exercise; $V_T$= tidal volume; V'E = minute ventilation; BR= breathing reserve; $V'E/V'CO_2$ = ventilatory equivalent for carbon dioxide. CWRCE = constant work-rate cycle ergometry; EET = exercise endurance time; IC = inspiratory capacity; Pre = Measurements pre treatment with lumacaftor/ivacaftor; Post = measurements after 6 months treatment with lumacaftor/ivacaftor.

assessment of inspiratory capacity during exercise demonstrated that these improvements were maintained at end-exercise. All three patients experienced less dyspnoea and less leg discomfort, while exercise limitation was often related to peripheral muscle fatigue and not to ventilatory constraints. Finally, in two patients we observed improvements in oxygen uptake values obtained during an incremental CPET, which is an important result as $V'O_2$ peak is an excellent general predictor of survival in CF.[5]

As a wide variety of exercise testing protocols is currently available with their own strengths and weaknesses, the decision about the most appropriate exercise test should be guided by the objective of the measurement. Incremental exercise protocols (incremental cycle or treadmill exercise tests) are more appropriate in the evaluation of the degree of exercise limitation, in the assessment of mechanisms of exercise limitation and/or in the prescription of training programs. Constant work-rate exercise test (CWRET) tLIM is considered more responsive for detecting improvement in exercise tolerance after an intervention.[2,6] In COPD patients, exercise training and interventions designed to improve ventilatory function (i.e. bronchodilators) showed an increase in endurance time.[2,6]

Improving dyspnoea and exercise tolerance are recognised as important goals in the treatment of CF, with the measurement of exercise endurance also considered a valuable component of CF assessment, particularly in response to treatment interventions with new drugs as modulators. In this case series we found evidence that LUM/IVA can increase inspiratory capacity, reduce exertional breathlessness and improve EET in patients with CF. Slowed increases in operating lung volume provided reductions in exertional breathlessness and improvements in symptom-limited exercise endurance. These improvements include sustained lung volume reduction as a result of enhanced tidal expiratory flow rates and lung emptying, with reduced resting and exercise lung hyperinflation observed in patient 3, together with a delay in the mechanical limitation to ventilation. Consequently, exertional dyspnoea was alleviated, leading to increases in EET. In addition to changes in dyspnoea, our patients who showed an increase in endurance time also experienced less leg discomfort. Although we recognize that both peripheral muscle dysfunction and deconditioning could be related to exercise limitation in CF, we did not evaluate muscle function in this study. We acknowledge that this is a case series with no control arm, so only interesting observations can be made. Constant work-rate exercise test, such as a cycle endurance test, confirmed its utility to assess change in exercise capacity following longer-term therapy with modulators.

## CRediT authorship contribution statement

Conception and design: DS. Acquisition of data: DS, AG, MV, MDP, BM. Analysis and interpretation: DS, MDP. Drafting the article: DS, AG, MV. All authors revised the intellectual content of the work and gave final approval of the version to be submitted.

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## Availability of data and materials

Available upon request.

## Declaration of Competing Interest

The authors declare that they have no financial and personal relationships with other people or organisations that could inappropriately influence their work.

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LETTER TO THE EDITOR

# Results of surgery versus stereotactic body radiotherapy for lung cancer

*Dear Editor,*

Historically, the best outcomes for early-stage lung cancer have been achieved through surgery, via lobectomy.[1] Nevertheless, stereotactic body radiotherapy (SBRT) has emerged as an effective treatment for stage I lung tumors unsuitable for surgery.[2]

From August 2012 to June 2018, 49 patients with lung cancer were submitted to SBRT and 232 patients underwent surgical resection (pathological stage above IIB and neuroendocrine subtype were excluded). See Table 1 for baseline data. Patients submitted to SBRT were considered not fit for surgery, 32 of them due to severe chronic obstructive pulmonary disease (COPD).

Lobectomy was the most frequent surgery (92.2%). Patients undergoing SBRT were submitted to different schemes, the most frequent being 46—60 Gy in 4 fractions ($n = 19$), followed by 30—34 Gy in 1 fraction ($n = 16$), 42.5—50 Gy in 5 fractions ($n = 12$) and 60 Gy in 3 fractions ($n = 2$).

Patients in the SBRT group were older, showed a higher burden of comorbidities, their mean value of FEV1 was lower and their incidence of COPD was higher, compating to patients in the surgical group. One limitation of our study is that we only distinguished the presence or absence of comorbidities, and not their severity. For tumours in stage IA, the SBRT group had a lower mean FEV1 and a higher incidence of COPD.

Progression was defined by imagiological criteria: 20% increase in unidimensional measurement or appearance of new lesions. All the patients had a computed tomography scan, performed every 6 months for surgical patients and 3—6 months for SBRT patients. Other studies, like positron emission tomography, were performed if doubts over disease progression remained. Twelve patients from the surgical group were lost to follow-up. Median survival comparison for surgical and SBRT groups including the results for stage IA patients are depicted in Table 2.

The groups did not reveal differences in median overall survival (OS) and distant progression free survival (PFS), but there were significant differences between surgical and SBRT groups on PFS and local PFS. For disease in stage IA alone, median survival rates are significantly higher in the surgical group for OS, PFS, local and distant PFS.

A propensity score-matching analysis was applied to reduce potential confounding. We matched 31 pairs of patients, using a propensity score based on age, sex, comorbidities like COPD, FEV1, stage and histology. We were not able to compare the two groups on OS due to zero deaths in one of the groups. No significant differences were found between the two groups for PFS (95%CI=0.1;25.3) [$p = 0.917$], local PFS 95%CI=0.1;20.6) [$p = 0.917$] and distant PFS (95%CI=0.1;279.1) [$p = 0.415$].

Lobectomy remains the standard for surgical management of NSCLC, although sublobar resection for NSCLC is still a controversial issue.[3] Rami-Porta and Tsuboi[3] reported that, in terms of survival, lobectomy and wedge resection are equivalent in patients aged more than 71 years; they also report that, in patients unable to undergo lobectomy, sublobar resection is an alternative that will confer similar prognosis. In our study, sublobar resection was performed in only 4 patients, not allowing a subanalysis.

Different stages had different survival and progression rates.[4] One possible confounding factor regarding the distribution of different stages is that the surgical group had a pathological stage while SBRT patients had a clinical stage. These results could also be biased owing to the very small number of patients included in the SBRT group, resulting in a large sample size difference, which could have significantly influenced the analytical power.

We subanalyzed patients in stage IA. This comparison allowed for a better interpretation of the results, as SBRT and surgical groups were more homogenous. However, patients in the SBRT group still presented a lower mean FEV1 and a higher incidence of COPD, and these could have been why the patients were considered unfit for surgery. Surgery has also the advantage of allowing a definitive pathologic diagnosis, accurate lymph node evaluation, and possible upstaging for adjuvant therapy.[5] The lower number of patients included in the propensity matched analysis raises doubts due to low precision results.

Surgery was the primary treatment and only unfit patients were submitted to SBRT, in accordance with guidelines. In RTOG 0236 (a multicenter phase II study),[6] 52 patients with medically inoperable NSCLC were treated with 60 Gy delivered in 3 fractions; long-term results showed an

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**Table 1** Clinicopathologic characteristics of the patients submitted to surgery and SBRT included in the study.

| | Thoracic Surgery Patients *n* = 232 | SBRT Patients *N* = 49 | p |
|---|---|---|---|
| Sex | **n (%)** | **n (%)** | **0.017** |
| Male | 154 (66.4%) | 41 (83.7%) | |
| Female | 78 (33.6%) | 8 (16.3%) | |
| | **Median (range)** | **Median (range)** | <**0.001** |
| Age (years) | 65.5 (35—88) | 71 (54—88) | |
| ECOG PS | **n (%)** | **n (%)** | 0.649 |
| 0 | 150 (64.7%) | 30 (61.2%) | |
| 1 | 82 (35.3%) | 17 (34.7%) | |
| 2 | 0 | 2 (4.1%) | |
| | **Median (range)** | **Median (range)** | <**0.001** |
| FEV1 | 96 (29.5—115) | 69.5 (32—121) | |
| Comorbidities | **n (%)** | **n (%)** | |
| COPD | 35 (15.1%) | 32 (65.3%) | <**0.001** |
| CVD | 43 (18.5%) | 5 (10.2%) | 0.159 |
| CKD | 11 (4.7%) | 2 (4.1%) | 0.174 |
| ILD | 5 (2.2%) | 1 (2.0%) | 0.719 |
| Histology | **n (%)** | **n (%)** | <**0.001** |
| Adenocarcinoma | 205 (88.4%) | 33 (67.3%) | |
| Squamous | 27 (11.6%) | 16 (32.7%) | |
| Stage | **n (%)** | **n (%)** | <**0.001** |
| IA | 99 (42.7%) | 41 (83.7%) | |
| IB | 87 (37.5%) | 5 (10.2%) | |
| IIA | 5 (2.2%) | 2 (4.1%) | |
| IIB | 41 (17.7%) | 1 (2.0%) | |

Table1 — CKD-chronic kidney failure; COPD-Chronic Obstructive Pulmonary Disease; CVD: Cardiovascular disease; ECOG PS- Eastern Cooperative Oncology Group Performance Status; FEV1-Forced Expiratory Volume in 1 S; ILD: Interstitial Lung Disease.

**Table 2** Median survival (months) in patients submitted to surgery versus SBRT.

| | Surgical patients -Median (95%IC) | SBRT Patients Median (95%IC) | p |
|---|---|---|---|
| OS | 68.243 (64.497—71.990) | 43.355 (36.028—50.682) | 0.099 |
| PFS | 69.625 (65.816—73.435) | 31.039 (24.063—38.014) | <**0.001** |
| Local PFS | 73.400 (69.979—76.821) | 34.494 (25.394—43.594) | <**0.001** |
| Distant PFS | 74.347 (71.116—77.578) | 42.948 (35.548—50.349) | 0.062 |
| | **Surgical Stage IA patients-Median (95%IC)** | **SBRT Stage IA Patients Median (95%IC)** | **p** |
| OS | 70.568 (65.153—75.983) | 42.949 (35.507—50.391) | **0.038** |
| PFS | 77.032 (71.728—81.337) | 32.588 (25.301—39.875) | <**0.001** |
| Local PFS | 77.904 (73.899—81.910) | 36.014 (26.508—45.520) | <**0.001** |
| Distant PFS | 78.710 (74.982—82.439) | 43.738 (36.345—51.131) | **0.009** |

OS of 40% after a median follow-up of 4 years, and 13% experienced locoregional recurrence at 3 years. In another study (RTOG 0618),[7] 33 operable patients were also treated with 60 Gy delivered in 3 fractions; the 2-year local failure rate was 8%. We expect further data on SBRT outcomes in patients fit to undergo surgery. Results of prospective randomized clinical trials are awaited.

Our cohort represents tumours in stages I-II and most of the patients were submitted to surgery (232 patients, versus 49 submitted to SBRT). SBRT was the preferred treatment in patients deemed unfit for surgery. Survival analysis showed significantly higher values in the surgical group, especially in stage IA, but SBRT remains a suitable option for inoperable patients.

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LETTER TO THE EDITOR

# Chylothorax as an unusual presentation of Bosutinib therapy toxicity

*Dear Editor,*

Tyrosine kinase inhibitors (TKIs) are the mainstay of the current treatment of Philadelphia chromosome positive chronic myeloid leukemia (CML). Pulmonary complications associated with TKIs are more frequently reported with Dasatinib, particularly pleural effusion, although they can also be secondary to Bosutinib therapy.[1-3] Here we present a case of a patient with CML treated with Bosutinib who developed a chylothorax.

A 68-year-old woman, non-smoker, with no history of significant comorbidities was diagnosed with chronic-phase CML in 2006. She was initially treated with Imatinib 400mg qd, achieving a complete molecular response. However, therapy was switched to Bosutinib 500mg qd in 2016, due to gastrointestinal intolerance. In 2021, she presented in the emergency department complaining of a one-month history of severe dyspnea (mMRC 3), dry cough and chest pain. On auscultation, there was a decrease in breath sounds on the right inferior lung field. There were no other abnormalities on physical examination.

A chest radiograph revealed a small volume bilateral pleural effusion, which was larger on the right. A CT-Scan of the thorax was then performed showing a bilateral free-flowing pleural effusion, which was larger on the right, and a partial collapse of the right middle lobe with no clear obstructive cause. A flexible bronchoscopy provided better characterization with the finding of right middle bronchus tapering, allowing the progression of the bronchoscope. A bronchoalveolar lavage and brushing were performed in that bronchial segment, with no abnormalities found. An ultrasound-guided diagnostic thoracocentesis was performed, with the removal of 26 mL of pleural effusion with a hazy and milky appearance, classified as a lymphocytic predominant exudate. The pleural fluid was categorized as a chylothorax after the biochemical examination (pleural fluid triglyceride concentration of 375 mg/dL). The pleural fluid culture, immunophenotyping and cytology exam were negative. Liver function tests were normal.

A clinical suspicion of a Bosutinib induced chylothorax was raised. Since all the criteria for stopping TKI were met, Bosutinib was withdrawn, with a complete resolution of the bilateral pleural effusion within five weeks, therefore confirming the diagnosis. Respiratory symptoms resolved within a week. The patient remains in complete molecular response after 6 months without TKI therapy.

Pulmonary toxicity is a common adverse effect of Dasatinib therapy, particularly pleural effusion, with a reported incidence as high as 39%.[4] Although the risk decreases over time, it can occur throughout the whole treatment. Bosutinib has also been associated with pleural effusion, with a reported incidence around 5% in the first-line setting and up to 17% in later-line settings[5]. Known risk factors for Dasatinib-related pleural effusion include cardiac disease, arterial hypertension, pulmonary disease, hypercholesterolemia, autoimmune disease, advance phase CML and age older than 60 years and are thought to be the same for Bosutinib.[4,6]

Management of Dasatinib-related pleural effusion is based on its estimated size on chest x-ray and the severity of symptoms. Small, asymptomatic pleural effusions (< 500 mL) may only require close monitoring; if symptomatic, they can be managed with temporary TKI suspension and treatment can resume at the same or a lower dose.[4,6] If the pleural effusion does not resolve with TKI suspension, diuretics or a short course of corticosteroids are options in stable patients. Severe pleural effusions which cause dyspnea may require thoracentesis.[4,6] For recurrent pleural effusions, switching to another TKI should be considered depending on severity, so that CML treatment is not compromised with further dose reductions.[6] There are no specific data regarding nutritional management of Dasatinib-related chylothorax, however there is a rationale to include a medium-chain triglyceride diet as an add-on strategy for large recurrent chylothorax. Similarly, no specific recommendations exist for the management of Bosutinib-related pleural effusions, but it seems reasonable to follow a similar strategy.

Although TKIs have revolutionized the treatment of patients with CML, there are clinically important pulmonary toxicities to be aware of. As far as we know, this is the first report of a Bosutinib-associated chylothorax. Other than older age, the patient had none of the risk factors known to be associated with Dasatinib-related pleural effusion. Therefore, and due to this infrequent presentation, a high clinical suspicion is required.

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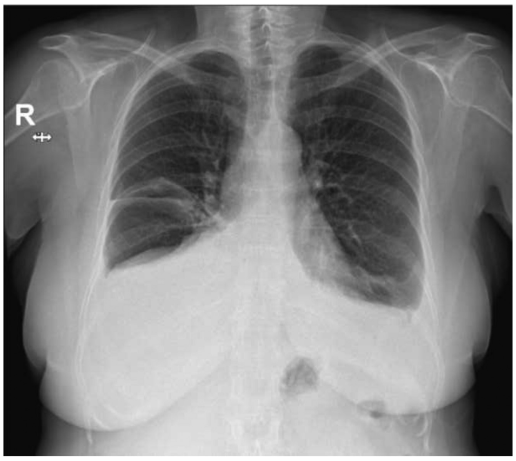


**Fig. 1**

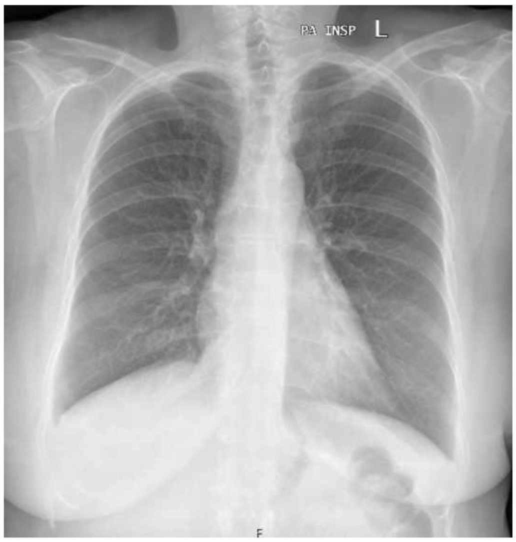


**Fig. 2**

## Patient consent

Written informed consent was obtained from the patient for publication of her clinical details and images.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

# Hypersensitivity pneumonitis, a differential diagnosis of cystic lung diseases

*To the Editor,*

Cystic lung disease (CLD) encompasses a broad set of uncommon disorders that can represent a diagnostic challenge, in part due to an increasing number of diseases with similar presentation.[1] Hypersensitivity pneumonitis (HP) is a complex and heterogeneous interstitial lung disease (ILD) caused by an exaggerated immune response to an inhaled antigen in predisposed individuals.[2]

Cysts have been reported in a small percentage of patients with non-fibrotic HP[3]; they are typically few (less than 5% of lung parenchyma), range from 3 to 25 mm in diameter and are associated with ground-glass opacities. The cysts resemble those of lymphoid interstitial pneumonia and are presumably caused by partial bronchial obstruction due to peribronchiolar lymphocytic infiltrate present in patients with HP.[4,5]

HP diagnosis is often difficult to achieve in part due to nonspecific clinical manifestations but also because radiological and histological patterns can mimic other interstitial and small airway disease. Taking this into account, a minority of patients may present thin-walled lung cysts as the main chest high-resolution computed tomography (HRCT) characteristic, which requires a differential diagnosis with others CLDs.

We present a case of a 54-year-old women, non-smoker, who owned parakeets and goldfinches and lived near a square frequently occupied by pigeons; her personal medical history included chronic kidney disease and dyslipidemia.

She was referred to our outpatient clinic complaining of fatigue and progressive dyspnea with moderate exertion in the previous year. Chest HRCT showed bilateral multiple cysts predominantly in the pulmonary inferior lobes (Fig. 1A,B), some traction bronchiectasis and limited areas of emphysema and mosaic attenuation. Serum specific IgGs were positive for parakeets and pigeons. Complete autoimmune study and VEGF-D were normal. Pulmonary function tests revealed FVC 89,9% and a severe-moderate decrease in DLCO (DLCO 49,4%, KCO of 57,3%). Bronchoalveolar lavage with differential cell count showed 15% of lymphocytes. The nonspecific nature of these results combined with the possibility of other CLD, like lymphocytic interstitial pneumonia, prompted a request for a lung biopsy; the histological examination revealed a cellular interstitial pneumonitis with peribronchiolar pattern and microgranulomas compatible with HP.

Once the diagnosis of HP was established, the patient was advised to avoid any contact with possible allergens and inhaled corticosteroid and bronchodilators were prescribed. Initially, the patient improved and remained stable, reporting only mild dyspnea (mMRC 0-1) during moderate/ hard exercises, especially after being in the square and exposed to pigeons and other birds; over time there was a substantial improvement in the respiratory functions tests, with a FVC of 93%, a DLCO of 66% and a KCO of 80%.

After ten years the patient experienced clinical and functional worsening (FVC 74%, DLCO 48% and KCO 66%) and was put on oral corticosteroids (prednisolone 5mg/day), with favorable response.

Currently, the patient is clinically and functionally stable (FVC 84%, DLCO 55% and KCO 72%); although HRCT shows no changes regarding multiple cysts, there are extensive areas with mosaic attenuation associated with ground glass opacities, traction bronchiectasis and loss of lobar volume (Fig. 1C,D).

Cystic lung diseases are increasingly recognized as a heterogeneous group of ILD with a broad spectrum of outcomes and consequences; the widespread use of HRCT has had an important role in this increased knowledge and understanding.[1] HP is a good prognosis disease often diagnosed by a combination of typical clinical history, positive serum precipitins and a characteristic bronchoalveolar lavage.[3] Cystic HP is a rare form of HP frequently associated with a challenging diagnosis[4]; in these cases, where there is an extensive overlap between clinical and radiographic features, lung biopsy and histopathologic evaluation may be crucial to establishing a confident diagnosis. Faced with this scenario it is important to weigh the need for a secure histopathological diagnosis against the risks of the medical procedure. In recent years and in part due to an increasing demand for histological evaluations in patients with comorbid conditions, poor overall health status, physical frailty and a more severe degree of lung function impairment the role of transbronchial cryobiopsy (TBLC) in ILD patients has grown. Nowadays, compared to surgical lung biopsy, TBLC offers a less

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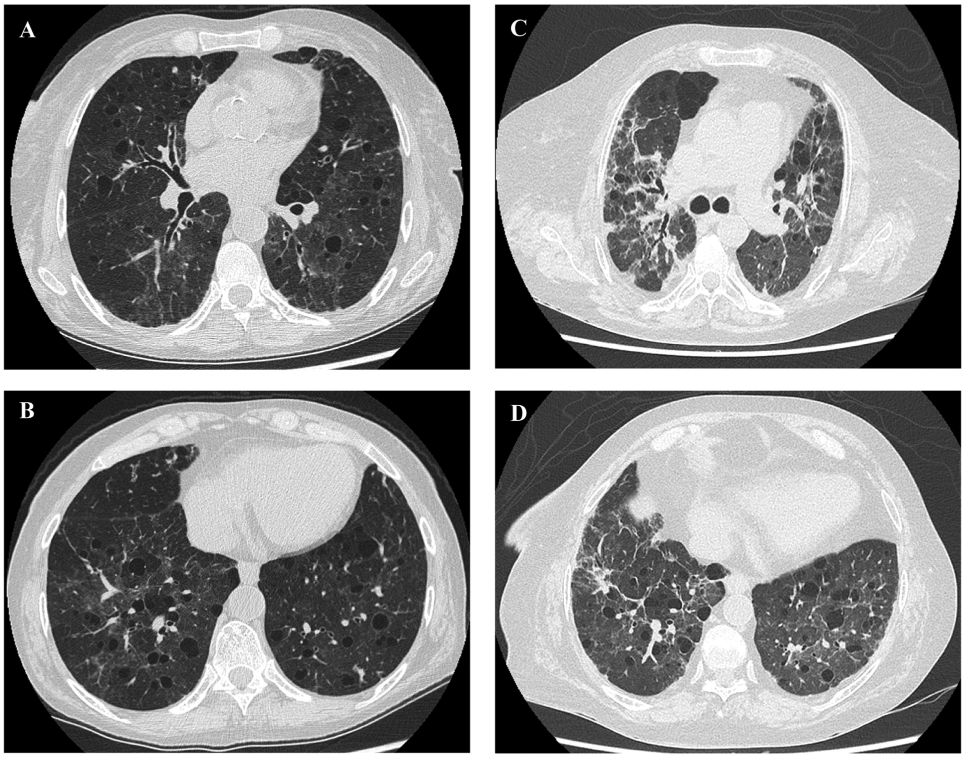


**Fig. 1** HRTC images showing bilateral pulmonary cysts in a hypersensitivity pneumonitis patient at diagnosis (A,B) and after a 10 year follow-up (C,D).

invasive diagnostic method that is almost as accurate as surgical lung biopsy but has a better safety profile.[6]

Furthermore, and similar to other non-cystic forms of HP, cystic HP can slowly progress over time, especially the inflammatory-fibrotic component, even after removing exposures and treating acute exacerbations; interestingly, the cystic component of the disease seems to remain stable.

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## Ethical considerations

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

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## CRediT authorship contribution statement

**E.M. Tinoco:** Writing — original draft, Writing — review & editing. **G. Bermudo:** Methodology, Writing — review & editing. **V. Vicens-Zygmunt:** Methodology, Writing — review & editing. **P. Luburich:** Writing — review & editing. **R. Llatjós:** Writing — review & editing. **M. Molina-Molina:** Writing — original draft, Methodology, Writing — review & editing.

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LETTER TO THE EDITOR

## Predicting lung nodules malignancy

*Dear Editor,*

Jacob, et al.[1] in their original article "Predicting lung nodules malignancy" established a prediction model that can be used to assess the probability of malignancy in a Portuguese population, thereby providing help for the diagnosis of lung nodules. They also argue that their model can help decide the need for a lung biopsy and, thus reduce useless invasive techniques.[1]

Every year, hundreds of thousands of patients are diagnosed with incidentally detected pulmonary nodules, and after lung cancer screening implementation, thousands more will be identified. However, the ideal approach for assessing pulmonary nodules is still vague, since most published guidelines[2] do not clearly state which strategy is accompanied by benefit outcomes, namely in surveillance, need for percutaneous/surgical biopsy or just clinical revaluation.

With the emergence of new approaches such as uniportal and non-intubated video-assisted thoracic surgery (VATS) as well as exciting innovations in intra-operative imaging, VATS not only remains a reliable management option for patients with pulmonary nodules, but also an increasingly attractive one as side effects from anaesthesia and surgical access trauma are further minimized, and surgical accuracy improved.[3]

Nowadays, awake non-intubated uniportal VATS wedge resection is one of the new frontiers in minimal invasive management of patients with solitary lung nodule and already a standard in the armamentarium of some Portuguese thoracic surgeons.[3] The emergence of image guided VATS, hybrid operating theatre and fluorescence thoracoscopy have all contributed to improved precision of VATS lung resection, and are becoming important adjuncts to lung sparing surgery when managing lung nodules diagnosis.

Local anaesthesia awake procedures provide lower costs, shorter hospital stay, shorter anaesthesia and operation times compared to general anaesthesia patients. Other advantages include increased ventilation, fewer respiratory complications, shorter recovery time and it is not traumatic for the immune system which allows for faster recovery.[4]

In conclusion, there is much debate on the best management of solitary pulmonary nodules. Even if they are mostly benign, they may represent an early-stage lung cancer. Minimally invasive surgical removal is probably the best approach to this insidious disease and should help keep VATS at the forefront of the diagnostic and therapeutic algorithm of lung nodules.

## Declaration of Competing Interest

The author has no conflicts of interest to declare.

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PHOTO

# Images: Secondary pulmonary alveolar proteinosis in brucellosis

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Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disease with specific features caused by the alveolar accumulation of surfactant, composed of proteins and lipids, due to dysfunctional pulmonary macrophages.[1] It is classified into two types primary PAP and PAP secondary to leukemia, lung infections, and inhalation of mineral particles or chemical material.[2] Secondary PAP (sPAP) is mainly caused by hematological disorders; sPAP associated with brucellosis is extremely rare. Here, we report a rare case of sPAP in brucellosis in a herdsman. Clinicians should consider the possibility of sPAP when chest radiography reveals abnormal findings and the bronchoalveolar lavage fluid (BALF) is milky.

A 41-year-old male herdsman was hospitalized due to repeated cough and expectoration for 5 years, aggravated with shortness of breath for 5 months. Seven months prior, he was diagnosed with brucellosis with the presentation of lung infection at a local hospital, which improved after one month of treatment, leading to his discharge. His vital signs were normal. Physical examination and routine blood tests revealed unremarkable findings except for the clubbing of his digits. The electrocardiogram was negative, but a lung CT result revealed scattered patchy and large fuzzy shadows (crazy-paving appearance) in the bilateral lungs (Fig. 1A). Simultaneously, bronchoscopy was performed, and the BALF revealed a characteristic milky appearance. Interestingly, after centrifuging the BALF sample at 1500 rpm for 5 min and using the cell pellet to make a smear, a large number of phospholipid-rich protein aggregates were easily observed for microscopic examination (Fig. 1B). Moreover, the Wright−Giemsa staining for the above cell pellet smear showed bluish-purple staining (Fig. 1C). Also, periodic acid-Schiff (PAS) staining revealed PAS-positive proteinaceous material on the smear (Fig. 1D). Moreover, after incubating 100 uL oil red O with 1 mL of the BALF sample for 10 min and centrifuging the stained sample at 1500 rpm for 5 min, we used the cell pellet to make a smear, which clearly revealed an orange aggregate (Fig. 1E). Consequently, PAP was suspected. However, a test for serum anti-granulocyte macrophage colony-stimulating factor (GM-CSF) antibody yielded negative results; therefore, he was diagnosed with sPAP in brucellosis, and received several courses of whole lung lavage, his condition improved, and he was discharged.

Recently, abnormalities in GM-CSF signaling are implicated in the pathogenesis of autoimmune PAP, which accounts for the vast majority of cases. However, sPAP is a rarer disorder, is not dependent on GM-CSF, and mainly occurs owing to a hematological disease.[3]

To our knowledge, this is the first report of PAP with a recent brucellosis history and GM-CSF antibody negativity. The

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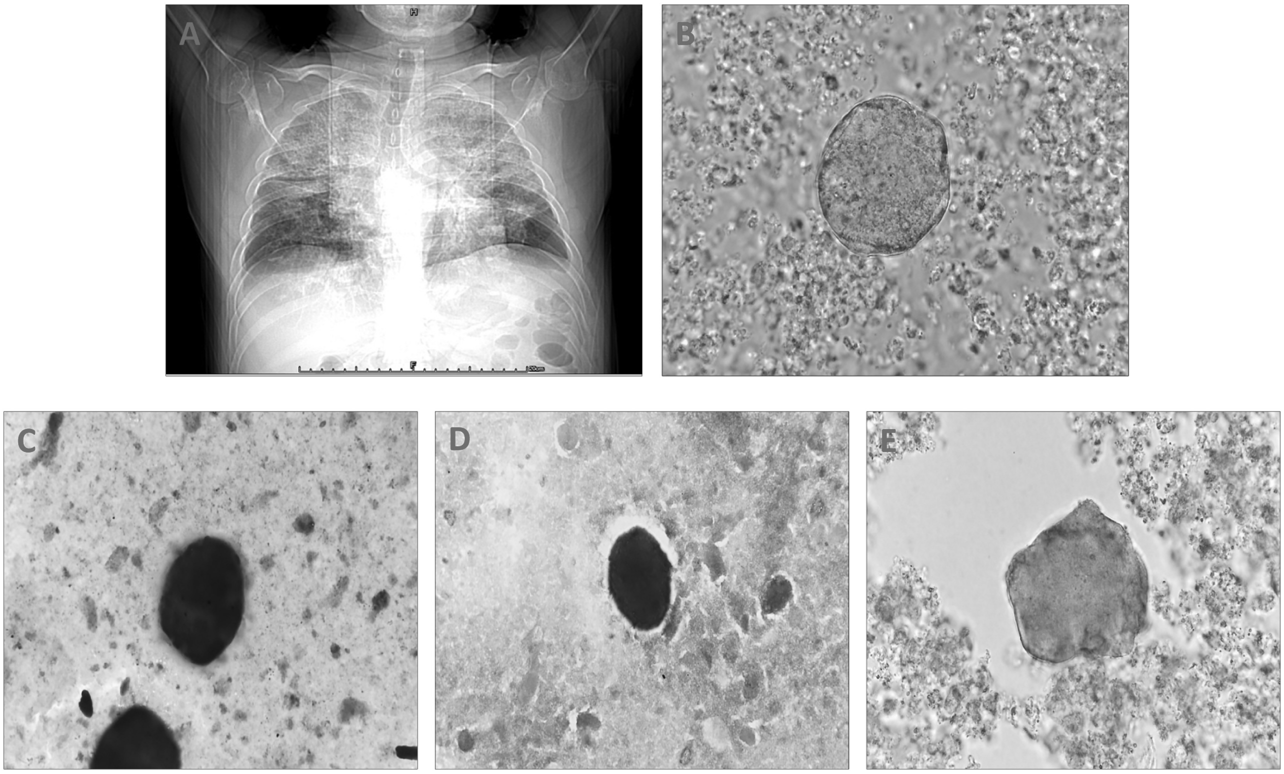


**Fig. 1** Secondary pulmonary alveolar proteinosis in brucellosis in a herdsman. (A) CT reveals a crazy-paving appearance on the bilateral lungs. (B) Phospholipid-rich protein aggregates are clearly observed on the BALF smear through a direct smear for microscopic examination (1000×). (C) Wright—Giemsa staining reveals bluish-purple staining (1000×). (D) Periodic acid-Schiff-positive proteinaceous material is observed (1000×). (E) Oil red O staining reveals an orange aggregate (1000×).

herdsman was diagnosed with sPAP in brucellosis. Moreover, our study suggests that if the crazy-paving appearance on CT or milky BALF are observed and characteristic globules of PAS-positive proteinaceous material are also observed on the BALF, PAP should be considered as a differential diagnosis.

## Ethical considerations

Written informed consent was obtained from this patient.

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## Consent from all authors

All authors reviewed this manuscript and agreed to submit this manuscipt.

## Declaration of Competing Interest

The authors declare that they have no conflict of interest.

## CRediT authorship contribution statement

**L. Yan:** Writing — original draft, Visualization. **Z. Wang:** Formal analysis, Writing — review & editing. **J. Zhao:** Formal analysis, Writing — review & editing. **J. Liu:** Writing — original draft, Formal analysis.

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