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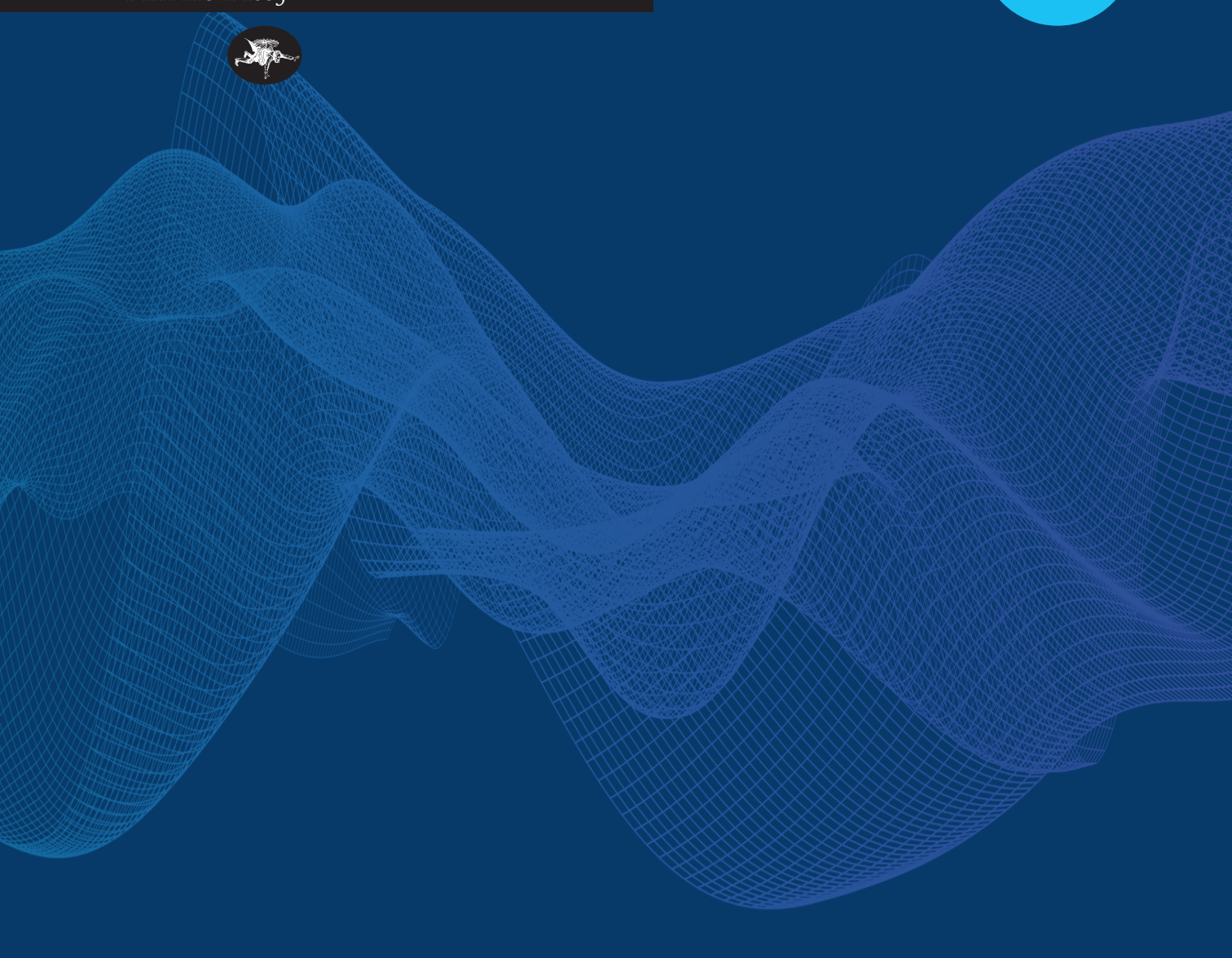

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Prevalence and risk factors of depression in patients with chronic obstructive airway disease: a tertiary care hospital, outpatient setting

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ABSTRACT

Background: Chronic obstructive airway disease (COPD) has been found to be associated with depression. An overlap of COPD and depression may cause poor quality of life and an increase in mortality. A meta-analysis found that the prevalence and risk factors of depression in patients with COPD have high heterogeneity and are limited in tertiary care hospital outpatient settings. This study thus aimed to evaluate the prevalence and risk factors of depression in patients with COPD using personal data in a tertiary care hospital outpatient setting.

Methods: This cross-sectional study included adult patients who were diagnosed with COPD according to the GOLD guidelines, had stable functional status within the past 4 weeks with the same treatment regimen, and had no history of other serious medical or surgical illness. A diagnosis of depression was made according to a score of 11 or higher on the hospital anxiety and depression scale (HADS). The prevalence and predictors of depression were then computed.

Results: The study enrolled and evaluated 150 patients with COPD, out of which 6 (4%) had depression. While the predictive model for depression comprised two factors, only severity of COPD was independently associated with depression. The adjusted odds ratio of severity of COPD was 5.20 (95% confidence interval of 1.75, 15.42; p = 0.003).

Conclusion: The prevalence of depression in patients with COPD in a tertiary care outpatient setting was low, at 4%. According to the study's comprehensive assessment, severity of COPD was the only factor associated with depression in patients with COPD.

Key words: COPD; depression; predictor; severity

Introduction

Chronic obstructive airway disease (COPD), mainly caused by smoking, is a respiratory disease related to several diseases such as obstructive sleep apnea, and psychiatric diseases [1–5]. In one study, compared with 39,431 controls, 39,587 patients with COPD had a higher risk of depression, with an odds ratio of 2.81 (95% confidence interval of 1.69, 4.66) [2]. A systematic review including three studies found that patients with COPD who had depression had a significantly lower quality of life (pooled r = 0.48; p < 0.001) at one year follow up [6].

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Contributions: SC and PS participated in the design of the study, the facilitation for data collection and interpretation of data. SC and KS analyzed data. SC contributed to quality control of data; drafted the manuscript, while all authors have made contributions to revisions of the manuscript. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate: The study protocol was approved by the institutional board review, Khon Kaen Hospital, Khon Kaen, Thailand (KEF60208). All participants signed a written informed consent to participate prior to the study.

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Several studies have found that depression worsens the quality of life in patients with COPD in the mental health category [7,8]. Additionally, being depressed is associated with uncontrolled COPD, with an odds ratio of 2.2 (95% confidence interval of 1.7, 2.8) [9].

The prevalence of depression in patients with COPD has been reported to be 24.6% (95% confidence interval of 20.0-28.6), with a range of 0–42% [10–12]. In patients with COPD, being depressed increased the risk of COPD exacerbation by 2.06 times (95% confidence interval 1.28, 3.31) and mortality by 1.27 times, as well as poor quality of life [13]. Early screening and treatment for depression may be crucial to improve the quality of life and outcomes of patients with COPD [11]. On the other hand, patients with COPD have a 2.81 higher chance of being depressed than matched controls (95% confidence interval 1.69, 4.66) [11]. A database study from Taiwan found that older age, female sex, income, and hospitalization were risk factors for depression in patients with COPD [14]. However, this study did not include personal risk factors such as symptoms or severity of COPD. Several studies have found that personal factors are related with depression, including living alone, using home oxygen therapy, and the COPD Assessment Test (CAT) [15–17]. Having a CAT score of more than 20 was found to increase risk of depression by 7.88 times [17]. A meta-analysis and review found that the prevalence and risk factors of depression in patients with COPD have large heterogeneity (I^2 of 89%) within the limited setting of tertiary care hospitals [11,18]. Given this background, this study aimed to evaluate the prevalence and risk factors of depression in patients with COPD using personal data in a tertiary care hospital outpatient setting.

Methods

This cross-sectional study was conducted at a COPD clinic at Khon Kaen Hospital in Khon Kaen, Thailand. The inclusion criteria were adult patients who were diagnosed with COPD according to the GOLD guidelines, had stable functional status within the past 4 weeks with the same treatment regimen, and had no history of other serious medical or surgical illnesses. Those who had been previously diagnosed with depression, had been treated at the clinic for less than 2 weeks, had any active medical, surgical, or psychiatric diseases, or had been treated with lung surgery or lung transplant were excluded. The study period was between February and March 2020. This study was a part of the psychiatric conditions in patients with COPD project, IRB approval no. KEF60208, at Khon Kaen Hospital, Thailand.

Eligible patients were asked to complete a questionnaire. The questionnaire comprised three parts: baseline characteristics, severity of COPD, and a depression questionnaire. Baseline characteristics included age, sex, education, occupation, income, smoking status, living status, onset of COPD diagnosis, comorbid diseases, and body mass index. Smoking status was categorized as non-smoker, current smoker, or previous smoker. The non-smoker status was defined as having never smoked or having smoked fewer than 100 cigarettes in a respondent's lifetime, while the current smoker status was defined as having smoked more than 100 cigarettes during the respondent's lifetime and still smoking. Those who had smoked more than 100 cigarettes during their lifetime but currently did not were categorized as previous smokers.

Severity of COPD was divided into group A, B, C, and D according to the number of exacerbations per year, number of exacerbations requiring hospitalization per year, dyspnea according to the modified medical research council dyspnea score (mMRC) [19]. Data regarding knowledge about pulmonary rehabilitation was also collected. Finally, the third part of the questionnaire was the hospital anxiety and depression scale (HADS) [20].This questionnaire comprised 7 items on a 3-point Likert scale. The total possible score of the questionnaire for anxiety or depression was 21 points. A score of 11 or more indicates a valid case of depression, with a sensitivity of 85.71% for the validated Thai version of the HADS [21,22]. Additionally, clinical data regarding treatment and COPD status were recorded from participants' medical charts. The primary outcome of this study was the presence of depression.

To calculate sample size, the study took as a baseline the previously reported 30% prevalence of depression in patients with COPD [23]. There were 240 patients treated at the COPD clinic, so using a

confidence interval of 95%, the required sample size was 138 patients.

For statistical analysis, eligible patients were divided into two groups according to the outcome: those with depression and those without. The studied variables were reported as mean (SD) for numerical variables and number (percentage) for categorical variables. Inferential statistics were used to compare the studied variables between those with depression to those without. Factors associated with depression were calculated by using logistic regression analysis. A univariate logistic regression analysis was used to calculate the p value and unadjusted odds ratio for the studied variables. Factors were input into the multiple logistic regression analysis using the backward method to provide the best model [24]. The factors remaining in the predictive model were those with a p of less than 0.20. All analyses were performed using STATA software (College Station, Texas, USA).

Results

There were 151 patients with COPD who met the study criteria. One patient was excluded due to having pulmonary tuberculosis. In total, 150 patients with COPD were enrolled and evaluated. There were 6 patients (4.0%) who had depression. Only one factor was significantly different between those with and without depression (Table 1): severity of COPD. The depression group had a significantly higher proportion of patients with grade-D COPD than those without depression. Grade-D severity of COPD was found more in those with depression than those without (50.0% vs 0.0%; p = 0.003). Notably, a smaller proportion of those with depression lived with their family compared to those without depression (66.7% vs. 91.0%; p = 0.052).

The predictive model for depression thus comprised two remaining factors: living with family and severity of COPD (Table 2). However, only severity of COPD was independently associated with depression. The adjusted odds ratio of severity of COPD was 5.20 (95% confidence interval of 1.75, 15.42; p = 0.003). Living with family members had an adjusted odds ratio of 4.30 (95% confidence interval of 0.53, 34.50; p = 0.169).

Discussion

This study found that only 4% of patients with COPD met the criteria for depression in a tertiary care hospital outpatient setting. The low rate of depression in patients with COPD in this setting may be explained by the diagnostic criteria. This study used a cutoff point of 11 on the HADS to indicate depression, which has a relatively low sensitivity, at 56.0%, but high specificity, at 92.1% [25]. When using a cutoff point of 8 on the HADS, a study from China found the prevalence of depression among COPD patients to be 13.65% [26]. However, the original study of HADS suggested using a score of 11 to indicate definite cases of depression [21]. Interestingly, a meta-analysis found that the prevalence of depression in patients with COPD ranged from 0% to 42%, with a heterogeneity level of 89% [12,18].

This study found that only severity of COPD was an independent factor for being depressed, with an adjusted odds ratio of 5.20 (Table 2). A population-based study from China found that patients with stage III-IV COPD were significantly affected with depression (p < 0.001) [26]. The present study used a more comprehensive assessment of COPD: the ABCD assessment tool. Half of the patients who met the criteria for depression were in category D (Table 2). The Chinese study explained that COPD patients may experience depression due to poor lung function. This present study added that depression in patients with COPD may be due to poor lung function, the number of exacerbations, and COPD symptoms. Another study found that high CAT score or symptom score (included in the ABCD tool) is associated with depression in patients with COPD [17].

As there are heterogeneities of risk factors for being depressed in patients with COPD [18], we compared our study with other two studies conducted in tertiary care settings [27,28]. Both of these previous studies found that symptoms were associated with depression. In one study, the depressed group had significantly higher dyspnea scores (2.6 vs 1.7; p < 0.001) than the non-depressed group [27], while another study found that the daily living scale had an adjusted odds ratio of 1.1 (95% confidence interval of 1.02, 1.2) for being depressed. Once again, the present study

Table 1. Baseline characteristics, severity, and treatment of patients with chronic obstructive pulmonary disease (COPD) categorized by presence of depression.

Factors	No depression n = 144	Depression n = 6	p
Mean (SD) age, years	62.6 (4.8)	66.2 (6.1)	0.913
Male sex	134 (93.0)	5 (83.3)	0.801
Education: college or higher	8 (5.5)	0	0.613
Occupation: farmers	40 (27.8)	1 (16.7)	0.258
Income, Baht per month			
< 15,000	134 (93.0)	6 (100)	0.930
15,000-30,000	8 (5.6)	0	
30,000-50,000	1 (0.7)	0	
> 50,000	1 (0.7)	0	
Smoking status			
Never	14 (9.7)	1 (16.7)	0.267
Current smokers	2 (1.4)	1 (16.7)	
Previous smokers	128 (88.9)	4 (66.7)	
Living status			
With family	131 (91.0)	4 (66.7)	0.052
Alone	13 (9.0)	2 (33.3)	
Mean (SD) age onset of COPD, years	59.4 (9.1)	61.0 (7.6)	0.751
Co-morbid diseases			
Hypertension	31 (21.5)	2 (33.3)	0.464
Dyslipidemia	2 (1.4)	0	0.771
Diabetes mellitus	11 (7.6)	0	0.482
Gout	9 (6.2)	0	0.528
Chronic kidney disease	2 (1.4)	0	0.771
Body mass index, kg/m^2			
<18.5	29 (20.1)	0	0.205
18.5-22.9	71 (49.3)	6 (100)	
23-24.9	18 (12.5)	0	
25-29.9	21 (14.6)	0	
> 30	5 (3.5)	0	
Severity of COPD			
A	59 (47.9)	1 (16.7)	0.003
B	57 (39.6)	2 (33.3)	
C	18 (12.5)	0	
D	0	3 (50.0)	
Current medication			
Salmeterol/fluticazone	129 (89.6)	5 (83.3)	0.627
Budesonide	1 (0.7)	0	0.838
Tiotropium	6 (4.2)	2 (33.3)	0.304
Berodual	92 (63.9)	3 (50.0)	0.956
Salbutamol	4 (2.8)	1 (16.7)	0.063
Theophylline	88 (61.1)	4 (66.7)	0.784
Pulmonary rehabilitation	74 (51.4)	3 (50.0)	0.310

Note. Data presented as number (percentage) unless indicated otherwise.

Table 2. Factors associated with depression in patients with chronic obstructive pulmonary disease (COPD) by logistic regression analysis.

Factors	Unadjusted odd ratio (95% confidence interval)	p	Adjusted Odd ratio (95% confidence interval)	p
Living with family	5.03 (0.84 -30.19)	0.077	4.30 (0.53 - 34.50)	0.169
Severity of COPD	5.54 (1.89 - 16.25)	0.002	5.20 (1.75 - 15.42)	0.003

Note. Data univariate association as determined by logistic regression model backward method: sex, age, body mass index, education, living status, smoking status, onset of COPD, co-morbid diseases, current medication, severity of COPD, and pulmonary rehabilitation.

showed a more comprehensive assessment related to depression in patients with COPD. The two previous studies also found that female sex was associated with depression. Female patients had a higher prevalence of depression compared with male patients (8.8% vs 1.3%; p = 0.044). However, we did not find this association. We input sex in the backward logistic regression analysis, which is more robust than the descriptive statistics used in the previous study, and sex was not retained in the predictive model (Table 2).

There are some limitations in this study. First, we used a high cutoff point (11 on the HADS) to ensure a definite depression diagnosis. This choice may have resulted in a low prevalence of depression in this study. However, this cutoff point has a high sensitivity, at 85.71% [22]. Even with the small numbers of patients with depression, a significant predictor for depression was still found, indicating a true predictor. Second, the results of this study may not apply to other study populations, as the study setting was a tertiary care hospital. Finally, certain comorbid diseases or treatments were not considered, such as obstructive sleep apnea [29–32].

Conclusion

In conclusion, the prevalence of depression in patients with COPD in a tertiary care outpatient setting was low, at 4%. This study's comprehensive assessment identified severity of COPD as the only factor associated with depression in patients with COPD. Further studies are required to confirm the results of this study.

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Original Research Article

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Knowledge and perceptions regarding pulmonary rehabilitation amongst Ecuadorian physicians following COVID-19 outbreak

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ABSTRACT

Background: Pulmonary rehabilitation is already an established technique for patients with chronic respiratory disease, aimed at improving breathlessness, exercise capacity, health status, and well-being. The aim of this study was to assess the knowledge and perceptions about pulmonary rehabilitation post-COVID-19 infection among Ecuadorian physicians. **Methods:** We conducted a cross-sectional online survey-based study using a 27-item questionnaire to assess the knowledge about specific topics related to pulmonary rehabilitation. The sample comprised Ecuadorian physicians who were currently enrolled to an active medical practice that included care to COVID-19 patients. Descriptive statistics were applied for demographic variables of interest. A chi-square goodness of fit test was used to determine whether the observed frequencies of each of the answers per query were within or outside of the expected frequencies by chance. **Results:** In total, 295 participants answered the survey, out of which 57.3% were general practitioners. Most agreed that COVID-19 infected patients must be followed-up with some measurement of respiratory function (81.4%, p=0.000), but only 18.3% (n=54, p=0.000) were aware of specific guidelines related to rehabilitation. 93.6% (n=276, p=0.000) considered that pulmonary rehabilitation provides a benefit, of any kind, to patients with past COVID-19 infection. **Conclusions:** Most physicians considered pulmonary rehabilitation beneficial following COVID-19. However, there is uncertainty on how to adequately follow up patients, complementary tests, and specific guidelines outlining rehabilitative interventions.

Key words: COVID-19, Knowledge, Latin America, perception, physicians, pulmonary rehabilitation

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Introduction

Coronavirus disease 2019 (COVID-19) is a contagious infectious disease that may lead to respiratory, physical, and generalized systemic dysfunction [1]. Asymptomatic infection, moderate illness, or severe pneumonia can cause respiratory failure and mortality [2]. Due to the many respiratory symptoms that can cause severe respiratory distress requiring extended mechanical ventilation, many COVID-19 patients are hospitalized [3,4]. In acute and recovery phases, severely and critically ill COVID-19 patients have pulmonary insufficiency, cognitive impairment, and dyskinesia, according to the Handbook of COVID-19 Prevention and Treatment [5]. Pulmonary rehabilitation may assist these patients by improving respiratory, mental, and physical symptoms, and minimizing consequences [5].

The American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement on pulmonary rehabilitation was first published in 2006 and defined pulmonary rehabilitation as "a comprehensive intervention based on a thorough assessment of the patient followed by patient-centric therapies that include, but are not limited to, exercised training, behavior change, and education designed to improve the physical and mental condition of people with respiratory disease and to promote the long-term adherence to health-enhancing behaviors" [6,7].

It is likely that patients with COVID-19 will need pulmonary rehabilitation during or directly after the hospitalization period, an approach recommended by the World Health Organization [8]. However, there is limited data on the safety and efficacy of pulmonary rehabilitation measures among post-COVID-19 patients. Similarly, healthcare providers may be unaware of the follow up after COVID-19 pneumonia, goals, benefits, indications, and procedural administration of rehabilitative interventions in daily practice, while the burden of COVID-19 patients continues to rise daily [9]. With this study our aim was to assess the knowledge and perceptions about pulmonary rehabilitation post-COVID-19 infection among Ecuadorian physicians.

Methods

Study design and participants

We conducted a cross-sectional online survey-based study using a non-probability convenience sampling method where 295 physicians where recruited. The sample comprised Ecuadorian physicians who, regardless of their specialty, were currently enrolled to an active medical practice that includes care to COVID-19 patients. Physicians who expressed no interest in participating in the study, physicians whose informed consent could not be obtained and/or physicians who initially consented but subsequently revoked their consent were excluded. The participants anonymously answered a non-validated 27-item questionnaire, designed by an expert panel of pulmonologists, to assess what they knew about specific topics of pulmonary rehabilitation after a COVID-19 infection based on the current literature and evidence-based recommendations [4-7,10-15].

Questionnaire

The first part of the questionnaire consisted of demographic information of each participant. The second part included 27 items which were grouped in domains regarding specific topics about pulmonary rehabilitation. The items were grouped as follows:

1. Follow up after COVID-19 pneumonia: Q1-Q4
2. Goals of pulmonary rehabilitation: Q5-Q6
3. Benefits of pulmonary rehabilitation: Q7-Q12
4. Indications of pulmonary rehabilitation: Q13-Q23
5. Procedure and administration of pulmonary rehabilitation: Q24-Q27.

For questions Q1-6 and Q19-26 participants could choose "true", "false" or "I don't know", while for questions Q7-18 and Q27 the answers were eithers "yes", "no" or "I don't know". Each question, grouped by topic, with its correct answers can be visualized in the Supplementary Table S1.

Statistical analysis

This study applies descriptive statistics for demographic variables of interest. Continuous data is presented as means and standard deviations if normality

is determined, whereas median and interquartile range are selected if the data does not follow a normal distribution; nominal data is presented as frequencies and percentages. Prior to be analyzed, participants were categorized according to the answers provided as "answered correctly" (if participant's answer matched the correct answer as per seen in Supplementary Table S1) or "answered incorrectly" (if participant's answer did not match the correct answer as per seen in Supplementary Table S1, including if participant chose "I don't know"). We also analyzed the correlation between specialty and years of experience on number of correct answers overall and per domain (Supplementary Table S2). We used the chi-square goodness of fit test to determine whether the observed frequencies of each of the answers per query were within or outside of the expected frequencies by chance. A Fisher's exact test was applied in the case of assumption violation. The statistical analyses were conducted using SPSS for Windows (version 25.0; SPSS Inc, Chicago, Illinois). A $p<0.05$ was regarded as statistically significant.

Results

Descriptive statistics of demographics

Out of the 295 participants, 52.5% (n=155) were males. Most physicians were general practitioners (57.3%, n=169), while 42.7% (n=126) had specialized in a medical field. Regarding specialties, the most common were pulmonary medicine and critical care (10.2%; n=30) and internal medicine (8.5%, n= 25). The sample's average years of experience was 13.0 (SD, 11.6). Table 1 summarizes sample's demographics. With respect to the questionnaire, the median percentage of correct answers was 67.0% (IQR, 20.0%). The general percentual score did not follow a normal distribution as revealed by Shapiro-Wilk test ($p=0.000$). The left skewed (S_{KP} = - 0.688) distribution for total percentage score of correct answers is depicted in Figure 1. The median general and domain scores are included in Table 1. The response rate was of 59%.

Table 1. Demographic information of surveyed population (n=295).

Characteristics	% (n)
Gender	
Male	52.5 (155)
Female	47.5 (140)
Years of practice (mean, SD)	13.0 (11.6)
Medical specialty	42.7 (126)
Pulmonary medicine and critical care	10.2 (30)
Internal medicine	8.5 (25)
Pediatrics	7.8 (23)
Allergology	2.4 (7)
Cardiology	1.4 (4)
Anesthesiology	1.4 (4)
Physical medicine and rehabilitation	0.7 (2)
Other	24.6 (31)
Answered correctly (median, IQR)	18.0 (5.0)
Follow up after COVID-19 pneumonia (Q_1-Q_4)	2.0 (1.0)
Goals of pulmonary rehabilitation (Q_5-Q_6)	2.0 (0.0)
Benefits of pulmonary rehabilitation (Q_7-Q_{12})	4.0 (1.0)
Indication of pulmonary rehabilitation (Q_{13}-Q_{23})	7.0 (2.0)
Procedure and administration of pulmonary rehabilitation (Q_{24}-Q_{27})	3.0 (1.0)

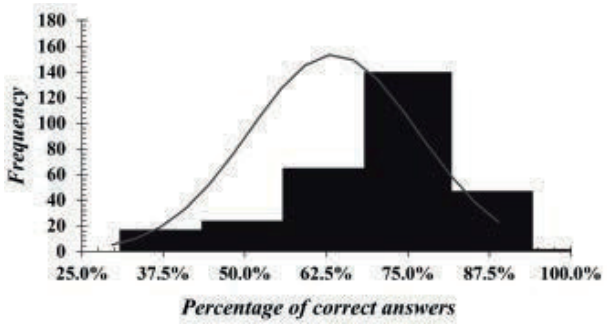

Figure 1. Distribution of total percentage score of correct answers.

Follow up after COVID-19 pneumonia

Most participants agreed that COVID-19 infected patients must be followed up with a measurement of respiratory function (81.4%, n=240; $\chi^2(1) = 116.017$, p=0.000) and exercise capacity (78.0%, n=230; $\chi^2(1) = 92.288$, p=0.000) at 12 weeks after hospital discharge (Figure 2, Supplementary Table S1). However, less than half (43.4%, n=128; $\chi^2(1) = 5.156$, p=0.000) of the sample asserted that radiological features in community acquired pneumonia are followed-up sooner than that for COVID-19 pneumonia. It was also worth noting that 18.3% (n=54; $\chi^2(1) = 118.539$, p=0.000) assumed that there are specific guidelines to follow up for rehabilitation after hospitalization for COVID-19 infection according to disease severity.

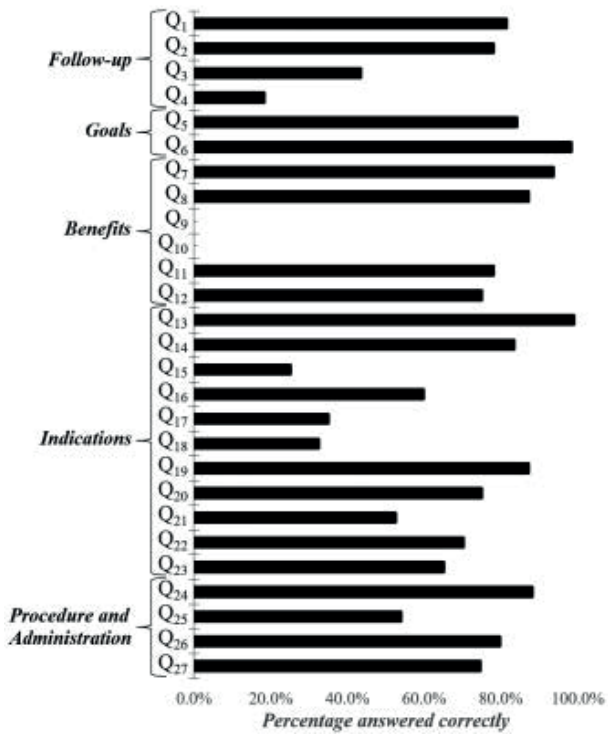

Figure 2. Percentage of participants who "answered correctly" each query per domain.

Goals of pulmonary rehabilitation

About 8 out of 10 (84.1%, n=248; $\chi^2(1) = 136.953$, p=0.000) physicians were certain that the short-term goal of pulmonary rehabilitation is to improve dyspnea, and nearly all the sample (98.3%, n=290; $\chi^2(1) = 275.339$, p=0.000) were acquainted with the fact that improvement in the patient's quality of live is the long-term goal (Figure 2, Supplementary Table S1).

Benefits of pulmonary rehabilitation

In general, 93.6% (n=276; $\chi^2(1) = 223.895$, p=0.000) physicians considered that pulmonary rehabilitation provides a benefit, of any kind, to patients with past COVID-19 infection. Roughly 9 in 10 (87.1%, n=257; $\chi^2(1) = 162.580$, p=0.000) participants claimed that pulmonary rehabilitation reduces morbidity in these patients. It is noteworthy, however, that when asked by disease severity groups, all the sample incorrectly assumed that this reduction in morbidity is observed in asymptomatic (100%, n=295) and mildly ill subjects (100%, n=295). Nevertheless, most physicians were conscious that this reduction in morbidity would indeed benefit patients with moderate (78%, n=230; $\chi^2(1) = 92.288$, p=0.000) and severe disease (74.9%, n=221; $\chi^2(1) = 73.251$, p=0.000) (Figure 2; Supplementary Table S1).

Indications of pulmonary rehabilitation

Nearly all the respondents considered complementary test to be useful to identify which patients with COVID-19 infection require pulmonary rehabilitation (99.0%, n=292; $\chi^2(1) = 283.122$, p=0.000); spirometry (83.4%, n=246; $\chi^2(1) = 131.556$, p=0.000) and the six-minute walk test (59.7%, n=176; $\chi^2(1) = 11.014$, p=0.001) were the best rated parameters in this regard. In contrast, a third or less reflected maximal

inspiratory pressure (34.9%, n=103; $\chi^2(1) = 26.851$, p=0.000), maximal expiratory pressure (32.5%, n=96; $\chi^2(1) = 35.963$, p=0.000) and DL_{CO} (25.1%, n=74; $\chi^2(1) = 73.251$, p=0.000) as useful methods to serve as indicators for referral to pulmonary rehabilitation. Also, if pulmonary rehabilitation was to be delivered in an inpatient setting, 65.1% (n=192; $\chi^2(1) = 26.851$, p=0.000) agreed that a focused pulmonary assessment needs to be conducted. Concerning specific scenarios, 87.1% (n=257; $\chi^2(1) = 162.580$, p=0.000) physicians asserted that COVID-19 infected patients with a moderate or severe course should receive pulmonary rehabilitation until 12 weeks after hospital discharge, 74.9 % (n=221; $\chi^2(1) = 73.251$, p=0.000) agreed that an associated pulmonary or neuromuscular comorbidity warrants physiotherapy for airway clearance even in mild disease and 70.2% (n=207; $\chi^2(1) = 48.003$, p=0.000) reaffirmed that hospitalized patients should receive rehabilitation at the bedside until safe for discharge to the home environment.

Procedure and administration of pulmonary rehabilitation

As a complex and long-term therapy, 88.1% (n=260; $\chi^2(1) = 171.610$, p=0.000) were thoughtful on how pulmonary rehabilitation requires administration by an interdisciplinary team. In terms of remote pulmonary rehabilitation, half of the participants (53.9%, n=159; $\chi^2(1) = 1.793$, p=0.181) were informed that the recommended goal of remote pulmonary rehabilitation is 2-3 on the Borg dyspnea scale score or mild to moderate breathlessness with exercise. Most of the sample recognized that pulmonary rehabilitation can be done at home with appropriate tools (79.7%, n=235; $\chi^2(1) = 103.814$, p=0.000) and that various exercises are recommended multiple times a week (74.6%, n=220; $\chi^2(1) = 71.271$, p=0.000).

Discussion

Due to COVID-19, the awareness and overall knowledge of pulmonary rehabilitation has become a topic of recent interest across several areas of medicine from primary care to highly specialized fields. In our study, the goal was to evaluate the knowledge and perceptions physicians had about the role of pulmonary rehabilitation in patients previously infected with COVID-19. In general, most participants agreed that COVID-19 patients should be followed after the initial infection with some measurement of respiratory function and exercise capacity, but very few were aware of the existence of specific guidelines on the subject. In a previous study exploring the perceptions of physicians towards pulmonary rehabilitation referrals in China conducted pre pandemic, Hao and colleagues found that while most of the respondents had previously heard about pulmonary rehabilitation and many knew the practice, very few referred patients for rehabilitation [9]. Therefore, raising awareness about the role of pulmonary rehabilitation and increasing the diffusion of evidence-based guidelines on the topic is an important area to begin addressing this issue.

Pulmonary rehabilitation has the goal to improve respiratory dynamics, counteract musculoskeletal immobilization, reduce the onset of subsequent complications/disabilities, and improve the quality of life [13]. In the case of COVID-19 survivors, a previous study found an improvement in the 6 minute walk test (6MWT), functional vital capacity (FVC), and the mental component of the SF-36 health survey among patients who completed a 3-week pulmonary rehabilitation program [16]. Another study by Zampogna and colleagues reported improvement in the short physical performance battery (SPPB) and six-minute walking distance assessed with the Barthel index among COVID-19 patients that required assisted ventilation or oxygen, and underwent pulmonary rehabilitation [17]. Consistent with existing literature, a majority of participants in our study agreed that the goals of pulmonary rehabilitation include improving patient's dyspnea and quality of life, while also reducing the morbidity associated with the virus.

Perhaps one area that is unclear at the moment is related to complementary testing to identify which patients are more likely to benefit from pulmonary rehabilitation. In our study, a majority considered assessing the physiological function of the respiratory system through spirometry, and the waking distance as useful indicators. However, less than a third considered the diffusing capacity for carbon monoxide (DL_{CO}) as a useful test. Earlier systematic reviews and meta-

analyses have found considerable lung dysfunction in COVID-19 patients after infection [18]. Among these patients, 39% showed altered DL_{CO}, while 15% presented restrictive respiratory patterns. Additionally to spirometry and DL_{CO}, the 6MWT may be useful to monitor changes in pulmonary function [19]. It is a simple, reproducible, and inexpensive test. Patients with severe pneumonia after recovery from COVID-19 had a non-statistically significant shorter mean 6MWT, according to a previous prospective study [20]. It is still unclear which role the 6MWT will play in following up COVID survivors, but it may provide information on a patient's ability to accomplish daily activities, and its correlation with peak oxygen uptake might help identify alterations in lung function [21].

Finally, most respondents in our study considered that pulmonary rehabilitation requires an interdisciplinary team but can also be done at home given the appropriate conditions. However, there are concerns about the lack of access to rehabilitative programs, either in-hospital, at the primary care, or community care level that have been documented in the past. In Portugal, it was estimated that roughly 0.5-2% of residents had access to pulmonary rehabilitation services, and this situation only aggravated since the beginning of the pandemic in 2020 [14]. Many programs were affected following international and national recommendations related to social distancing and contact prevention, while some shifted to remote care using telehealth solutions. This is an interesting area to explore in the future, where self-management or education modules in the realm of telerehabilitation may be adopted for both patients and healthcare providers [17,22]. Whether pulmonary rehabilitation is delivered remotely or inperson, it should preserve the basic components, including i) exercise training; ii) education; and iii) behavior change, and an essential understanding of the selection criteria, emergency plans, outcome measures, intervention design, and technology/equipments [14].

Strengths and limitations

In light of our findings, there are several limitations worth mentioning. Our study assessed knowledge and perceptions towards pulmonary rehabilitation using a non-validated survey. Since the survey is based on physicians' self-declaration, there may be differences in perceiving and expressing their current understanding on pulmonary rehabilitation for post-COVID-19 patients. Since the majority of participants had no specialization in any medical field, and roughly 10% were specialized in pulmonary medicine or critical care, familiarity with pulmonary rehabilitation may have been limited in the sample. Therefore, our results may not be generalizable to all physicians, and can differ from the perceptions expressed in other regions. However, to the best of our knowledge, our study is one of the first to assess specific perceptions and knowledge towards pulmonary rehabilitation among Ecuadorian physicians, providing valuable insight for designing future interventions.

Conclusions

COVID-19 has put under pression and will continue to challenge healthcare systems globally, including rehabilitation provision. Most physicians in our research considered pulmonary rehabilitation effective, however, patient follow up, supplementary testing, and rehabilitative therapeutic protocols are unclear. Increasing healthcare professionals' understanding and use of pulmonary rehabilitation may improve COVID survivors' symptoms and quality of life. Therefore, we encourage international societies to review and establish patient rehabilitation programs and promote awareness and expertise among healthcare personnel who will manage these patients.

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Online supplementary material

Supplementary Table 1. Percentages and frequencies of participants who "answered correctly" and "answered incorrectly" on each of the questions per domain.

Supplementary Table 2. Correlation between specialty and years of experience on number of correct answers overall and per domain.

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Original Research Article

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Gas exchange abnormalities in Long COVID are driven by the alteration of the vascular component

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ABSTRACT

Background: There are uncertainties whether the impairment of lung diffusing capacity in COVID-19 is due to an alteration in the diffusive conductance of the alveolar membrane (Dm), or an alteration of the alveolar capillary volume (Vc), or a combination of both. The combined measurement DL_{NO} and DL_{CO} diffusion, owing to NO higher affinity and faster reaction rate with haemoglobin compared to CO, enables the simultaneous and rapid determination of both Vc and Dm. The aim of the present study was to better identify the precise cause of post-COVID-19 diffusion impairment.

Methods: Using the combined NO and CO gas transfer techniques (DL_{NO} and DL_{CO}), it is possible to better understand whether gas exchange abnormalities are due to membrane or alveolar capillary volume components. The present study was aimed at evaluating pulmonary gas exchange one year after severe COVID-19.

Results: The cohort included 33 survivors to severe COVID-19 (median age 67 years, 70% male) with no pre-existing lung disease, who underwent clinical, lung function and imaging assessments at 12 months due to persistence of respiratory symptoms or radiological impairment. The gas exchange abnormalities were mainly determined by the compromise of the vascular component as demonstrated by vascular pattern of gas exchange impairment (*i.e.,* $DL_{NO}/DL_{CO} \geq 110\%$, 76% of the sample), and by a reduction of the Vc (73%), while the Dm was reduced only in 9% of the entire sample. We did not find a correlation between the gas exchange impairment and the extent of the chest CT alterations (DL_{CO} p = 0.059 and DLNO p = 0.054), which on average were found to be mild (11% of the parenchyma).

Conclusion: In COVID-19 survivors who are still symptomatic or have minimal CT findings at one year, gas exchange abnormalities are determined by impairment of the vascular component, rather than the diffusive component of the alveolar membrane.

Key words: COVID-19, gas exchange, DL_{CO}, DL_{NO}, capillary volume, alveolar-capillary membrane.

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Contributions: GI, CC, LN, FR, PB, SS and FdM wrote the manuscript. AC, AA, SV and GC read and corrected were needed. All authors took part in the discussion leading up to the manuscript. The authors read and approved the final manuscript.

Ethic approval: This observational study was approved by the local Ethics Committee (Comitato Etico di Bergamo, Italy. N°37/2020); Informed consent was obtained from the patients.

Availability of data and material: Not applicable.

Conflict of interest: The authors declare that they have no competing interests.

Introduction

The sequelae of SARS-CoV-2 infection are an element of concern. Many studies show an increased prevalence of pulmonary function abnormalities at 3 and 6 months, in particular a mild impairment of pulmonary gas diffusion is described. This is often associated with persistence of radiological abnormalities, such as the presence of ground-glass areas or reticular opacities at chest CT scan [1, 2]. The pulmonary diffusing capacity of carbon monoxide (DL_{CO}) is the most sensitive pulmonary function test in the assessment of gas exchange at the alveolar-capillary membrane. Specifically, this examination is determined by two resistances arranged in series: the pulmonary membrane diffusing capacity (Dm) for carbon monoxide (CO) and the rate of carbon monoxide uptake by blood in the alveolar capillary volume (Vc). Notably, both components are involved in SARS-CoV-2 infection [3]. However, a reduction of the classical DL_{CO} is mainly driven by the vascular compartment, with the potential risk of shadowing alterations of Dm in the study of COVID-19 sequelae. This is, because DL_{CO} can better measure the defects in microvascular alterations while DL_{NO} is affected more by the membrane defects [4]. To overcome this limitation, it is possible to evaluate the transfer of nitric oxide (DL_{NO}) in association with DL_{CO}. Indeed, nitric oxide (NO) has a higher affinity and faster reaction with haemoglobin than CO, making the contribution of the second resistance negligible (i.e., NO uptake by blood) and eventually allowing the isolated measurement of the diffusive component (i.e., Dm). Thus, using the combined NO and CO gas transfer techniques, it is possible to obtain the evaluation of Dm and Vc in a single breath experiment [3, 4]. In COVID-19 survivors, radiological studies have shown that DL_{CO} is negatively correlated with the rate of lung volume involvement [1]. Furthermore, 3-6 months after infection, DL_{NO} and DL_{CO} inversely correlated with persisting CT ground glass opacities, but these were more frequently associated with DL_{NO} than DL_{CO} decrease. These data suggest that an impairment of DL_{NO} may be present during the recovery from COVID-19, possibly due to loss of alveolar units with alveolar membrane damage, but relatively preserved capillary volume [5].

The aim of the present study was to evaluate gas exchange one year after COVID-19, using the combined DL_{NO}/DL_{CO} technique in patients with radiological abnormalities or symptoms that persist 12 months after discharge; moreover, the correlation between gas exchange impairment and CT radiological findings was investigated.

Methods

This observational study was approved by the local Ethics Committee (Comitato Etico di Bergamo, Italy. N°37/2020). Informed consent was obtained from the patients.

Patients

The cohort under study includes severe COVID-19 survivors without pre-existing pulmonary disease admitted to our hospital (Papa Giovanni XXIII, Bergamo, Italy) between February 25 and May 2, 2020 (first wave), who underwent repeated clinical and pulmonary function evaluation up to 12 months after discharge. Patients with persistent symptoms (*i.e.*, dyspnea with a mMRC≥1 or cough) and/or with the persistence of chest-CT abnormalities have been enrolled. The exclusion criteria were: (a) suboptimal pulmonary function tests (PFT) reproducibility, (b) low-quality CT data, and c) onset of severe COVID-19 unrelated complications after discharge.

Procedures

Spirometry and plethysmography were assessed using the Platinum Elite Body Plethysmograph equipped with rapid gas analysers (MGC Diagnostics Corporation, USA), while the simultaneous measurement of DL_{NO} and DL_{CO} was assessed with the HypAir System (Medisoft, Belgium) with a breath-hold of 4 seconds, using the following gas mixtures: He 14%, CO 0.3%, O_2 21% balanced with N_2, and 40 ppb NO balanced with N_2 for DL_{NO}. DM and Vc were directly obtained from DL_{NO}, assuming a ΘNO of 4.5 mL blood/min/mmHg, and directly measuring ΘCO from Hb and PAO_2 [3]. All tests were performed by trained respiratory technicians following current ATS/

ERS standards. Pulmonary function tests (PFTs) results were interpreted by two experienced pulmonologists (CC and GI), in accordance with current guidelines at time of testing [6]. Standard PFTs parameters included: forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV_1), FEV_1/FVC ratio, and total lung capacity (TLC). Diffusing capacity for nitric oxide (DL_{NO}), diffusing capacity for carbon monoxide during combined testing (DL_{CO}no, DL_{CO} from here on), alveolar membrane diffusing capacity (DM), pulmonary capillary blood volume (VC), and alveolar volume during combined testing (VAno, VA DL_{NO} from here on) were recorded. The dyspnea intensity was assessed using the modified Medical Research Council (mMRC) dyspnea scale.

Unenhanced Chest CT scans were acquired supine at complete inspiration, covering the lung bases to the apex, using a 64- or 16-slice scanner (Brilliance 64 and MX 16-slice; Philips Medical Systems, Best, Netherlands) with the parameters previously specified [1]. Qualitative evaluations included the assessment of the presence of consolidation.

Chest CT scans were analyzed using the 3D Slicer open-source software, version 4.8.1 (https://www.slicer.org), which allowed the quantification of the percentage of compromised lung tissue. As formerly described [1], the lung parenchyma was first segmented and separated from the airways via the Chest Imaging Platform extension and the Airway Segmentation Module. The regions with an image density over -800 HU were finally classified as pathological. A manual editing step addressed any inaccuracies before the measurement.

Statistical Analysis

Standard PFTs parameters were expressed as absolute values, and z-scores and considered impaired when lower than the lower limit of normal range (LLN) defined by the Global Lung Function Initiative reference equations for spirometry and lung volumes. Combined DL_{NO}/DL_{CO} values were expressed as absolute values and z-score and considered impaired when lower than the LLN defined by most recent reference equations by Zavorsky et al [7]. The severity of DL_{CO} and DL_{NO} impairment was evaluated also based on z-score results, assuming a prior evidence of lung disease [7]. DL_{CO} and DL_{NO} ratio, expressed as absolute and as a percentage of the median value taken from a reference healthy population [3], was used to classify the prevalent combined DL_{NO}/DL_{CO} result (vascular pattern if more than 110%, interstitial pattern if less than 95%, indeterminate pattern for values in between) [8]. Descriptive statistics were used to summarize the baseline characteristics of patients. Continuous variables were expressed as median and interquartile range (IQR). Comparison of continuous variables was conducted using the Mann-Whitney U test. Categorical variables were expressed as absolute counts and percentages and were analyzed with Fisher's exact test. Correlation was assessed using the Pearson's correlation coefficient. All reported p are two sided and a $p < 0.05$ was considered significant. Statistical analysis was done using SPSS 27.0 (SPSS, Inc., Chicago, IL, USA).

Results

This study included 33 patients. Anthropometric and clinical data are reported in table 1, while functional and imaging characteristics of the patients are showed in table 2. Median age was 67 (61-70) and males were 70% of our sample. One patient showed obstruction in the year after enrolment (3%), 14 (54%) had reduced DL_{CO}, and median DL_{CO} values were mildly reduced (DL_{CO} z-score value -1.64 (-2.55 - -0.85)). DL_{CO} reduction was mild in 49%, moderate in 6% and severe in any patients. Median values for DL_{NO} were within normal range in our sample (DL_{NO} z-score -1.55 (-2.53 - -0.62)). Fifteen patients (46%) showed a DL_{NO} reduction, that was mild in 39% and moderate in 6% of pathologic cases (no severe alteration), while 14 (42%) had both DL_{CO} and DL_{NO} values reduced. VA was reduced in 10 (30%) patients, while FVC and TLC in 1 and 4 cases, respectively (3% and 12%).

Median Vc was mildly reduced, with z-score values of -2.12 (-3.12 - -1.59), and impaired in 24 patients (73%), while Dm median value was normal, with z-score 0.30 (-1.04 – 1.61), and lower than the LLN in 3 (9%).

Figure 1 shows single cases data of Vc z-score

Table 1. Patients' anthropometric characteristics, symptoms score and biochemistry data (whole sample and according to gas exchange pattern).

	All patients	Interstitial and indeterminate pattern	Vascular pattern	P
Number	33	8	25	
Age (years)	67.0 (61.0-71.0)	62.0 (55.5 – 66.8)	67.0 (63.0 – 72.0)	0.107
Males (%)	70	88	64	0.212
Number of days from admission to testing date (days)	491 (475 – 537)	501 (477 – 556)	491 (475 – 538)	0.578
Height (cm)	170 (164-177)	173 (170 – 179)	169 (161 – 177)	0.150
Weight (kg)	84 (72 – 95)	106 (84 – 122)	80 (72 – 88)	0.022
BMI (kg/m^2)	29.1 (26.1-33.4)	33.4 (28.6 – 39.7)	28.0 (25.7 – 32.2)	0.067
Hb (mg/L)	14.5 (13.6-15.7)	16.2 (14.7 – 16.9)	14.4 (13.3 – 15.1)	0.012
D-dimer (ng/ml)	367 (277-593)	318 (215 – 463)	466 (277 – 709)	0.331
mMRC (n)	1 (0-1)	1 (0-2)	1 (0-1)	0.206

Data are reported as median (IQR) (continuous/numerical variables) or number (%) (binary/categorical variables). Abbreviations: mMRC = modified Medical Research Council.

and Dm z-score in patients grouped according to the DL_{CO} status. Eighteen patients (55% of the whole sample) showed a reduced DL_{CO}, while 15 patients (45%) showed a normal DL_{CO}, seven out of which with Vc under the LLN. Four patients demonstrated a contemporary reduction of both Dm and Vc.

Gas exchange abnormality pattern and correlation with imaging

The radiological impairment detectable with long-term chest CT scan was low, about 10% of the overall parenchyma (Table 2). We found a close correlation between DL_{CO} and DL_{NO} (figure 1), with r = 0.95 (p < 0.001). Correlation between DL_{CO}, DL_{NO} and the amount of abnormal CT involvement resulted modest and non significant in both cases (r = -0.332, p = 0.059, and r = -0.338, p = 0.054, respectively). Eight patients (24% of the whole sample) demonstrated an interstitial or indeterminate pattern (*i.e.,* a DL_{NO}/DL_{CO}<110%), while 25 (76%) a vascular pattern of gas exchange (*i.e.,* DL_{NO}/DL_{CO}≥110%) (Table 1). The only significant differences between these two groups included Vc absolute value, lower as expected in patients with vascular impairment, the level of haemoglobin, significantly reduced in patients with the vascular pattern, BMI, lower in those with vascular pattern and VA z-score, abnormally low in the non-vascular pattern group. We found no significant correlation between the values of DL_{NO}/DL_{CO} % and the CT percent involvement, as showed in figure 2.

Discussion

The main findings of this study, aimed at evaluating the one-year effects of COVID-19 infection on gas exchange and correlation with CT imaging abnormalities, can be summarized as follows: (a) DL_{CO} has a high sensitivity in the assessment of long-term COVID-19 sequelae, with 54% of patients either symptomatic or with radiological abnormalities 12 months after infection still having impairment of this test; (b) however, most patients (76%) demonstrates a vascular pattern of gas exchange (*i.e.,* DL_{NO}/DL_{CO}≥110%) and there are patients with normal DL_{CO} showing a significant decrease in capillary volume, which is the most common impairment in these patients (73%), while Dm is reduced only in 9% of the whole sample; (c) there is no correlation between gas exchange abnormalities and the extent of CT abnormal involvement which was on average mild.

The predominant histological pattern of lung injury in COVID-19 deceased patients is diffuse alveolar damage, often associated with hyaline membrane formation and atypical hyperplasia of pneumocytes. How-

Table 2. Patients' lung function and imaging (whole sample and according to gas exchange pattern).

	All patients	Interstitial and indeterminate pattern	Vascular pattern	P
Number	33	8	25	-
FVC (L)	3.69 (3.12 – 4.19)	3.75 (3.25 – 4.24)	3.61 (3.01 – 4.19)	0.578
FVC (z-score)	-1.13 (-0.88 – 0-61)	-0.91 (-1.33 – 1.03)	0.06 (-0.60 – 0.61)	0.107
FEV_1 (L)	2.84 (2.40 – 3.43)	3.20 (2.35 – 3.60)	2.75 (2.40 – 3.43)	0.606
FEV_1 (z-score)	-0.07 (-0.62 – 0.56)	-0.58 (-0.94 – 0.21)	0.07 (-0.59 – 0.77)	0.098
FEV_1/FVC (n)	0.80 (0.73 – 0.85)	0.79 (0.73 – 0.86)	0.80 (0.73 – 0.85)	0.885
FEV_1/FVC (z-score)	0.12 (-0.62 – 0.92)	0.29 (-1.57 – 1.35)	0.12 (-0.47 – 0.92)	0.984
TLC (L)	5.98 (5.09 – 6.48)	5.68 (5.29 – 6.24)	6.02 (4.91 – 6.62)	0.821
TLC (z-score)	-0.29 (-1.14 – 0.52)	-1.31 (-1.98 – 0.20)	0.00 (-0.77 – 0.58)	0.107
VA (L)	5.40 (4.53 – 5.86)	5.17 (4.50 – 5.55)	5.40 (4.52 – 5.93)	0.696
VA (z-score)	-0.84 (-1.90 – 0.11)	-2.02 (-2.19 - -0.52)	-0.58 (-1.51 – 0.28)	0.032
DL_{NO} (mLmin/mmHg)	99 (79 – 114)	105 (94 – 128)	93 (77 – 112)	0.138
DL_{NO} (z-score)	-1.55 (-2.53 - -0.62)	-2.00 (-2.39 - -0.78)	-1-13 (-2.81 - -0.45)	0.821
DL_{CO} (mLmin/mmHg)	17.7 (13.8 – 20.8)	21.3 (18.1 – 26.8)	17.2 (13.1 – 19.4)	0.009
DL_{CO} (z-score)	-1.67 (-2.55 - -0.85)	-1.46 (-2.14 - -0.58)	-1.75 (-2.87 - -0.85)	0.352
Vc (mL)	34 (31 – 45)	44 (36 – 52)	33 (28 – 41)	0.02
Vc (z-score)	-2.12 (-3.12 - -1.59)	-2.28 (-2.6 - -1.31)	-2.07 (-3.14 - -1.63)	0.496
Dm	124 (99 – 143)	125 (110 – 144)	124 (93 - 144)	0.726
Dm (z-score)	0.30 (-1.04 – 1.61)	-0.47 (-1.27 – 0.74)	0.67 (-0.90 – 1.80)	0.374
DL_{NO}/DL_{CO} (n)	5.57 (5.29 – 5.82)	5.06 (4.86 – 5.15)	5.65 (5.5 – 5.86)	-
DL_{NO}/DL_{CO} (%)	116 (110 – 122)	106 (102 – 108)	118 (115 – 122)	-
Breath hold time (s)	4.6 (4.5 – 5.2)	4.8 (4.5 – 5.2)	4.6 (4.5 – 5.2)	0.918
FVC reduction (%)	3	13	0	0.242
Obstruction (%)	3	13	0	0.242
Restriction (%)	12	25	8	0.241
VA reduction (%)	30	63	20	0.036
DL_{NO} reduction (%)	46	62	40	0.240
DL_{CO} reduction (%)	54	50	56	0.541
DL_{NO} and DL_{CO} reduction (%)	42	50	40	0.461
Vc reduction (%)	73	63	76	0.374
Dm reduction (%)	9	0	12	0.422
Vc and Dm reduction (%)	9	0	12	0.505
CT lung involvement (%)	11 (9-13)	10 (0-14)	11 (8-14)	0.757
Consolidation (%)	6	0	10	0.646

Data are reported as median (IQR) (continuous/numerical variables) or number (%) (binary/categorical variables). Vascular pattern: $DL_{NO}/DL_{CO} \geq 110\%$; interstitial or indeterminate pattern: $DL_{NO}/DL_{CO} < 110\%$. p are computed between the two groups with different gas exchange pattern by the independent Mann-Whitney test (continuous variables) or Fisher test (binary variables). Abbreviations: DL_{CO} = diffusion capacity for carbon monoxide, DL_{NO} = diffusion capacity for nitric oxide, VA = alveolar volume, Dm = alveolar membrane diffusing capacity, Vc = capillary volume, FEV_1 = forced expiratory volume in the first second, FVC = forced vital capacity, TLC = total lung capacity, LLN = lower limit of normal, mMRC = modified Medical Research Council.

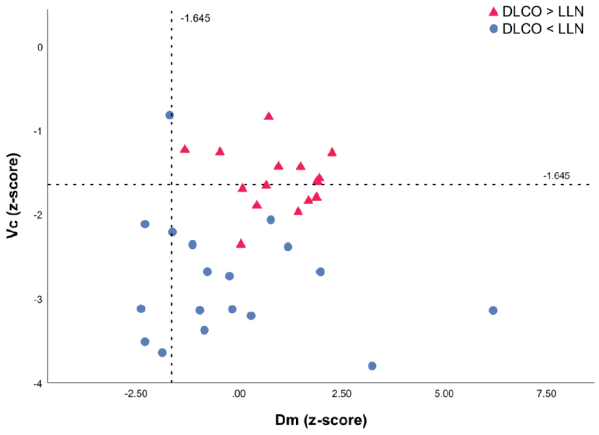

Figure 1. Vc (pulmonary capillary blood volume) and DM (alveolar membrane diffusing capacity) single patients' data of cases grouped according to DL_{CO} reduction.

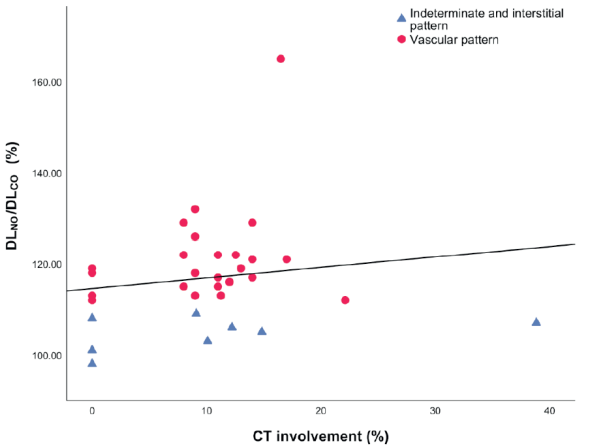

Figure 2. Correlation between lung involvement % at CT (computerized tomography) and DL_{NO}/DL_{CO} ratio, (the gas exchange pattern), (i.e. vascular pattern if more than 110%, interstitial pattern if less than 95%, indeterminate pattern for values in between).

ever, capillary endothelitis and fibrinous microthrombi with angiogenesis within the interalveolar septa are also described [9]. An analysis of morpho-phenotypic changes by transbronchial lung cryobiopsy in patients with persistent symptoms and residual parenchymal lung disease on average 3 months after recovery from COVID-19 revealed three different clusters of cases: chronic fibrosing, acute/subacute and a vascular form. The latter cluster was characterized by diffuse vascular increase and dilatation or distortion (capillaries and venules) within the otherwise normal parenchyma [10]. In the present study, in patients still symptomatic or with persistent chest CT abnormalities one year after COVID-19, decreased Vc was identified as the primary mechanism of gas exchange impairment. A previous article by Barisione *et al.* investigated the role of DL_{NO} in patients recovering from mild to severe COVID-19 pneumonia. The authors found a DL_{CO} reduction in 20% of the cases, but a DL_{NO} reduction in 57% of the patients, therefore they concluded that the discrepancy is likely due to loss of alveolar units by alveolar membrane damage. We found a higher percentage of patients with DL_{CO} alteration after one year of severe COVID-19 pneumonia, with a reduction of DL_{NO} and DL_{CO} (46 and 54%, respectively), but only 9% have an agreement between the two tests. Furthermore, only 9% of the whole sample showed a reduction in Dm, while 73% showed a reduction in Vc. Considering these results, we found that capillary volume impairment is the predominant alteration in long COVID-19. Given the greater sensitivity of DL_{CO} for capillary volume and of DL_{NO} for Dm, the conclusions of Barisione *et al.* (i.e loss of alveolar units by alveolar membrane damage) are reasonable. At least three major differences between the present study and that of Barisione *et al.* can be described. First, we enrolled only patients with severe COVID-19, while they also enrolled patients with mild COVID-19 who did not require hospitalization. Second, we evaluated patients after a longer time post infection, specifically 12 months. Finally, in our population the parenchymal involvement of CT scans is mild on average (about 10% vs 20% in the study by Barisione *et al.*). Núñez-Fernández and colleagues also assessed the role of DL_{NO} in COVID-19 survivors, both at 3 and 12 months, showing a reduction in diffusion mainly explained by Dm reduction secondary to the damage and loss of alveolar units [11]. In their study VC and VA significantly improved over time, while DMCO increased less. This led the authors to conclude that COVID-19 survivors diffusion improves over time due to an expansion of the perfusion component, with the reduction in the alveolar surface area being greater than the microvascular damage, a hypothesis against the conclusion of our study where diffusion alterations are mainly explained by Vc reductions.

Our results are instead similar to two recently

published studies. Dal Negro *et al.* demonstrated that patients still symptomatic after 12-16 months showed lower values of DL_{CO}, DL_{NO} and Vc despite a complete radiological resolution of COVID-19 [12]. Seccombe *et al.* also described a population of severe COVID-19 survivors who, after 2 months, showed a mild reduction both in Dm and Vc (z-score –1.19 ±1.05 and –1.41±1.20), with patients after 4 and 8 months showing a normalization of Dm (z-score -1.41±0.78) but persistent Vc impairment (-2.29±0.56) [13].

These contradictory findings still lack a definite explanation, but we hypothesize that the heterogeneity of diagnostic devices and examined populations may contribute to the varied results in combined DL_{NO}/DL_{CO} evaluation. For example, compared to the population studied by Núñez-Fernández *et al.*, our sample is predominantly composed of males (56% vs 67%), slightly older (62 vs 67 years old), and none of our patients had a prior COPD diagnosis. Notably, differences are observed in the combined DL_{NO}/DL_{CO} status, with our patients more frequently experiencing a reduction in DL_{CO} (9.6% vs 54%) and DL_{NO} (19.3% vs 46%) one year after hospitalization.

The choice of diagnostic equipment may also contribute to the different results reported in the literature. Our measurements were conducted using the HypAir system, similar to the approach taken by Dal Negro and Seccombe, whereas patients in the studies by Barisione and Núñez-Fernández were tested with the MasterScreen PFT system. To address these potential differences, our results were calculated using the most recent reference equations published by Zavorsky *et al.*, which also account for the diagnostic equipment.

Symptomatic patients 12 months after infection can be identified as "long-covid" cases, once other cardiopulmonary or neurological diseases have been excluded. Although definitive results are still lacking, there is evidence suggesting systemic capillary compromise in these patients. For instance, in a study including long-term COVID-19 patients with persisting symptoms, population was evaluated by sublingual video microscopy. The Authors found that COVID-19 leaves a persistent capillary rarefaction up to 18 months after infection [14]. Our results are consistent with this hypothesis. In fact, more than seven out of ten patients show a reduction in capillary volume, and most patients (76%) demonstrates a vascular pattern of gas exchange (*i.e.,* DL_{NO}/DL_{CO}≥110%) despite non-specific imaging and a DL_{CO} sometimes within normal limits. In these cases, we can hypothesize that the reduction in capillary volume is balanced by an increase in membrane conductance, in terms of efficiency or surface area.

This study has some limitations. First, it is a single centre study with no formal a priori assessment of sample size. However, the number of enrolled patients is comparable with previous pathophysiological studies. Second, we did not include a control group of asymptomatic patients with normal chest CT or without an history of COVID-19 infection; in any case, if we had found the same pattern in these subjects, our conclusions would not have changed. Finally, we did not apply more sophisticated imaging techniques or processing procedures to study pulmonary vasculature – it was not distinguished from dense alterations, assuming the same contribution across patients – that could have helped to better define the degree and characteristics of gas exchange impairment.

Conclusion

In conclusion, in COVID-19 survivors who are still symptomatic or have minimal CT impairment at one year, gas exchange abnormalities are determined by the vascular component. This condition may be present despite normal DL_{CO}. Our findings are consistent with previous works, describing systemic capillary impairment in patients with long COVID-19.

Abbreviations:

ATS: American Thoracic Society;
Chest CT: computed tomography of the chest;
CO: carbon monoxide;
COVID-19: Coronavirus Disease 2019;
CT: computerized tomography;
DL_{CO}: diffusing capacity of carbon monoxide;
DL_{NO}: diffusing capacity of nitric oxide;
DM: alveolar membrane diffusing capacity;
DMCO: membrane diffusing capacity for carbon monoxide;
ERS: European Respiratory Society;
FEV_1: forced expiratory volume in the first second;

FVC: forced vital capacity;
TLC: total lung capacity;
IQR: interquartile range;
LLN: lower limit of normal range;
mMRC; modified Medical Research Council;
NO: nitric oxide;
ϴNO: nitric oxide's diffusion;
PFT: pulmonary function tests;
VA: alveolar volume;
VAno or VA DL_{NO}: alveolar volume during combined testing;
Vc: pulmonary capillary blood volume;

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Review

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Usability of inhaler devices: a parameter currently misused

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ABSTRACT

Inhalation represents the most convenient route for delivering respiratory drugs. Delivery systems showed a huge technological progress and several pocket inhalers had been engineered over the last decades for clinical use. Despite the growing technological efforts aimed to simplify the inhalation procedures and optimize the therapeutic outcomes, the effectiveness of drug inhalation through inhalers still represents a major challenge in respiratory medicine. Patients may actually incur in different types of critical errors when using all inhalers and are not capable to inhale throughout all devices equally well. Therefore, the choice of the most suitable and convenient device to prescribe still is a critical issue in real life. Usability is the only comprehensive parameter consenting the effective and objective assessment of pocket inhalers' performance, and allowing their objective comparison and ranking. Unpredictable discrepancies are in fact easily detectable between inhalers (even belonging to the same class) in terms of Usability, independently of the patient's awareness. The reasons were described and discussed for each class of inhalers presently available. Usability is a multidimensional parameter that is much more multifaceted and complex than usually presumed. Usability takes origin from the integrated, balanced and objective assessment of the role played by several factors from different domains, such as: factors related to patient's beliefs, to patients' behavioural components, to device engineering and to the overall cost. Usability is the key parameter for assessing and optimizing the appropriateness of any inhalation treatment through whatever device. Usability would also represent a key investigational instrument for supporting the future development of innovative and more performing inhaler devices objectively.

Key words: Usability, Inhaler devices, MDIs, DPIs, SMIs, Respiratory disorders

Introduction

There is consolidated evidence that the inhalation route is the major option for treating acute and chronic respiratory disorders (airway obstruction in particular) as the drugs assumed via inhalation provide some substantial advantages when compared to systemic therapies: they target the lung directly, consent to reduce the delivered dose, promote a quicker onset of action and allows a better therapeutic index [1, 2]. Nevertheless, the delivery of pharmacological agents through inhalers still represents a hot issue in respiratory medicine, particularly for the long-term management of obstructive airway disorders (Bronchial Asthma and Chronic Obstructive Pulmonary Disease - COPD).

In parallel with the development of several innovative molecules, a huge technological progress also occurred in delivery systems over the last decades, mainly aimed to improve the lung deposition of the drug(s) to inhale, to simplify the patients' procedures for a proper inhalation, and to increase the patients' adherence and the compliance to respiratory treatments (Table 1).

Nevertheless, the effectiveness of drug(s) through inhalers still represents a major clinical challenge. The real life

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Table 1. The major evolutive steps of pocket inhalation devices.

1956 the 1st MDI Ricker Lab. 3 M
1960 the ultrasonic nebulizers
1971 the 1° DPI (the Spinhaler)
1980 the 1° spacer device
1987 the Montreal Protocol
1990 the MDIs CFC free
1995 the novel DPIs
2004 the 1° SMI (the Respimat)
2010-2014 the simplified DPIs (oped-inhale-close)
2016 the DuoResp technology
2020 the re-usable SMIs
MID – the Aerosphere technology

effectiveness of inhalation actually depends on several factors, either patient- and device-dependent in origin, that can variably affect and modulate the clinical outcomes, even substantially [3-7]. Unfortunately, despite respiratory drugs are preferably delivered via the inhalation route, the choice of the right inhaler to prescribe still is too frequently guided empirically in real life. In other words, this choice proves usually largely independent of the knowledge of the technological characteristics of the inhalers and of their peculiar performance, still being almost uniquely based on patients' and/or caregivers' perceptions and beliefs [7-9].

The variable engineering of portable inhalers sometimes contributes to magnify the problem as their intrinsic characteristics can peculiarly affect the effectiveness of the therapeutic strategy *per se*. In particular, the capability of inhalers to allow the inhalation of a sufficient respirable fraction of the drug to assume (such as, with a particle size ≤ 6 μ); to ensure a good reproducibility, the precision and the stability of the dose delivered, together with a comfortable usability in daily life still are crucial aspects of the disease management of chronic obstructive disorders, particularly in children and adolescents, in elderly, in fragile patients, and in lower compliant subjects in general [3-6, 7-10]. On the other hand, the improper use of inhalers was showed to influence dramatically the health care impact of respiratory medicine in terms of hospitalizations (+47%); unscheduled visits (+ 62%); courses of antimicrobics and of systemic steroids (+50% and +54%, respectively); working days off (+47%) [11].

A huge number of pocket inhalers, variably shaped, entered progressively the market and are widely used either for delivering single or combined respiratory drugs (Table 1). The technological imprinting of each class of these devices and their peculiar and unavoidable limitations can affect Usability substantially due to several patient- and device-dependent factors [12].

In general terms, three are the basic families of pocket devices presently available: 1) the Metered Dose Inhalers (MDIs): the first inhalers appeared in the '60s for delivering pre-dosed respiratory drugs and still largely used in clinical practice; 2) the Dry Powder Inhalers (DPIs): available since the '70s, they were increasingly prescribed in daily practice for managing asthma and COPD; 3) the Soft Mist Inhalers (SMIs), available since the beginning of the present century and still represented by only one device (the Respimat).

Metered Dose Inhalers (MDIs)

MDIs are the oldest and the cheapest family of pocket inhalers. In the past, a volatile propellant, the chlorofluorocarbon (CFC, such as a class of Freon), was added for allowing the drug emission from the canister. However, as it was stated that CFC contributes to ozone depletion in the upper atmosphere by the Montreal Protocol of 1987 (and confirmed in nine following revisions, up to the Kingali Protocol of 2016), this propellant was replaced by international agreement with the hidrofluoroalcan (HFA) as an environmental safer alternative.

Patients and health care professionals still perceive MDIs as the most intuitive and the easiest devices to use. Unfortunately, the effective inhalation from MDIs highly depends on several factors that are strictly related to the patient's dexterity, cognition and cooperation. The drug emission usually occurs at high speed (around 80km/h) from the canister. Consequently, a sufficient patient's coordination and a sufficient educational level are required for a proper actuation and inhalation. Otherwise, either the lung deposition of

the inhaled drug and the expected clinical results can be significantly compromised. Old patients, fragile individuals, subjects with physical and/or cognitive limitations, children and adolescents (mainly asthmatics, who frequently tend to deny their respiratory handicap and do not accept to spend time enough for improving inhalation procedures), and, in general, those patients not educated to the MDIs' use are not likely to obtain the expected clinical outcomes, independently of the drug(s) prescribed [13].

In real life, both patients and health care professionals (sometimes, doctors included) are too frequently unaware of the major factors that can modify the effectiveness of respiratory treatments to assume or prescribed via MDIs, namely: the high emission velocity of the drug; the coordination needed for achieving the required inhalation flow rate; the variable deposition rate of the drug particulate along the airways, the variability of the dose consistency also due to significant changes in their emitted drug cloud occurring with some MDIs at different filling of the same canister [14]. Moreover, the plume of the drug emitted from the MDI results variable in shape and consistency according to the device peculiarities [15, 16].

All these aspects that are strictly related to the delivery via MDIs are practically unknown to patients who usually base their criteria of judgment on subjective perceptions only. Unfortunately, also the majority of studies carried out for investigating and comparing different MDIs in clinical practice are merely focused on patients' beliefs only, and "perception of inhalation", "ease of use", "preference", "attractivity", or "intuitivity" are the unique variables considered and frequently misused as synonyms of "Usability". The major critical aspects of MDIs' use are reported in Figures 1 and 2.

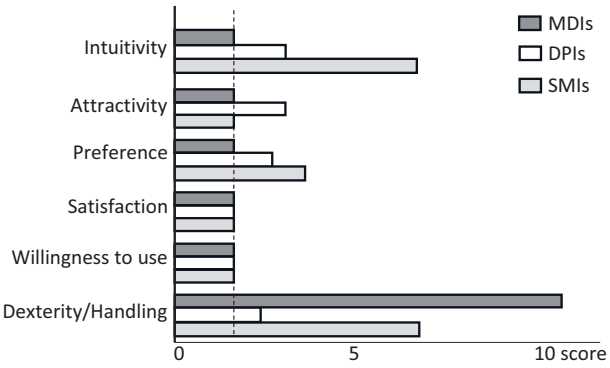

Figure 1. Patient's dependent major critical aspects affecting the judgment of an inhaler device.

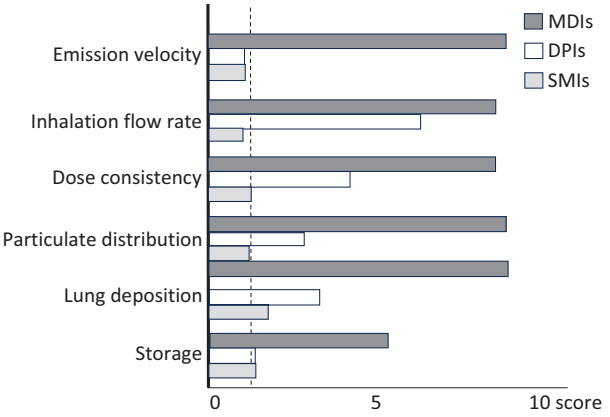

Figure 2. Device dependent major critical aspects contributing to rank inhaler devices.

Dry Powder Inhalers (DPIs)

Since the '70s, but particularly since 1995 when the most innovative DPIs appeared in the market, DPIs represented a valuable step forward in inhalation strategies. On the other hand, they do not require any propellant; inhalation procedures have been simplified in terms of number of actions needed for their actuation, thus being the patient's cooperation and compliance improved. Moreover, a dose counter was added for allowing a higher patients' awareness of residual doses still available in the device; the lung deposition of drugs was increased; the variability of the inhaled dose reduced; the dose consistency optimized, and the incidence of local and systemic side effects quite lowered [17-19].

In the absence of any propellant, either the deaggregation and the aerosolization of dry powdered drugs to inhale depend on patients' inspiratory flow rate (and/or the flow acceleration) generated through the device and on the subsequent pressure drop produced during the forced inspiratory manoeuvre [18-24]: both actions peculiarly related to the technical characteristics of the device.

Consequently, DPIs can be ranked by their technological characteristics, namely: their intrinsic airflow

resistance, their pressure drop/flow rates, and their turbulence generated through the device [6, 25-27]. DPIs can be differentiated by their intrinsic resistive regimen (such as, a constant depending on their original design) as: low resistance (<5 Mbar 1/2 L/min –1; mid); mid resistance (5-10 Mbar 1/2 L/min –1), and in high resistance DPIs (>10 Mbar 1/2 L/min –1) [20, 25].

The de-aggregation of powdered drug(s); the size of particulate to inhale; the lung deposition within the airways, and the dose consistency largely depend on the inspiratory flow rate generated by the patient and the subsequent turbulence produced by the pressure drop occurring inside the DPI [1, 18-22]. As a consequence, the patient is required to produce an inspiratory flow rate (IFR) strong enough for overcoming the peculiar intrinsic resistance (IR) of the device in use.

If the IFR/IR ratio is considered, two are the main conditions leading to an ineffective drug inhalation: 1) a too limited IFR (the upper factor of the ratio) and, 2) a too low IR (the lower factor of the ratio). When IR is too low, the ratio tends to ∞ in these cases and the IFR required for overcoming IR is so high that also healthy individuals can't always reach the threshold needed. Therefore, the message generally assumed that those DPIs characterized by a very low IR should be preferred because more suitable and reliable, are largely misleading in terms of effectiveness of inhalation.

On the other hand, when IR is too high (the lower factor of the ratio), the ratio tends to 0 even if the IFR required is relatively low: in these cases, the strength required to overcome IR can result so high that a large proportion of obstructive patients (i.e., the most compromised in terms of lung function) can't achieve the required IFR in real life due to their limitations in lung mechanics [27].

All these aspects are insufficiently disclosed or neglected even if they highly contribute to DPIs Usability in real life. Moreover, size, volume, gripping, number of manoeuvres required for actuation, and understanding of inhalation procedures make DPIs different from each other: all characteristics that can change substantially the patients' acceptability and usability.

Table 2 reports the most prescribed DPIs listed by their intrinsic resistance and their required inspiratory flow rate, together with the n. of maneuvers needed for their actuation (Table 2), while the major critical aspects of MDIs' use are reported in Figures 1 and 2.

Soft Mist Inhalers (SMIs)

The family of SMIs still is represented by one device only: the Respimat, that is presently also available in its rechargeable version. The drug(s) emitted from

Table 2. Characteristics of different DPIs: n. maneuvers required for actuation; their intrinsic resistance; inspiratory flow rate required for a proper and effective inhalation.

DPIs	n. maneuvers	DPI Resistance ($kPa^{0.5}$ L/min)	Inspiratory Flow Rate (L/min)	
Breezhaler	7	0.017	111	low resistance DPIs
Aerolizer	6	0.019	102	
Accuhaler/Diskus	4	0.027	72	mid resistance DPIs
Novolizer	3	0.027	72	
Ellipta	3	0.028	70	
Genuair	3	0.028-0.031	64	
Spiromax	3	0.031	62	
Turbohaler	4	0.036-0.039	54	
Nexthaler	3	0.036-0.042	54	
Easyhaler	3	0.037-0.042	50	
Clickhaler	3	0.039	50	
Twisthaler	3	0.044	44	high resistance DPIs
Handihaler	8	0.058	37	

the SMI does not need any propellant. In this case the dose delivery is assured by mechanical forces that produce two fine jets of drug solution converging at a pre-set angle. The collision of these two jets generates the typical soft mist emission [28-31].

When compared to MDIs, velocity of emission from the SMI is much lower (5-10km/h) when compared to that one of MDIs, being the risk for patients' insufficient coordination and the incidence of errors of inhalation procedures quite reduced, thus providing a higher Usability. Moreover, the dose consistency proved constant with the SMI regardless of the level of the canister filling [14]. However, also the use of SMIs requires some patient's involvement particularly in terms of dexterity for loading the dose to inhale. The major critical aspects of SMI use are reported in Figures 1 and 2.

The concept of Usability

Although the ideal inhaler still is missing, it was already stated a few years ago that the ideal inhaler should be unavoidably: 1) *effective*: able to consent the inhalation of a sufficient fraction of drug with a particle size ≤ 6 μ, regardless of the patient's inspiratory flow rate produced; 2) *reproducible*: able to always consent the inhalation of the same respirable fraction of the drug; 3) *precise*: allowing the patient to be always aware of the residual doses still available in the device [12]; 4) *stable*: able to protect the drug(s) from the effects of temperature and humidity changes; 5) *comfortable*: easy to transport and use, particularly in critical conditions; 6) *convenient*: containing a number of doses enough to cover a long-term use, and hopefully rechargeable; 7) *versatile*: to be possibly used with different drugs; 8) *environmental compatible*: without any chemical contaminant; 9) *affordable*: of acceptable cost [2, 12].

Anyway, regardless their proximity to the ideal profile, two are the major assumptions on inhaler devices that are definitively consolidated: a) each inhaler presently available is not exempt from some critical errors in their actuation and current use [32], and, b) subjects are not capable to inhale throughout each devices equally well and effectively [33]: in other words the rule "one size fits for all" is not valid with inhalers [23], and can represent a barrier for the proper management or airway diseases. Usually, data on optimal flow rates needed for a proper inhalation are derived from *in vitro* studies that do not always reflect real life conditions. However, even in the presence of normal cognition and manual dexterity, subjects' basic airway and lung conditions may variably affect the extent of inspiratory airflow rate and the performance of inhalers [27]

The concept of Usability just arises from the integrated weighing of all these basic assumptions. In other words, Usability is the comprehensive parameter which is able to reproduce quantitatively the relative role played by all main factors (not merely those patient-dependent, but also those device-dependent) that can affect the performance and the convenience of each device presently available on the market.

As different domains of judgment variably contribute to Usability, its objective assessment does require a multi-domain approach, and can then only take origin from the balanced evaluation of different clusters of factors, variably interacting in the process. Some factors are those mostly depending on the patient's side of the problem (as currently usually done), but other crucial criteria are those involving the knowledge and the awareness of the technical peculiarities of the inhaler (to use or/and to prescribe, respectively), together with those related to the quality of nursing specifically required for allowing the patient to inhale properly and effectively through the device. Moreover, even the patient's socio-economic status and the operational setting should be carefully considered. Finally, the overall cost and its different components also play a role (Figure 3). In particular, differently from what is generally presumed, it does not merely correspond to the cost of the drug. The real life cost should be actually implemented with the cost of resources spent in the educational strategy of the patient (up to making him independent in the proper use of the device) and with the cost of patient's failed outcomes due to the ineffective use of the inhaler prescribed without a sufficient educational approach [34].

All these variables should be extensively checked and weighed because each of them contributes *per se* to

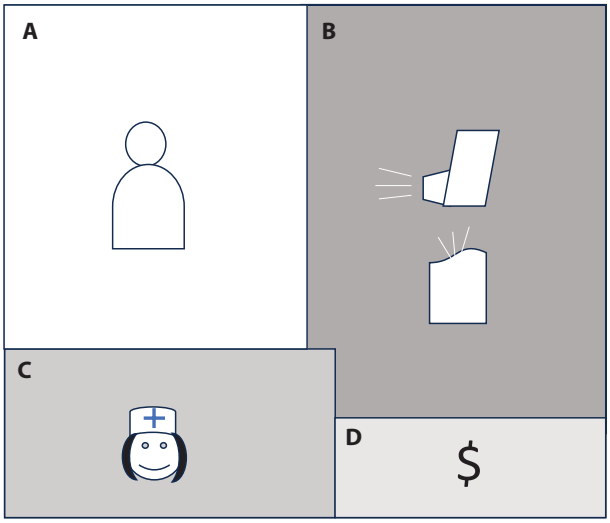

Figure 3. The main components of Usability: a) the patient's dimension; b) the inhalation technology; c) the nursing effectiveness; d) the economic burden.

Usability in real life. Definitively, Usability is a multifaceted parameter consisting of a complex merging of several factors related either to the patient's profile and to the device's characteristics, variably mixed. Only the integrated assessment of all these components will consent health care professionals to ranking and/or comparing objectively inhaler devices in terms of their Usability.

When Usability of inhaler devices are compared by the Global Usability Score (GUS), unsuspected discrepancies are easily found even between devices belonging to the same family, as in the case of MDIs and DPIs, both in asthma and in COPD [35-36]. In these cases, mayor differences in their Usability appears predominantly due to the intrinsic characteristics and engineering of the devices (particularly in the case of DPIs), followed by the quality of nursing provided, and by the overall cost [38-39]. In other words, a substantial dichotomy between the role of patients' subjectivity and the role of objective factors affecting inhalation easily appears and can be quantified in real life in terms of effective Usability.

Unfortunately, the choice (when possible) of the inhaler device to prescribe still is too frequently empirically guided in clinical practice [23], being the technological characteristics and the effective performance of different devices usually underestimated or neglected, while criteria merely based on patients' perception are usually privileged [37, 39-42]. The net result is that, if specific investigational tools are not used, only the patient's viewpoint is currently assumed as corresponding to Usability and is erroneously regarded as a synonymous.

Usability should be much more valued and quantified before prescribing one inhaler as the therapeutic outcomes can be substantially influenced by this choice. Indeed, a recent Delphi Consensus Statement confirmed that the choice of the inhaler should be considered as important as that one of respiratory molecule(s) in terms of disease management of respiratory disorders [11]. In a multinational survey more than 30% of primary and secondary care physicians affirmed to choose the device before considering the respiratory drug to prescribe. Moreover, 87% of UK health professionals claimed their concern about the possible occurrence of problems related to therapeutic prescriptions if the inhaler is not specified, and 86% of physicians were strongly convinced that inhalers are not interchangeable being their unmotivated substitution a frequent cause of negative outcomes [43].

However, it is incredible that the extraordinary evolution in pocket delivery systems observed over the last decades did not match to a proportional improvement of specific instruments devoted to assessing the effects of this technological progress. The GUS questionnaire, particularly in its short and quick version, would represent a reliable response to this unmet need also for clinical purposes. Meanwhile, the patients' subjectivity and beliefs inexplicably remain the only criteria adopted for judging inhaler devices in the large proportion of cases and of clinical studies. Therefore, the true assessment of Usability still represents a hot issue indeed, while it should recognize a primary position in the decisional pathway for deciding the appropriateness of therapeutic strategies (Figure 4).

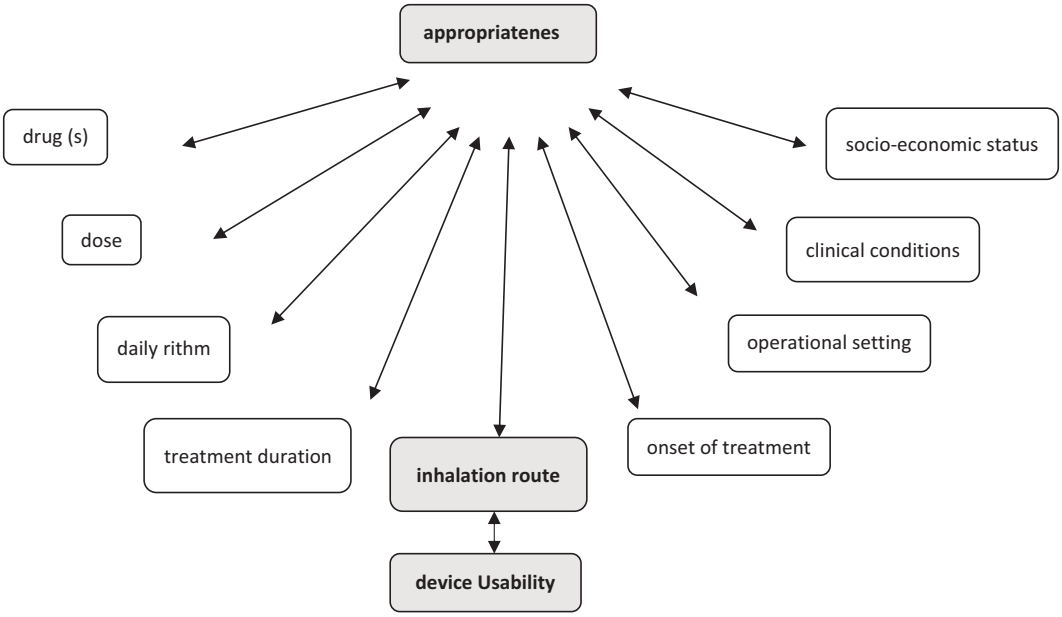

Figure 4. Positioning of device Usability within the decisional pathway for the appropriateness of respiratory therapeutic interventions.

Conclusions

The choice of the most suitable inhalation device to prescribe still is a complex issue indeed. Usability is the multidimensional parameter that could integrate and quantify the role of all decisional components, such as, device technology, patient's beliefs and behaviours, and overall cost.

As Usability is largely independent from subjective factors, it would represent a helpful tool for comparing and ranking the performance of inhalation devices on an objective basis. Usability can then be regarded as an extraordinary tool for supporting doctors and other health care professionals in their operational decisions in clinical practice, fully according to the concept of personalized therapy.

Finally, Usability would be used as a key investigational tool for supporting and stimulating the incoming development of novel and more performing inhalers in the next future objectively.

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Case report

When sarcoidosis hits down: a case of prostatic sarcoidosis

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ABSTRACT

A 69-year-old North African male with established diagnosis of sarcoidosis underwent a stereotactic prostate biopsy with fusion technique. At the histological analysis, non-necrotizing micro-granulomas were highlighted in 2 samples, while the immunohistochemical staining resulted negative for CK903/p63/racemase. To the best of our knowledge, only 16 cases of prostatic sarcoidosis have been reported in literature. With this case report we describe an incidental diagnosis of prostatic involvement of sarcoidotic disease and briefly review and discuss the available literature on the topic.

Key words: Sarcoidosis, Prostate, Urogenital involvement of sarcoidosis

Introduction

Sarcoidosis is a systemic granulomatous disease that primarily affects the lungs and the lymphatic system [1]. It commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and more rarely other organs, may also be involved [1]. In general, the diagnosis is established when clinic-radiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas [1]. The latest international guidelines on treatment of sarcoidosis recommend treating patients either for risk of death and/or permanent disability (danger), or to improve quality of life. However, they do not provide specific indications about the management of urological involvement [2]. Related to the urological system, manifestations of sarcoidosis include nephrolithiasis and nephrocalcinosis, inflammatory infiltration of the tubular interstitium leading to granulomatous interstitial nephritis, sarcoid infiltration of the kidneys resembling renal lymphoma, rare direct bladder, epididymis and testis involvement [3].

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Contributions: AM and GB have substantially contributed to the conception and the writing of the present manuscript, therefore they should both be considered as first authors. DA, FG and RT reviewed the literature and collected the data regarding the case. MC produced the figures and edited the section on pathology. EC and SC reviewed and edited the manuscript.

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Although quite rare, sarcoid infiltration in the reproductive tract has been described in autopsies by non-necrotizing micro-granulomas in genitourinary organs in 5% of cases [3].

Little evidence is available about the symptoms, the diagnostic and prognostic features of sarcoid prostate involvement in patients affected by sarcoidosis. With the present case report we aimed to expand the knowledge about this rare clinical occurrence.

Case presentation

A 69-years-old African male with a past medical history of type 2-diabetes, arterial hypertension, chronic kidney failure and retinal maculopathy, was diagnosed with sarcoidosis in 2013 after the incidental finding of hilar lymphadenopathy at chest radiography. Hilar and mediastinal lymph nodes enlargement was confirmed at computed tomography (CT) scan, that showed also pulmonary involvement consisting of bilaterally diffused subpleural and peribronchovascular nodules. Thereafter, the patient underwent bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) that lead to the confirmed diagnosis of sarcoidosis. At the time of diagnosis, sarcoid involvement of eyes, skin and heart was excluded. A systemic steroid treatment was initially started in consideration of the diffuse bilateral lung micronodules and lymphadenopathy, being discontinued 1 year later because of poor compliance. After few months, a CT scan showed worsening of nodular subpleural interstitial lung disease, and therefore steroid treatment with methylprednisolone was started again. At a follow up visit in 2015 steroid therapy was stopped because of normal pulmonary function tests and poor treatment compliance.

In July 2020, the patient was admitted to our Respiratory Intensive Care Unit at the University Hospital of Modena (Italy) due to acute respiratory failure following the worsening of sarcoidosis pulmonary involvement, complicated by sepsis.

The patient underwent a full-body CT scan which identified a prostatic inhomogeneous nodule mass and multiple hyperdense spinal lesions. Prostate-specific Antigen (PSA) level was in normal range. A magnetic resonance (MR) of the lower abdomen was performed confirming the presence of a capsulated nodule in the middle prostatic lobe. MR images revealed a heterogeneous signal intensity with good contrast enhancement, colliquating areas within the nodule with haemorrhagic content and small multiple focal lesions of the pelvis bones (Figure 1). A full-body bone scintigraphy was then performed showing inhomogeneous tracer accumulation at the level of dorsal vertebrae, inconsistent with malignant origin.

Pulmonary function tests highlighted a mild non-reversible airflow obstruction. The patient was discharged and was prescribed a 6-month systemic steroid treatment together with inhaled corticosteroids/long acting β_2 agonist, which lead to a complete resolution of sporadic wheezing and dyspnoea. PSA level remained normal during the following 12 months. In December 2021, a stereotactic prostate biopsy with fusion technique was performed; the histological analysis of the 10 collected samples showed gland hyperplasia, lobular atrophy, and a non-specific chronic inflammation. At hematoxylin and eosin staining two non-necrotizing micro-granulomas were highlighted, and the immunohistochemical staining was negative for CK903/p63/racemase (Figures 2 and 3). As a collateral finding, a lithiasic intra-luminal formation was described. Giving the histology, diagnosis of prostatic sarcoidosis was made. Therefore, urologic follow up with PSA measurement after 4 and 8 months was recommended, while the ongoing therapy was left unchanged, due to the absence of symptoms potentially related to sarcoidosis. PSA was within its normal values also 18 months after the biopsy.

Discussion and conclusions

With this case report we described a biopsy-proven prostate involvement of sarcoidosis in a >65-year African male. Only other few cases and autoptic series are reported in literature.

A review by K. Kodama and colleagues reported that among 60 males with sarcoid involvement of reproductive organs, the epididymis was hit in 73%

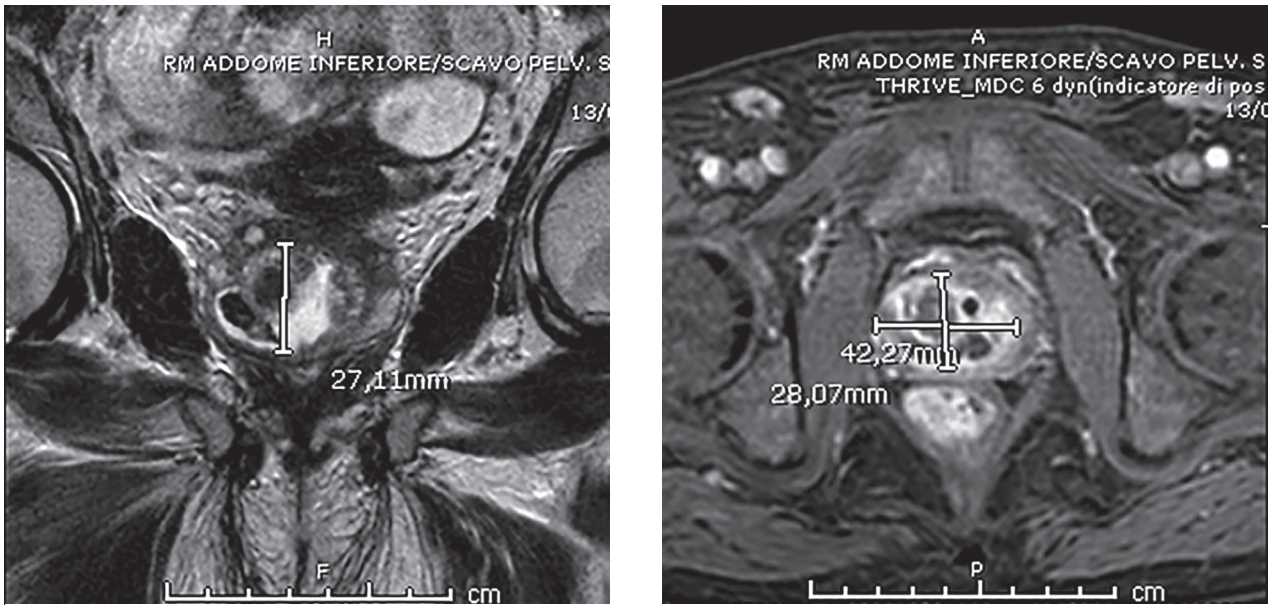

Figure 1. MRI of inferior abdomen and pelvic cavity: nodulation to the middle prostatic lobe, with heterogeneous signal intensity characterized by colliquate areas and areas with haemorrhagic content, having transverse diameters of about 4.2 x 2.8 cm and longitudinal extension of about 2.7 cm. The nodulation appears capsulated, without significant restriction to the evaluation of diffusion but with fair contrast enhancement predominantly peripheral and paramedian left. The peripheral glandular part appears poorly represented from the right side, that is compressed by the described nodulation. The left peripheral glandular part is more represented, with low-intensity focal length in T2 sequences weighed about 3 mm showing restriction of signals to the evaluation of diffusion and discrete contrast enhancement (PIRADS=4).

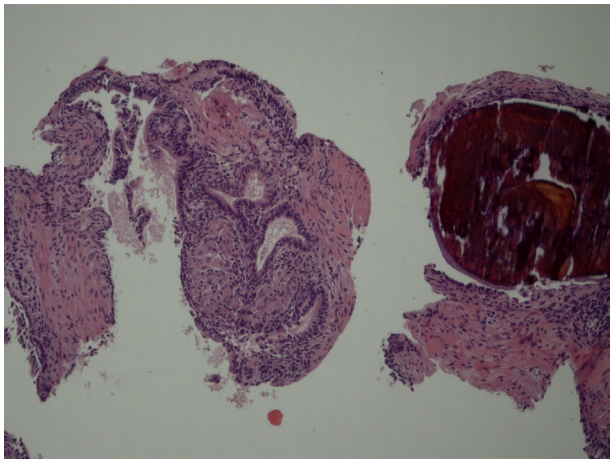

Figure 2. Hematoxylin and eosin stain, 10x magnification: needle biopsy of prostatic tissue with intraluminal calcification, alongside a non-necrotizing microgranuloma next to a normal prostatic gland structure.

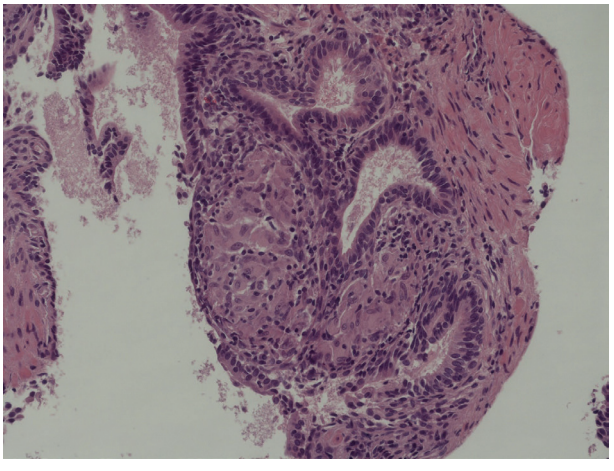

Figure 3. Hematoxylin eosin stain, 20x magnification: same slide with greater magnification on the microgranuloma.

of cases, the testis in 47%, and the spermatic cord and prostate in 3% [4]. As regards sarcoid prostatic involvement, according to the cases reported in literature the average age at diagnosis is 58 years, prevalence is higher in African ethnicity and the peripheral prostatic regions are mostly affected at histology [5].

Three out of the 16 (18.8%) men with histologically confirmed sarcoidosis described in literature suffered from related symptoms, 4 were asymptomatic, while no detailed information at this regard were available for the remaining [6–9].

Little scientific evidence is available as regards the implications of prostatic sarcoidosis on fertility and on risk of local infection. In the case report by A. Osanami and colleagues the patient presented with symptoms similar to prostatitis (urinary retention and fever) and a rapid decline of the renal function. Tests were conducted to exclude other possible autoimmune diseases until a kidney and prostate biopsy confirmed sarcoid infiltration of the prostate and tubulointerstitial nephritis. The patient recovered completely following systemic steroid therapy, thus suggesting the necessity of a prompt and accurate diagnosis of this rare occurrence in order to avoid undesired collateral implications [9].

Moreover, diagnostic imaging seems helpful in diagnosing prostatic involvement of sarcoidosis as described by a mild uptake of prostate at the 18-fluorodeoxyglucose positron emission tomography (18-F FDG PET) [9]. In our case, MR played a key role in the differential diagnosis of prostatic nodularity, suggesting the suspicion of a granulomatous disease. Nonetheless, almost all the reported cases required organ biopsy sampling to confirm diagnosis.

It is also worth mentioning that sarcoid infiltrates of the bone tissue may act as a confounding factor during the staging of prostatic cancer [10]. In such particular cases invasive procedures might be crucial to prove diagnosis.

The histological and imaging findings in our case confirmed the prostatic peripheral areas as the most frequently involved. However, the micro-granulomas found in our sample were localized within the parenchyma, distinguishing the present case from most of the reported ones [5]. Interestingly, the values of PSA remained within normal levels during the 12 months follow up between RM and biopsy, at difference with other reported cases, thus suggesting that PSA may not be a reliable diagnostic marker in the suspicion of prostatic sarcoidosis [5–8]. Such hypothesis is strengthened by the fact that our patient was not affected nor by IPB neither by prostate cancer, two common causes of PSA elevation that might therefore interfere with sarcoidosis as regards the PSA levels. Generally, serum PSA levels vary according to patient age and race. Any process that disrupts the normal architecture, especially the basal cell layer of the prostate, allows diffusion of PSA from prostatic ductal system into the microvasculature. Therefore, elevated serum PSA concentration is seen with acute prostatitis, chronic prostatitis including granulomatous prostatitis-like sarcoidosis, infarcts, hyperplasia, and transiently following biopsy as well as with prostatic adenocarcinoma [7]. Therefore, we can hypothesize that when sarcoid involvement of prostate occurs, PSA levels may be within the normal range in the early stages of local disease and then increase with its progression.

Moreover, our patient has never developed lower urinary tract symptoms (LUTS) before undergoing the prostate biopsy, similarly to the majority of the cases reported in literature. This may be consistent with the normal PSA level in the same period.

As further support to our hypothesis, it should be noticed that the case described by S.K. Mulpuru and colleagues presented elevated PSA levels together with symptoms, possibly meaning a more advanced local involvement [7]; other cases reported with elevated PSA levels had concomitant prostate cancer [6]. Unfortunately, very few reported cases mentioned information on PSA level.

In conclusion, prostate sarcoidosis remains a very rare condition. However, when patients already diagnosed with sarcoidosis complain about LUTS and/or are found with imaging evidence of prostatic enlargement and/or nodular abnormalities, or increased uptake at 18-F FDG PET, sarcoid prostatic infiltration should be considered, regardless of the PSA level. With this clinical scenario, and especially in case of patients of African ethnicity, prostate biopsy may be indicated.

Abbreviations:

CT: Computed tomography
EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration
PSA: Prostate-specific antigen
MR: Magnetic resonance
18-F FDG PET: 18-fluorodeoxyglucose positron emission tomography
LUTS: Lower urinary tract symptoms

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Case Report

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Use of venovenous (VV) extracorporeal membrane oxygenation (ECMO) in near-fatal asthma: a case series

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ABSTRACT

Introduction: Status asthmaticus (SA) and near-fatal asthma (NFA) are life-threatening conditions that continue to present a management challenge for physicians. Extracorporeal Membrane Oxygenation (ECMO) has been employed as a last resort in treating these patients.

Case presentation: We described six patients who were admitted to the ICU for NFA and received ECMO treatment at a high-complexity institution in Cali, Colombia, between 2015 and 2019. All patients are registered in the ELSO registry. Baseline patient characteristics, arterial blood gases (ABG), ventilatory parameters, and complications were collected as specified in the ELSO registry form. Efficacy was analyzed in terms of the improvement in respiratory acidosis, the number of ventilator-free days (VFD), and a reduction in mechanical power (MP). MP, which refers to the energy associated with the mechanical forces involved in breathing and the functioning of the respiratory system, was calculated using a mathematical formula. Safety was evaluated based on the incidence of complications. After 12 hours of ECMO, we achieved a correction of respiratory acidosis, a significant decrease in all ventilatory parameters, and a reduction in MP ranging from 52.8% to 89%. There was one mortality. Among the five surviving patients, all except one, who required a tracheostomy, had a high VFD score, with a mode of 26 days, demonstrating a reduction in ventilation time.

Conclusion: Further randomized controlled trials are needed to fully understand the efficacy and safety profiles of ECMO in SA/NFA. MP is being widely used to achieve safer ventilation, and although more data is required, it appears to be a promising option for evaluating the risk of developing VILI and the success of the therapy.

Key words: Status asthmaticus, Near-Fatal Asthma, Extracorporeal Membrane Oxygenation, Mechanical Power, Case Series.

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Availability of data and material: All data and material are available for sharing if needed.

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Introduction

Status asthmaticus (SA) and near-fatal asthma (NFA) are life-threatening conditions that continue to present a treatment challenge for physicians. SA represents an acute, severe asthma exacerbation that does not respond to initial therapy, while NFA refers to SA that progresses to respiratory failure [1]. Data from around the world suggests that the frequency of patients requiring intensive care unit (ICU) admission for asthma exacerbations has decreased from 10% to approximately 2-4% [2]. However, among patients in the ICU, the need for mechanical ventilation (MV) has remained consistent at around 36%, with a hospital mortality rate of up to 9.8% [2–4].

In certain circumstances, conventional treatments for asthma, such as bronchodilators, corticosteroids, and mechanical ventilation (MV), may prove insufficient. In such cases, several adjunct therapies must be initiated, such as ketamine, general anesthesia, and, as a last resort, extracorporeal membrane oxygenation (ECMO) [1,5]. The guidelines from the Extracorporeal Life Support Organization (ELSO) for adult respiratory failure specify the indications for ECMO therapy, including conditions like CO_2 retention syndromes [6], such as asthma.

The primary goal of ECMO therapy is to correct tissue hypoxia, but evidence suggests that one of its significant benefits is reducing the frequency of ventilator-induced lung injury (VILI), a common complication of MV. Mechanical power (MP), defined as the amount of energy delivered to the respiratory system by a mechanical ventilator per tidal cycle and ventilating frequency, determined by volume, pressure, flow, and respiratory rate [7,8] (Figure 1), is a novel concept intrinsically related to the development of VILI. We believe that by reducing MP, we can contribute to the prevention of VILI.

The objective of this article is to describe a series of six patients with NFA who received ECMO as a last resort, with a particular emphasis on monitoring and preventing VILI using MP.

Materials and methods

We conducted a retrospective search of patients admitted to the ICU for NFA who received ECMO at a high-complexity institution in Cali, Colombia, between 2015 and 2019. All patients had a history of poorly controlled asthma and were experiencing an episode of SA/NFA. They all received standard treatment consisting on beta-2 agonist and anticholinergic inhalers, intravenous (IV) steroids, and magnesium sulfate, in addition to adjunct therapies such as ketamine or inhalational anesthetics like sevoflurane. Moreover, they met the criteria outlined in the ELSO guidelines for managing hypercapnic respiratory failure in adults: CO_2 retention despite MV and high Plateau Pressure (Pplat > 30 cm H_2O), PaO_2/FiO_2 < 80 for at least 3 hours, or pH < 7.25 for at least 3 hours, when conventional medical management strategies had been exhausted [6]. All patients are included in the ELSO registry.

Patients underwent cannulation in the operating room. All but one patient were cannulated using the internal jugular vein with a double-lumen cannula (AVALON® #27, the smallest available). The remaining patient was cannulated via the right femoral vein using a BIOMEDICUS® #21 cannula, after unsuccessful attempts to cannulate the internal jugular vein, despite performing a venodisection. All patients were successfully placed on venovenous (VV) ECMO.

Baseline patient characteristics, arterial blood gases (ABG), and ventilatory parameters were collected as per the ELSO registry form [9]. Pre-ECMO ABG and ventilatory parameters were recorded as close as possible to ECMO initiation, within a 6-hour window prior to starting ECMO. Post-ECMO ABG and post-ECMO ventilatory parameters were collected around 24 hours after ECMO initiation, with measurements not taken prior to 18 hours or after 30 hours. Additional data included parameters related to ECMO gas flow, ECMO time, the need for blood products, inotropic and vasoactive support, complications, ICU duration, and mortality. Complications were documented according to the ELSO guidelines [6,9].

$$\text{Mechanical Power} = \frac{\text{VE X (Peak Pressure + PEEP + F/6)}}{20}$$

VE, minute ventilation; PEEP, Positive end-expiratory pressure; F, inspiratory flow

Figure 1. Mechanical Power Formula Proposed by Giosa *et al.*

Case series presentation

Case 1

A 29-year-old female, who had experienced her last severe asthma attack three years earlier, requiring intubation and MV, was a regular user of beta-2 inhalers, using them approximately twice a week. She initially presented at another healthcare facility with a severe asthma exacerbation, where standard treatment for her acute asthma attack was initiated but showed a poor response, leading to intubation with oxygen administered through Bag-Valve-Mask (BVM) ventilation. She was then transferred to our emergency department. Her vital signs at admission were as follows: blood pressure 152/120 mmHg, heart rate 149 beats per minute, respiratory rate 12 breaths per minute, oxygen saturation (SO_2) at 97%, and a temperature of 37 degrees Celsius. Physical examination revealed the use of accessory muscles, universal wheezing, and rhonchi in both pulmonary fields. The patient was then connected to a ventilator in pressure control mode, with settings detailed in Table 1. A chest X-ray indicated signs of hyperinflation without other abnormal findings. Initial ABG documentation revealed severe respiratory acidosis. She was subsequently transferred to the ICU for hypercapnic respiratory failure in the context of SA/NFA, with a poor response to standard care.

Upon ICU admission, the patient required high airway pressures, resulting in barotrauma, hemodynamic decompensation, and cardiopulmonary arrest. She responded to cardiorespiratory resuscitation, and vasoactive support with norepinephrine was initiated, requiring high doses, leading to the initiation of vasopressin. Despite continuous nebulization with salbutamol, she persisted with severe bronchospasm, prompting the administration of ketamine infusion and general anesthesia with sevoflurane. A chest X-ray revealed a right pneumothorax, which was treated with thoracostomy, resulting in a secondary bronchopleural fistula of 50% (Figure 2). Additionally, ABG results indicated further respiratory acidosis, requiring high ventilatory parameters with a MP of 14 joules/min. VV ECMO was initiated. Blood gases and ventilatory parameters slightly improved during the first 12 hours of ECMO, with a decrease in MP of 61.5% (Table 1). The patient was on ECMO for a total of 11 days (Table 2). However, she experienced several pulmonary, hematologic, renal, and infectious complications and

Table 1. Patient's overview, pre and post ECMO ABG's and ventilatory settings.

	Patient 1		**Patient 2**		**Patient 3**		**Patient 4**		**Patient 5**		**Patient 6**	
Gender	Female		Female		Female		Female		Female		Male	
Age	29		33		53		55		17		49	
Weight	65		60		45		70		90		60	
ECMO ABG	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
pH	6.99	7.47	6.8	7.3	6.97	7.41	7.01	7.5	7.01	7.36	6.90	7.49
$PaCO_2$ (mmHg)	121	37	183.4	33.2	148.2	35	124	42.8	100	42	125	32
PaO_2 (mmHg)	112	158	74.2	65.1	167	134	83	65.9	191	42	206	63
HCO_3 (mmol/L)	28	26.4	28.3	18.1	-*	24	35	29.9	22	23	-*	24
SaO_2 (%)	95	99	71.2	91	100	99	90	94.8	95	90	99	94
Pre ECMO Ventilatory settings	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Respiratory rate (rpm)	14	14	10	18	14	10	8	18	22	10	18	10
FiO_2 (%)	52	24	90	21	80	40	70	32	100	30	65	30
PIP (cm H_2O)	39	23	57	24	30	10	49	22	49	18	40	22
PEEP (cm H_2O)	7	8	2	10	5	5	9	8	8	8	8	8
Paw (cm H_2O)	10	11	17	14	16	7	19	10	18	12	11	14
Mechanical Power (Joules/min)	14	5.4	7.2	3.4	9.5	2	11	1.9	20.2	2.2	15.6	4

*Undetectable HCO_3 values.

died 13 days after her ICU admission (Table 3). Her ventilator-free days (VFD) score was 0.

Case 2

A 33-year-old woman, who had experienced her last acute asthma attack a month earlier, sought medical attention at a primary health center due to a progressive shortness of breath and wheezing that did not improve with inhalation therapy with beta-2 agonist and anticholinergic inhalers at home. Initially, she was prescribed an IV steroid regimen and inhalation therapy with short-acting beta-2 agonist for an acute asthmatic episode, along with non-invasive mechanical ventilation (NIMV), with a poor response. Consequently, she was referred to our institution as a life-threatening emergency. Upon admission, her vital signs were as follows: blood pressure 146/81 mmHg, heart rate 130 beats per minute, respiratory rate 32 breaths per minute, SO_2 at 96%, and a temperature of 36 degrees Celsius. Physical examination revealed the use of accessory muscles, decreased breath sounds, and universal expiratory wheezing. Standard therapy was initiated, and a chest X-ray indicated air trapping without other abnormal findings. Initial ABG analysis showed respiratory acidosis. However, the patient's

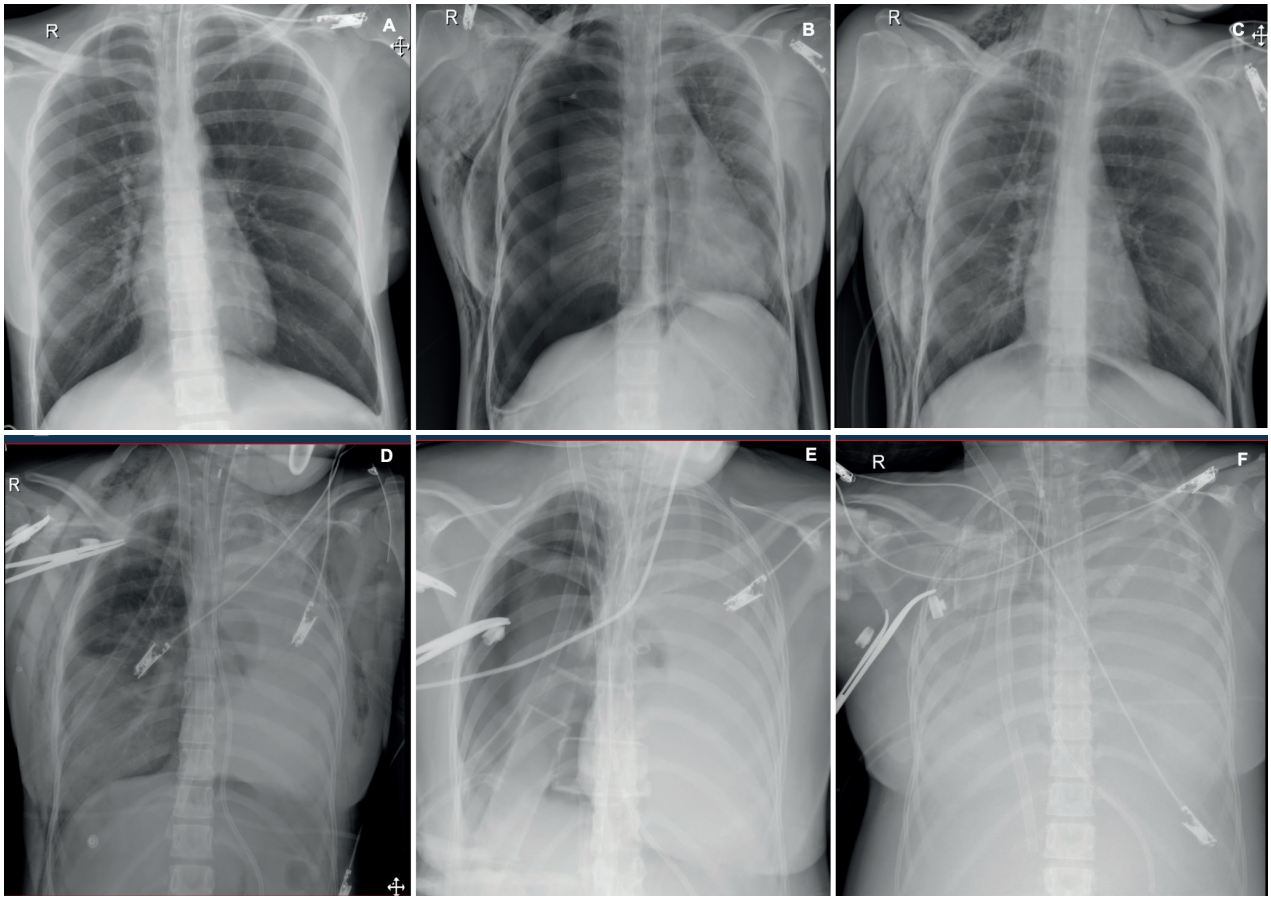

Figure 2. Sequential chest X-ray of case 1. A. Signs of pulmonary hyperinflation with diaphragmatic flattening. Orotracheal tube in proper position, there are no consolidations and pleural angles are free. B. Severe right pneumothorax, subcutaneous emphysema, displacement of mediastinal structures to the left. Presence of a nasogastric tube. C. Mild pulmonary expansion with large subcutaneous emphysema. The chest tube is directed towards the pulmonary apex, a superior vena cava catheter is placed. D. Complete opacity of the left hemithorax with ipsilateral displacement of mediastinal structures, suggestive of atelectasis and presence of a hernia in the right lung. There is subcutaneous emphysema on both pulmonary fields. E. Severe right pneumothorax with complete collapse of the lung, right chest tube, mediastinal displacement to the left. F. Complete opacity of both pulmonary fields due to massive pleural effusion, right chest tubes and displacement of the trachea to the right. R: right side.

Table 2. ECMO indication, parameters and support

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Indication for ECMO	Hypercapnic respiratory failure Respiratory acidosis Right bronchopleural fistula 50% (Barotrauma) Cardiac arrest	Hypercapnic respiratory failure Respiratory acidosis VILI	Hypercapnic respiratory failure Respiratory acidosis	Hypercapnic respiratory failure Respiratory acidosis	Hypercapnic respiratory failure Respiratory acidosis	Hypercapnic respiratory failure Respiratory acidosis
Flow (L/min)	3,5	3,2	2	3	3,4	3
FiO_2 (%)	80	40	40	30	90	100
Gas flow (L/min)	2	3.5	3.5	2	3	4
ECMO time (h)	288	168	96	144	168	144
Blood transfusion						
RBC	16	3	2	4	2	0
FFP	20	0	0	0	0	0
Cryo	15	0	0	0	0	0
Vasoactive support (days)	12	6	N/A	4	N/A	4
Inotropic support (days)	2	6	N/A	N/A	N/A	N/A
Hemodialysis	Yes	No	No	No	No	No

VILI, ventilator induced lung injury; RBC, red concentrate blood; FFP, fresh frozen plasma; Cryo, cryoprecipitate.

Table 3. Patient complications during and posterior to ECMO and outcomes.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Mechanical complications						
Circuit-related	No	No	No	No	No	No
Cannula-related	No	No	No	No	No	No
Medical complications						
Hemorrhage	No	No	No	No	No	No
Neurologic	No	No	No	TIA	No	No
Renal	AKI	No	No	No	No	No
Cardiovascular	Cardiac arrest, Ventricular fibrillation	Left ventricular dysfunction	No	Tamponade	No	No
Pulmonary	Left Pneumothorax, pulmonary hemorrhage	No	No	No	No	No
Metabolic	DIC	No	No	No	No	Hemolysis
Infectious	VAP	No	No	No	No	Pneumonia
Patient limb	No	No	No	No	No	No
VFD	0	23	26	9	26	26
ICU stay	13	9	8	18	8	11
Total Hospital Stay	13	11	9	19	0	0
Mortality	Yes	No	No	No	No	No

VAP, ventilator-associated pneumonia; DIC, disseminated intravascular coagulation; VFD, ventilator free-days.

condition worsened, and she became desaturated and fatigued, requiring intubation and the initiation of MV for hypercapnic respiratory failure.

Ventilating the patient proved challenging due to high airway resistance, leading to the administration of neuromuscular blockade with vecuronium and optimization of sedation with a ketamine infusion. A blood sample revealed an elevated white blood cell count, suggesting pneumonia, so antibiotics were initiated. The patient was then transferred to the ICU, where standard medical care continued, and nebulized adrenaline was added to the management. Nevertheless, her oxygen saturation continued to decline (SO_2 84%), and she became hypotensive (blood pressure 80/40 mmHg), with persistently high airway resistance. Vasoactive support and general anesthesia with sevoflurane were introduced. New ABG revealed mixed acidosis and severe hypercapnia, which proved refractory to management, with a MP of 7.2 J/min, prompting the initiation of ECMO (Figure 3). All microbiologic cultures and acute-phase reactants yielded negative results, and bronchoscopy revealed no remarkable findings, leading to the suspension of antibiotics. ABG values improved, as did ventilatory parameters, with a 53% decrease in MP (Table 1). Five days after ECMO initiation, the patient was successfully weaned from MV, achieving a VFD score of 23. She remained on ECMO for one more day, totaling 6 days (Table 2). A transthoracic echocardiogram reported moderate ventricular dysfunction with no other complications. She was discharged after a total of 11 days (Table 3) (Figure 4).

Case 3

A 53-year-old woman sought care at an external institution due to 3 days of worsening dyspnea and a dry cough. She presented with tachypnea, use of accessory muscles, and generalized wheezing in both lung fields. Inhalation therapy with a beta-2 agonist and an IV steroid regimen was initiated, but the patient had a poor response, leading to intubation and the initiation of MV. Subsequently, she was transferred to our institution. Upon admission, her vital signs were as follows: blood pressure 135/75 mmHg, heart rate 120 beats per minute, respiratory rate 35 breaths per minute, SO_2 at 98%, and a temperature of 36 degrees Celsius. Physical examination revealed decreased breath sounds and wheezing. Standard care for SA was initiated and MV was continued. A chest X-ray showed no remarkable

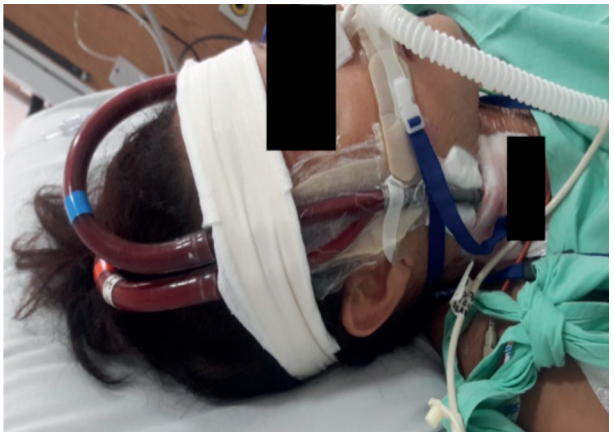

Figure 3. Appearance of the 27 Fr Avalon cannula located in the right internal jugular vein in the veno-venous system, under ultrasound guidance.

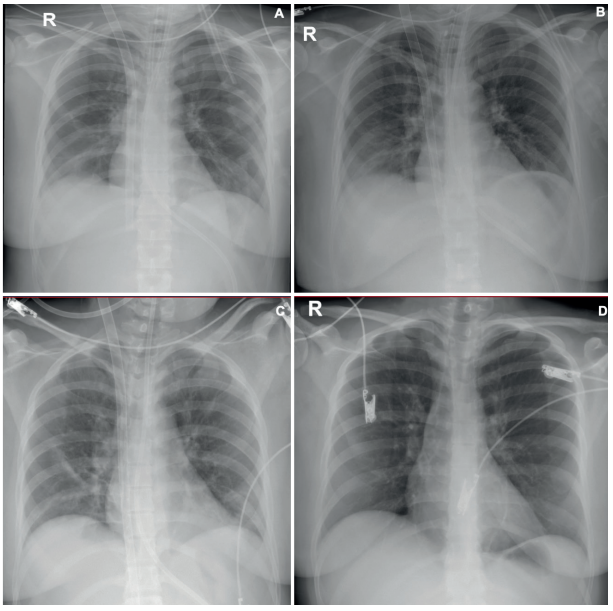

Figure 4. Sequential chest X-ray of case 2. A. thickening of the peribronchial weave, nasogastric tube, ECMO cannula in place and right subclavian catheter with its distal end in the right atrium. There are no areas of consolidation or pleural effusion. B. Veiling of the right costophrenic angle due to a small pleural effusion, with no areas of consolidation. C. Small band of right flat atelectasis, patent airway, presence of ECMO cannula and right subclavian catheter. D. Recovery chest X-ray showing a normal cardiac silhouette, normal pulmonary fields and a normal mediastinum.

findings besides air trapping7, and the initial ABG analysis indicated respiratory acidosis.

Despite continuous salbutamol nebulization and ketamine infusion, the patient continued to have a poor response, experiencing high airway pressures that hindered adequate ventilation. Respiratory acidosis worsened, and MP reached 9.5 J/min (Table 1). Consequently, she was transferred to the ICU, where the medical team determined that she would benefit from VV ECMO. After 12 hours of ECMO, the patient achieved normocapnia, had adequate oxygenation, and experienced a 79% decrease in MP. A sputum chain polymerase reaction was positive for rhinovirus/enterovirus, while her white blood cell count was normal, and acute phase reactants were negative. She was weaned from MV two days later with a VFD score of 26. Her ECMO support lasted for a total of 4 days (Table 2), and she did not encounter any complications. The patient was discharged after a total of 9 days (Table 3).

Case 4

A 55-year-old female patient consulted an external institution due to progressive dyspnea. She was tachypneic, requiring the use of accessory muscles, and her SO_2 dropped below 80% despite management with NIMV, terbutaline and dexamethasone nebulizations, and IV steroid. The patient was subsequently transferred to our institution with the following vital signs: blood pressure 153/93 mmHg, heart rate 126 beats per minute, respiratory rate 27 breaths per minute, SO_2 at 93%, and a temperature of 35.7 degrees Celsius. She displayed no neurological response. Intubation was performed and MV was initiated along with standard care. A chest X-ray revealed air trapping, and the initial ABG analysis indicated respiratory acidosis. She was then transferred to the ICU, where management continued, adding neuromuscular blockade, ketamine, and prophylactic antibiotics due to the possibility of bronchoaspiration. Vasoactive support was also initiated.

Despite these interventions, the patient continued to experience severe bronchospasm, respiratory acidosis, and high ventilatory parameters, with a MP of 11 J/min (Table 2). ECMO was considered, but during the procedure, the patient suffered cardiac tamponade, requiring drainage through a pericardial window. Following the procedure, anisocoria was documented but resolved within 24 hours, suggesting a transient ischemic attack. A cerebral computerized tomography (CT) scan yielded unremarkable results (Table 3). Gas exchange began to improve, as did ventilatory parameters, with a decrease in MP of 82.8% (Table 1). An attempt to extubate was made 3 days after ECMO initiation, but the patient exhibited agitation, dyspnea, and severe bronchospasm, requiring reintubation, despite normal ABG. Two days later, a tracheostomy was performed due to persistent bronchospasm. ECMO support continued for a total of 6 days (Table 2). After 18 days in the ICU, when there was no evidence of bronchospasm and her oxygenation was adequate, she was transferred to the intermediate care unit to continue the weaning process from MV and undergo pulmonary rehabilitation. The patient experienced no other complications and was discharged after a total of 19 days with a VFD score of 9 (Table 3) (Figure 5).

Case 5

A 17-year-old female patient arrived at an external primary care center with a two-hour history of worsening dyspnea and a dry cough. Initial treatment included nebulizations with a short-acting beta-2 agonist, IV steroid, and magnesium sulfate. Despite these interventions, the patient did not respond well and her respiratory condition continued to deteriorate, necessitating an urgent transfer to our institution. Upon admission, she was in respiratory failure with altered sensorium, requiring immediate intubation and MV. Her vital signs were as follows: blood pressure 137/84 mmHg, heart rate 101 beats per minute, respiratory rate 40 breaths per minute, SO_2 98%, and temperature 36.7 degrees Celsius. During the physical examination, she exhibited the use of accessory muscles, basal bilateral hypoventilation, and universal inspiratory and expiratory wheezing. Standard management was initiated. Chest X-ray revealed air trapping, and the first ABG showed severe respiratory acidosis. Furthermore, high airway pressures and a MP of 20.2 J/min were documented, leading to the initiation of ECMO. The patient exhibited rapid

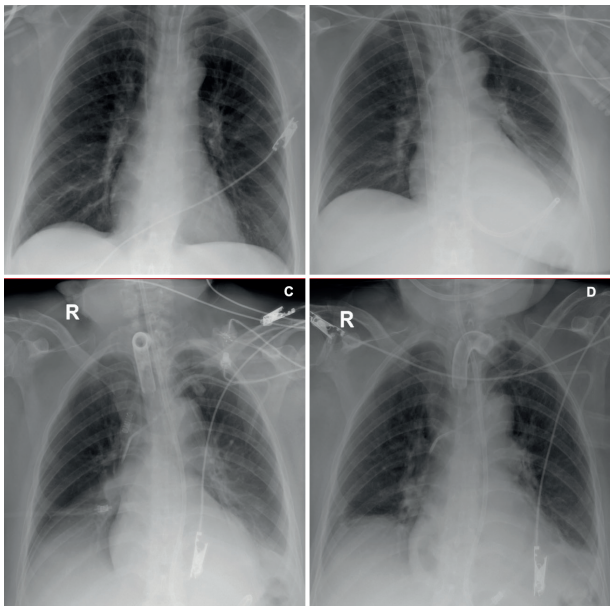

Figure 5. Sequential chest X-ray of case 4. A. Chest X-ray with adequate pulmonary expansion, orotracheal tube correctly positioned. B. A left basal opacity is identified, secondary to pleural effusion with increased retrocardiac density due to atelectasis/consolidation, presence of ECMO cannula in right jugular vein. C. Tracheostomy cannula, pulmonary congestion and bilateral pleural effusion. D. Tracheostomy cannula, unremarkable pulmonary hila, subsegmentary bilateral basal atelectasis with small pleural effusion, enteral feeding tube and left subclavian catheter.

improvement in ABG (Table 1), with a subsequent decrease in MP by 89.2%. After two days, she was successfully extubated, achieving a VFD score of 26. ECMO support continued for a total of 8 days (Table 2). The patient experienced no complications and was discharged after 8 days (Table 3).

Case 6

A 49-year-old male patient sought medical attention at a peripheral primary healthcare facility due to a gradual onset of dyspnea, bronchospasm, and cyanosis. Initial treatment consisted of inhalation therapy with beta-2 agonist and anticholinergic inhalers but yielded a limited response, prompting the need for intubation and the subsequent transfer to our institution. Upon admission, the patient exhibited the following vital signs: blood pressure 196/91 mmHg, heart rate 125 beats per minute, respiratory rate 22 breaths per minute, SO_2 73%, and a temperature of 36 degrees Celsius. During the physical examination, diffuse wheezing was observed. The orotracheal tube was changed from 7.0 to 8.0, and MV was initiated in conjunction with standard therapy. A chest X-ray showed hyperinflation, with no other apparent findings. The patient showed no response to initial management, presenting severe respiratory acidosis, high airway resistance, and a MP of 15.6 J/min. Consequently, he was promptly transferred to the operating room, where ECMO was initiated, and vasoactive support was added. After 12 hours, the patient exhibited mild improvement but remained hypoxemic. MP had decreased by 74.4% (Table 1). After 2 days, he was extubated but experienced desaturation without hemodynamic instability or an increase in respiratory effort. Therefore, NIMV was continued, resulting in a VFD score of 26. The patient also exhibited symptoms of fever and hemoptysis, which prompted the collection of cultures and the initiation of antibiotic treatment. Given the suspicion of pneumonia, a chest X-ray was requested, which revealed a right basal consolidation. Additionally, a bronchoscopy was performed, revealing the presence of a foreign object in the right mainstem bronchus, which was subsequently extracted. It was a 12 cm long, hollow plastic fragment, that resembled an aspiration probe. While the object's exact origin could not be definitively determined, there was suspicion that it may have been introduced at the primary care health center during respiratory therapy or intubation, as this type of probe is not used in our institution. Following this procedure, ABG values returned to normal, and the airway obstruction resolved. However, the patient developed moderate thrombocytopenia and hemolysis. Considering the risk-benefit relationship, ECMO was removed after 5 days (Table 2). The patient experienced no further complications and was discharged after a total of 11 days (Table 3) (Figure 6).

Discussion

Over the past decade, ECMO has emerged as a last-resort treatment for patients with SA and NFA who do not respond to standard medical therapy. While the available evidence primarily derives from case reports and retrospective cohort studies, ECMO

appears to be an effective rescue therapy, contributing to a reduction in asthma-related mortality rates [10]. In the context of acute respiratory distress syndrome (ARDS), survival rates are estimated to be approximately 67% for patients who are successfully weaned off ECMO, with a 52% survival rate upon hospital discharge. In contrast, when ECMO is utilized in other medical scenarios, such as cardiac arrest, cardiogenic shock, or following cardiac surgery with cardiopulmonary bypass, reported survival rates typically fall within the range of 20% to 30% [11].

As mentioned earlier, while the correction of respiratory acidosis remains a crucial goal in ECMO therapy, preventing VILI is one of the critical factors influencing the mortality of these patients. In fact, the sole mortality in this case series was observed in a patient who had already developed VILI and extensive barotrauma before ECMO initiation. Ventilator-related causes of VILI include large tidal volumes, high pressures, elevated respiratory rates, and large inspiratory flow rates, all of which contribute to the MP equation, as well as pneumothorax [12]. Despite emerging evidence regarding MP, there are no established goals or "normal" limits [7]. However, it is expected that as pulmonary compromise worsens, the threshold for VILI becomes lower. The thresholds for stress, strain, power, and energy may vary, but they depend on the degree of underlying tissue integrity and the extent of the injury [13].

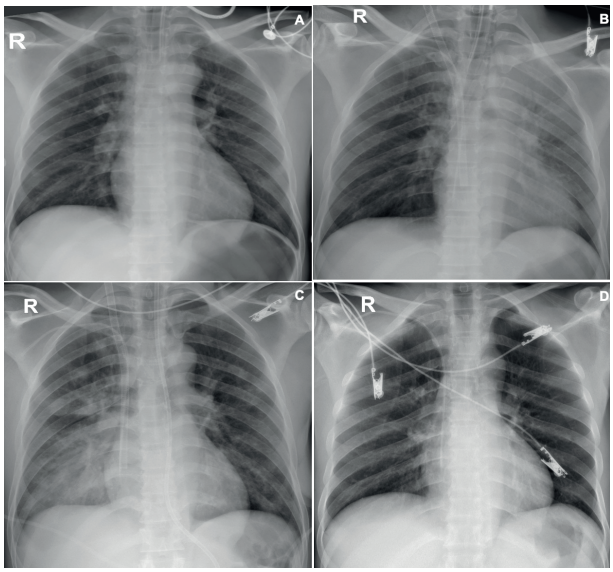

Figure 6. Sequential chest x-ray of case 6. A. Normal cardio aortic silhouette, central trachea, normal mediastinum, orotracheal tube in proper position. There are no consolidations, adequate pulmonary expansion. An image is observed that may correspond to a probe projected to the right intermediate bronchus. B. central trachea, orotracheal tube correctly positioned, right jugular cannula ending in the right atrium. Appearance of consolidation with air bronchogram in the left upper lobe. C. Opacity in the right lower lobe, ECMO cannula in position, enteral feeding tube. There is no evidence of pleural effusion. This image is posterior to the extraction of the foreign body located in the right intermediate bronchus. D. Image prior to discharge showing a normal trachea, normal cardiac silhouette, mediastinum and lung fields. There is no evidence of pneumothorax or pleural effusion.

Nevertheless, a reduction in MP as an indicator of the risk of developing VILI should be considered a safety measure in therapy. Therefore, when evaluating the efficacy of ECMO, one should not only focus on ABG values but also on the decrease in ventilatory parameters, especially those variables contributing to MP. Calculating MP can be complex, involving mathematical processes and the manipulation of the ventilator to measure certain variables. Some simpler formulas have been proposed, such as the one described by Giosa *et al.* (Figure 1), which we used in this case series [14]. This formula is intended for use in volume-controlled ventilation and includes variables like minute ventilation, peak pressure, positive end-expiratory pressure (PEEP), and inspiratory flow.

It should be noted that the formula proposed by Giosa *et al.* made a significant assumption that could introduce bias in calculations. This assumption involved a fixed value for respiratory system resistance at 10 cm H_2O/L/sec, which is an average value commonly found in the literature for mechanically ventilated patients [14]. However, certain conditions, such as COPD and asthma, primarily impact airway resistance, potentially leading to higher respiratory system resistance values and consequently an increase in mechanical power [14,15]. Nevertheless, during the development of this simplified formula, a secondary analysis was conducted on patients with respiratory system resistances greater than 15 cm H_2O/L/sec, with a median value of 18.9 cm H_2O/L/sec. This analysis revealed a minor underestimation bias, which still ensures the accuracy of the formula when applied to patients with elevated resistances [14].

In our case series experience, we observed that after 12 hours of ECMO support, not only did we achieve correction of respiratory acidosis, but we also noted a significant reduction in all ventilatory parameters and a decrease in MP ranging from 52.8% to 89% (Tables 1 and 3). Furthermore, among the 5 surviving patients, all but one, who required a tracheostomy, had a high VFD score, with a mode 26 days (Table 3). This highlights a substantial reduction in ventilation time.

On the other hand, ECMO is a complex process that demands specific resources and multidisciplinary management and may result in serious, and even fatal, complications [16]. These complications can be categorized as mechanical or medical, with the former being associated with the circuit and cannulation process, device-related issues, insertion complications, anticoagulation, or the therapy's effects on distal organs [17]. Common complications reported include cardiovascular issues (particularly the need for inotropes during therapy), renal problems, culture-proven infections, the presence of clots in the oxygenator, and hemorrhagic complications (mainly related to cannula and surgical site bleeding) [11,17]. Survival rates for these complications range from 47% to 58%, decreasing to 28% to 30% for rarer but more severe complications like central nervous system infarction and hemorrhage, as well as disseminated intravascular coagulation, respectively [18].

A retrospective cohort study, based on the ELSO registry, analyzed survival and complication rates in 1257 cases. Out of these, 24 patients received ECMO for SA, while the remaining cases were non-asthmatic. Asthmatic patients were younger, received less MV before ECMO initiation, had shorter ECMO durations, exhibited greater acidosis, and less hypoxia. The survival rate among asthmatics was 83.3% compared to 50% in the non-asthmatic group. The complication rate was 79.2%, with mechanical and bleeding complications being the most prevalent [5]. Similarly, in our experience, the survival rate is high (83%), as evident in this case series where only one out of six patients died. We encountered a total of 9 complications, with cardiovascular issues being the most common. Apart from a cardiac tamponade during cannulation, no patient experienced significant hemorrhage.

Conclusions

ECMO finds utility in a diverse range of medical scenarios, including the management of SA/NFA when conventional treatments prove ineffective. Our experience indicates that ECMO is an effective therapy capable of addressing acidosis and mitigating VILI, resulting in a notably high survival rate, despite the relatively elevated complication rate (40.2%) [19]. It is crucial to recognize that ECMO serves as a life-saving intervention for critical situations. Additionally, the growing use of MP as a tool to enhance safe ventilation is promising, even though more extensive data is required for a comprehensive evaluation of its role in assessing the risk of VILI development and the overall success of ECMO therapy.

Abbreviations

SA: Status asthmaticus
NFA: Near fatal asthma
ICU: Intensive Care Unit
MV: Mechanical ventilation
ECMO Extracorporeal membrane oxygenation
ELSO: Extracorporeal life support organization
CO_2: Carbon dioxide
VILI: Ventilator induced lung injury
MP: Mechanical power
IV: Intravenous
P_{plat}: Plateau pressure
cm H_2O: Centimeter of water
PaO_2/FiO: Oxygen arterial pressure/inspired fraction of oxygen
CNS: Central nervous system
ABG: Arterial blood gasses
VFD: Ventilator-free days
SO_2: Oxygen saturation
BE: Base excess
VV: Venovenous
BVM: Bag-Valve-Mask
$PaCO_2$: Arterial carbon dioxide tension
PO_2: Partial pressure of oxygen
HCO_3: Bicarbonate
NIMV: Non-invasive mechanical ventilation
CT: Computerized tomography
PEEP: Positive end-expiratory pressure
ARDS: Acute respiratory distress syndrome

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Case Report

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Kyphoscoliosis complicating asthma with fixed airway obstruction

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ABSTRACT

Introduction: Kyphoscoliosis is present in up to 2% of the juvenile population and can have deleterious effects on respiratory mechanics, leading to chronic respiratory failure later on in adult life.

Case presentation: Hereby we describe a 53-year-old patient with severe uncontrolled asthma who presented with chronic hypercapnic respiratory failure. During her medical workup, she was noted to have several comorbidities leading to her respiratory failure. The patient had radiological evidence of bronchiectasis with recurrent episodes of infection, and a severe deformity of the spine due to Kyphoscoliosis. Probably the kyphotic component of this deformity had worsened due to a long history of oral steroid use leading to severe osteoporosis and consequent vertebral compression fractures reaching a Cobb angle of 73 degrees. This was probably caused by the patient's non-compliance with inhaler therapy and an excessive reliance on oral steroid use. Her respiratory failure was treated with domiciliary noninvasive positive pressure ventilation and 24-hour oxygen therapy and her symptoms improved.

Conclusion: A multidisciplinary approach across different specialities is necessary when managing such a patient with kyphoscoliosis, bronchiectasis, asthma with airflow limitation with respiratory failure.

Key words: Kyphoscoliosis, Respiratory failure, Non-invasive ventilation

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Authors' contributions: All authors were involved in collecting data and writing/finalising case report and discussion.

Ethics approval and consent to participate: Written consent obtained and submitted.

Consent for publication: All authors consent to publication.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Introduction

Kyphoscoliosis is defined as "a deviation of the normal curvature of the spine in the sagittal and coronal planes and can include a rotation of the spinal axis"[1, 2] . Adult scoliosis is defined as a lateral deviation of more than 10 degrees in the lateral plane, and kyphosis in the sagittal plane as measured by the Cobb angle, which is formed by the intersection of two lines, one parallel to the top and the other parallel to the bottom vertebrae of the scoliotic or kyphotic curves [1, 3]. We present a 53 year old patient with severe uncontrolled asthma who presented with chronic hypercapnic respiratory failure.

Case report

A 53-year-old woman presented with a 3-day history of worsening shortness of breath on walking a few metres on the flat associated with a cough productive of a large volume of greenish sputum and fever.

On examination, the patient's respiratory rate was 16 breaths/ minute, she had a pulse rate of 110 beats/ minute with a temperature of 39 degrees Celsius, with an oxygen saturation of 85% on air. Auscultation of the chest revealed diffuse wheezing in both lung areas. Arterial blood gases taken while the patient was on oxygen concentration of 28% via venturi mask showed pH 7.34, $PaCO_2$ 86 mmHg, PaO_2 75.1 mmHg, oxygen saturation 93%, lactate 0.6 mmol/litre, and HCO_3^- 48.2 mmol/µl.

On examining the patient's notes, it was noted that she had also suffered from asthma for the previous 20 years and she had been prescribed a fluticasone 250mcg inhaler 2 puffs twice daily and salmeterol 25 mcg inhaler 2 puffs twice daily via metered dose inhaler (pmdi). She had also been prescribed 2 puffs of 100mcg salbutamol on an as-required basis via pmdi. Total IgE was 80 international units/ml (Range 0-30), while IGE to House dust mite 1.58iu/ml (0-0.34) Cat 0.45(0.034). Eosinophil count 0.04(0-0.06x10^{-9}per l). An HRCT thorax taken two years before admission (Figure 1) had shown evidence of Bronchiectasis which had already been detected by another HRCT 6 years previous to the first. Regular treatment included prophylactic azithromycin 500mg three times a week.

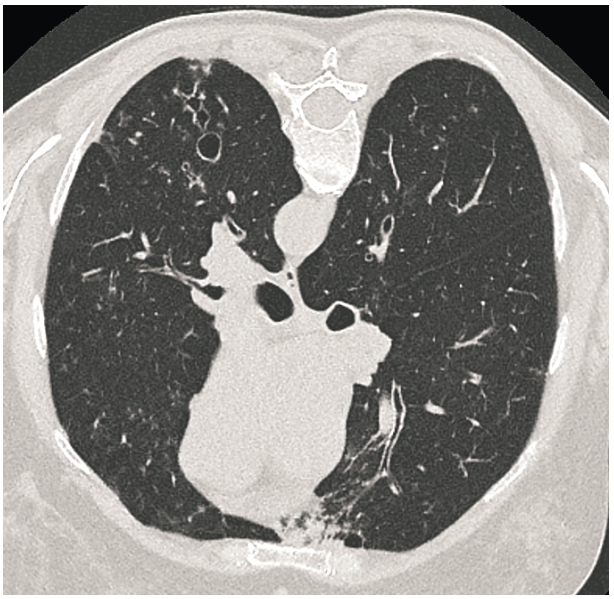


Figure 1. HRCT showing non tapering bronchioles with Signet ring appearance and classic tram track sign appearance of bronchi anteriorly, in keeping with bronchiectasis.

Notwithstanding, she had been persistently symptomatic with frequent visits to her family doctor, or the emergency room up to 3-4 times per month. General practitioner and hospital outpatient notes expressed the opinion that the patient had been poorly compliant with inhaler therapy and often resorted to Beta-agonists via inhalers or nebulizers. She also required regular courses of oral steroids 3-5- times a year. She had also refused a trial of treatment with anti-IgE therapy omalizumab, and was not considered for anti-IL5 therapy because of the low eosinophil counts.

Her lung function tests which included plethysmography and spirometry with a bronchodilator challenge at a medical outpatients (MOP) visit, 28 months before this presentation, were as per Table 1. The FEV_1

Table 1. Plethysmography results 2 years prior to admission.

			% predicted
FEV_1	Volume	0.48 Litre	21%
FVC	Volume	1.28 Litre	43%
FEV_1/FVC	Ratio	0.38	
TLC	Volume	6.45 Litre	143%
Residual Volume	Volume	5.16 Litre	343%
RV/TLC	Ratio	0.8	

and FVC were 21% and 43% of the predicted value respectively. FEV_1/FVC ratio of 38% suggesting a diagnosis of COPD, and labelled GOLD 4. On plethysmography which was performed on a separate occasion, the Residual Volume was significantly high both when compared to the predicted value and as a fraction of the total lung capacity. A reversibility of 17% of FEV_1 was noted on lung function performed on another follow up visit.

Routine blood tests on admission were unremarkable with a C reactive protein level of 40mg/L. A respiratory screen for common respiratory viruses and bacteria (including *Influenza A, B and C, corona NL63, 229E, OC43, HKU1, Metapneumo virus A* and *B, adenovirus, rhinovirus, respiratory syncytial A* and *B, Mycoplasma Pneumonia, Haemophilus influenzae B, Strep. Pneumoniae, Chlamydia Pneumoniae, Klebsiella Pneumoniae, Legionella Pneumophilia/Longbeachae, Moraxella Catarrhalis, Bordatella species, Staphyloccus aureus,* and COVID-19) was negative, as well as a specimen of sputum which also cultured no bacteria.

A chest x-ray (Figure 2) was reported as showing airspace shadowing possibly as result of right lower zone consolidation and the presence of kyphoscoliosis was suspected.

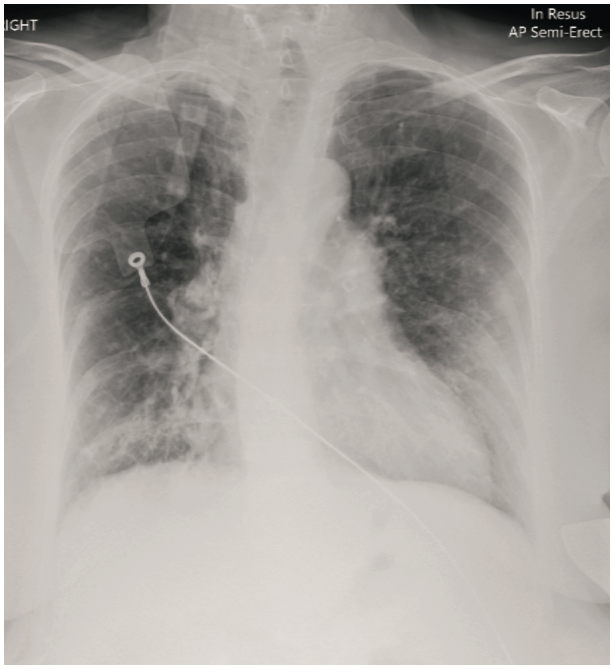


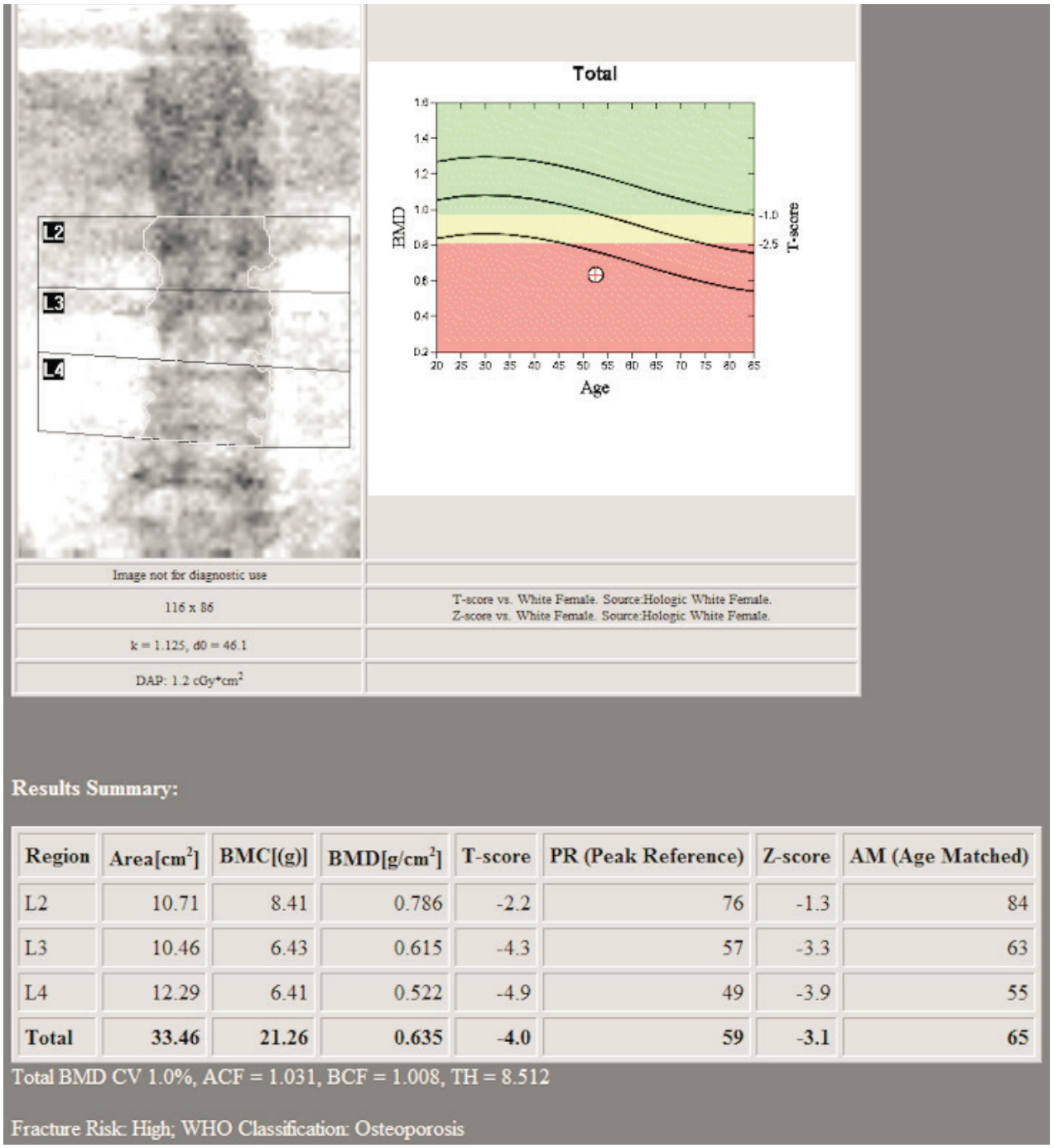
Figure 2. Chest X-ray taken on admission showing airspace shadowing in the right lower zone consolidation and the presence of kyphoscoliosis.

She was started on 28% oxygen and given 5mg of salbutamol and 0.5mg ipratropium bromide via nebulizer , followed by 100mg IV hydrocortisone, 4.5g of piperacillin/tazobactam IV three times daily and a single infusion of intravenous magnesium sulphate of 2g over 30 minutes. She was immediately started on non-invasive ventilation for her acute on chronic hypercapnoeic respiratory failure. She was admitted to hospital where her clinical condition, as well as her arterial blood gas results (Table 2), improved over the next few days; however she remained breathless on exertion on walking around 20m. At that point she was discharged from hospital on a tailing down dose of prednisone and her regular inhaler therapy. Bilevel domiciliary NIV was started at 16 cm IPAP and 5 cm EPAP during the night. She was also prescribed 24-hour oxygen therapy capped at 28% oxygen.

A rheumatology review was organized. A previous bone density result which had been performed a few months before admission showed evidence of severe osteoporosis with a T score of -4.0 and collapse of a number of thoracic vertebrae (Figure 3). This was considered to be most likely due to years of recurrent courses of oral steroids by the patient. In view of this, she was prescribed a yearly 15mg dose of intravenous zoledronic acid, a bisphosphonate. Kyphoscoliosis was confirmed on a scoliogram which reported a right convex thoracic component with a Cobb angle of approximately 19 degree and a left convex lumbar component with a Cobb angle of 16 degrees (Figures 4 and 5). Kyphosis was confirmed on lateral chest x-rays which showed a Cobb angles 73 degrees (Figure 6)..

Table 2. Arterial blood gas results prior to and after initiation of NIV therapy

	ABG during exacerbation on O_2 via 28% Venturi mask (prior to iniation of NIV therapy)	**ABG on NIV**	**Reference Range**
pH	7.34	7.46	7.35 - 7.45
pCO_2	86 mmHg	43.9 mmHg	35 - 45 mmHg
pO_2	75.1 mmHg	66.1 mmHg	80 - 100 mmHg
SO_2	93%	94.5%	95 - 99%
HCO_3^-	48.2 mmol/L	37.2 mmol/L	22 - 26 mmol/L



Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L2	10.71	8.41	0.786	-2.2	76	-1.3	84
L3	10.46	6.43	0.615	-4.3	57	-3.3	63
L4	12.29	6.41	0.522	-4.9	49	-3.9	55
Total	**33.46**	**21.26**	**0.635**	**-4.0**	**59**	**-3.1**	**65**

Figure 3. Bone densitometry result showing evidence of osteoporosis with T-score of -0.4.

Unfortunately, compliance with NIV therapy was also an issue and she relied mostly on oxygen therapy via concentrator.

Discussion

On reviewing her case, multiple factors were considered to be contributing to her type 2 respiratory failure. First of all, the patient had been diagnosed

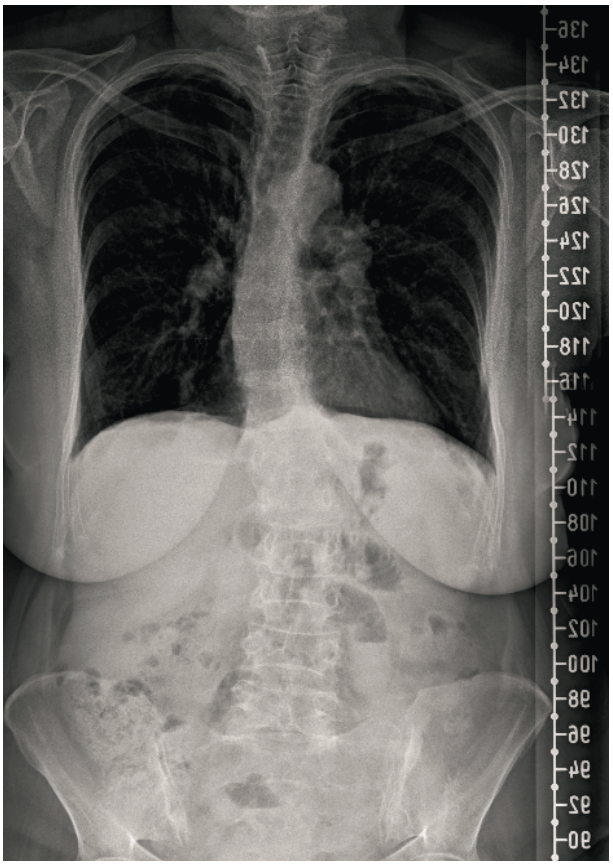


Figure 4. Scoliogram showing thoracolumbar sigmoid scoliosis, with a right convex thoracic component with a Cobb angle of approximately 19 degree and a left convex lumbar component with a Cobb angle of 16 degrees.

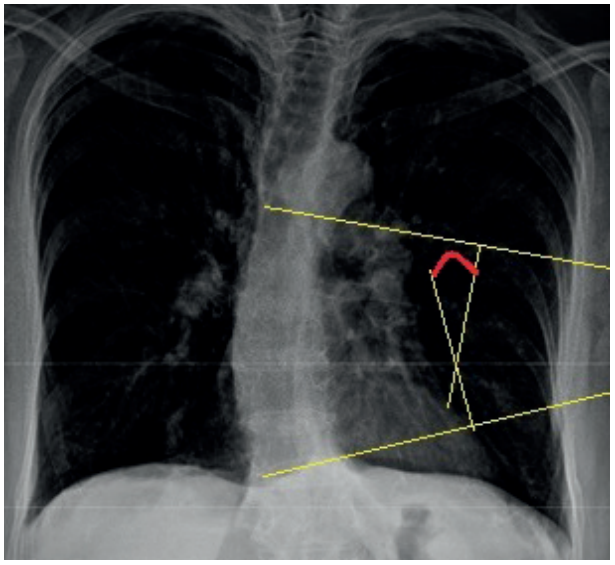


Figure 5. Chest X-ray showing thoracic scoliosis with a Cobb angle of 19 degress.

with asthma over 20 years before. Her medical notes revealed that previous caring physicians had expressed the opinion that the patient was poorly compliant to her regular preventer inhaler therapy and often resorted to beta agonist via inhalers or nebulizers. She also had a longstanding history of regular exacerbations requiring multiple courses of oral steroids and antibiotics.

The Pulmonary function tests suggested that the patient might have suffered from COPD Stage 4 [4]. As the patient was a non-smoker this obstructive airway deficit was more likely to be secondary to long-term uncontrolled asthma, which GINA guidelines more appropriately describe differently as airway remodeling and refer to it as "Asthma with airflow limitation" [5].

Asthma patients with fixed airway obstruction have a worse disease course with increase in symptoms, exacerbations and higher mortality. These patients exhibit a progressive decline in FEV_1 and an exacerbation rate similar to patients with COPD, which is indeed higher than that of asthma patients with no fixed airway obstruction [4, 5].

The presence of bronchiectasis was probably both the consequence of respiratory infections but also a frequent trigger for subsequent acute asthma attacks, which created a vicious cycle with a progressive loss of lung function with every episode as described by Ni Y et al [6]. The diagnosis satisfied the criteria for the definition by the European Respiratory Society guideline on Bronchiectasis as, "a chronic respiratory disease

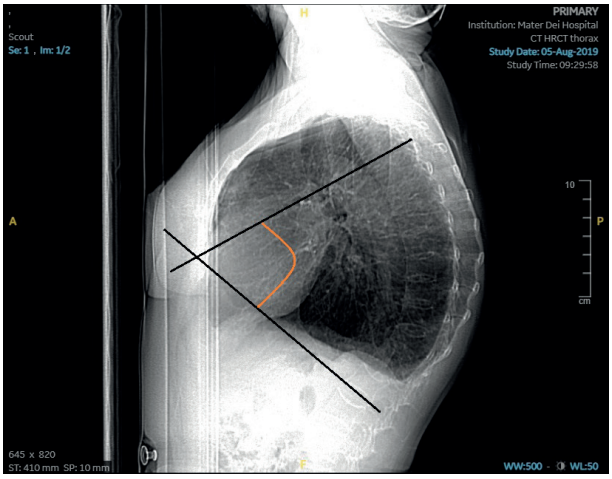


Figure 6. Lateral Chest x-ray showing thoracic kyphosis with a Cobb angle of 73 degrees.

characterized by a clinical syndrome of cough, sputum production and bronchial infection, and radiologically by abnormal and permanent dilatation of the bronchi" [7]. The HRCT taken both at 9 and 3 years prior to the admission both had clearly documented classical "Signet ring" and "tramline" radiological signs of bronchiectasis (Figure 1).

Furthermore, the patient had confounding restrictive lung disease caused by a severe kyphoscoliosis. The patient probably may have had initially a moderate form of idiopathic kyphoscoliosis which was further aggravated over many years by the development of severe osteoporosis, likely to be due to the frequent courses of oral steroids which greatly accentuated the kyphotic curves as indicated by the cobb angle of 73 degrees of the kyphotic curve (Normal <10 degrees). While NIV was successful in this patient during the acute episode, Adıgüzel et al. report that 20% of patients with kyphoscoliosis admitted to intensive care for acute respiratory failure needed intubation where accompanying sepsis was the main reason [8].

Most cases of kyphoscoliosis in adults are idiopathic with genetic, epigenetic, and environmental contributors. It is estimated that up to 2% of the adolescent population may have some degree of kyphoscoliosis [9], amongst whom only 0.4% result in significant clinical problems [9]. Idiopathic kyphoscoliosis has mostly a benign clinical course [1]. However, many cases of kyphoscoliosis are not idiopathic but are the result of loss of muscular support caused by neurological disease, for example muscular dystrophy, cerebral palsy or motor neuron disease [10]. This second possibility was clearly not the cause in this patient and will not be discussed in this paper.

Many countries have school screening programmes for children and adolescents aged 10-18 for the presence of kyphoscoliosis. The US Preventive Services Task Force (USPSTF) concluded that "current evidence is insufficient to assess the benefits and the harms of this screening" [11]. However, it determined that the concurrent of use of the forward bend test, the scoliometer and Moire topography had a 93.8% sensitivity and 99.2% specificity to detect idiopathic scoliosis" [11]. While bent over, palms pressed together and arms dangling, the scoliometer (inclinometer) measures the curvature of the patient's spine, providing objective measurement for possible referral [9]. While Moire imaging by projecting 3D images on the trunk is useful, radiographic examination of the spine remains the gold standard [12].

In adolescent idiopathic scoliosis bracing is recommended for patients with a Cobb angle between 25-45 degrees [9, 13]. There are two types of braces either soft or rigid including 25 different designs [13]. Surgery is reserved only for immature skeletons with a Cobb angle >45 degrees in adolescents; however the description of the various techniques is outside the scope of this paper [9]. The USPSTF found adequate evidence to justify the use of braces, and inadequate evidence for treatment with exercise and surgery [11].

Physical therapy has also been suggested to be helpful in adolescent kyphoscoliosis, in a systematic review of the literature by Gonzales-Galves et al., and suggested that strengthening was more important than stretching in kyphosis while both are important for lordosis [14]. They also conclude that randomized controlled studies are necessary to establish which are the best exercises [14].

Severe Kyphoscoliosis leads to diminished chest wall compliance and impaired respiratory mechanics, leading to progressive hypoventilation, chronic hypercapnic respiratory failure, and hypoxemia [8]. Lung function tests are of a restrictive pattern, with a decrease in total lung capacity and vital capacity, but normal residual volume and a resultant increase in the RV/TLC ratio [1, 2]. In the case reported here the residual volume was greatly increased probably because of severe obstructive airways disease, while the Forced Vital Capacity was greatly decreased by both diseases. In fact the RV/TLC ratio was greatly increased as shown on Table 1.

A functional assessment should be included in these patients. In fact, a 6-minute walk test has been shown to predict the degree of limitation in respiratory function better than pulmonary function tests or arterial blood gases [15]. This was not considered necessary in this case because the patient had dyspnoea on minimal exertion and abnormal arterial blood gases at rest.

Bergofsky et al. in his classical description of 1959 reported three main anatomical changes in the lungs of kyphoscoliosis patients, namely chronic pulmonary

emphysema with bronchial obstruction, changes in the small vessels of the lung, and tangled and compressed vessels. The authors further described that these changes not only reduce lung volume but also distort it by the infoldings of the vertebral column and changing the angulation of the ribs affecting chest expansion [16].

The compliance of the respiratory system and respiratory muscle strength is related to the Cobb angle [2]. When the angle is <50°, there is minimal effect on respiratory system compliance, however, when Cobb's angle is larger i.e., between 50–100°, the compliance of respiration decreases [2]. The disordered elastic load on the respiratory muscles leads to rapid shallow breathing and low tidal volume and shortened inspiratory time [2, 17]. Other measurements that may assist in predicting the effect of KS on vital capacity include the sagittal diameter of the thoracic cage and the total lung area [17, 18].

The patient had a Cobb angle of 19 degrees of her scoliosis and 73 degrees for her kyphosis, indicating that steroid-induced osteoporosis had a greater impact on the kyphosis than the scoliosis (Figures 4-6). The associated vertebral compression fractures would have certainly aggravated the Cobb angle of the kyphotic component.

Tzelelepis et al. suggest the following indications for NIV in the long term treatment of KS, (i) symptoms such as headache, fatigue or dyspnoea, (ii) signs of Cor Pulmonale such as lower limb oedema, (iii) daytime arterial pCO_2 of >45 mm Hg, (iv) <88% nocturnal arterial oxygen saturation [2]. Long term NIV has been shown to reduce the number and duration of hospitalizations and probably increase survival. However, this evidence is not yet supported by randomized controlled studies [2, 19]. In fact, a prospective study done by Gonzalez et al. showed that symptoms in 16 severe kyphoscoliosis patients treated with non-invasive positive pressure ventilation (NIPPV) over a period of 36 months significantly improved with NIV therapy when compared with baseline values. These patients showed a significant improvement in both Pemax and Pimax and nocturnal haemoglobin saturation over the study period, with a better quality of life [20].

Management of patients with kyphoscoliosis and type 2 respiratory failure requires a multidisciplinary approach, which involves various other healthcare professionals. Immunization with Pneumococcal and Influenza vaccines, smoking cessation, keeping an ideal body weight and prompt treatment of acute respiratory infections together with regular exercise are recommended so as to preserve lung function and improve quality of life [2, 9].

Cejudo et al. found that a 10-minute warm-up, 30 minutes of leg exercises on an ergometer cycle and 20 minutes of upper and lower body strength exercises resulted in a decrease in arterial pCO_2 and improvement in peripheral muscle strength, dyspnoea and an improvement in the quality of life when compared with controls after 12 weeks [21]. Fuschillo et al. reported that pulmonary rehabilitation improved muscle strength, endurance and quality of life only for a short time, but did not prevent deterioration after one year [22].

Kinnear et al. report that as spinal TB, and poliomyelitis are becoming less frequent, and the numbers of patients with KS affected by these diseases continue to decrease. Nowadays most patients needing NIV at present are older patients with Idiopathic kyphoscoliosis However, mortality after 25 years of NIV was reported to be 40% [23].

Conclusion

This case clearly outlines the drastic effects severe kyphoscoliosis can have in patients with other underlying common respiratory conditions such as asthma and/or COPD especially when aggravated by steroid induced osteoporosis of the spine . Such an outcome could have been avoided by good patient compliance to inhaler therapy. Domiciliary NIV and 24-hour oxygen therapy via concentrator for respiratory failure offers improvement in symptoms and longer survival together with other supportive measures. Management of such patients requires a multidisciplinary approach across specialities.

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L'angolo della Cultura (non solo Medicina…)

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Cantami, o Musa, con molta passione

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"In questo mestiere di poetare,
non è la calda ispirazione che crea l'idea felice,
ma è l'idea felice che crea il calore ispirato" .
Cesare Pavese

"Le parole cantano.
Esse feriscono. Esse insegnano.
Esse santificano. Esse ci hanno liberato dall'ignoranza
e dal nostro barbaro passato".
Leo C. Rosten, scrittore polacco.

"Cantami, o diva, l'ira funesta del pelide Achille…". È il primo verso della nostra letteratura. È la struttura del proemio: all'inizio c'è un'*invocatio* (invocazione), con la quale il poeta esordisce invocando la musa per ispirare il suo canto e dargli la forza per narrare i fatti raccontati nel resto del poema. Egli compie quest'azione perché deve diventare lo strumento mediante il quale la Musa canta agli uomini le gesta degli eroi e ciò che è narrato nel poema. Il poeta invoca solamente una musa poiché, ai tempi di Omero, le muse non erano ancora nove a patrocinare le varie ramificazioni dell'arte. Analizzando bene il testo, osserviamo che il soggetto di 'canta' è la Musa, non il poeta. Egli è come invasato dalla divinità che ha il potere di stravolgere la coscienza degli uomini, e, attraverso questo stato di 'possessione', è la divinità stessa a parlare, sotto spoglie umane. Tale connubio ha origini antichissime, che si perdono nei meandri del tempo e può avere anche risvolti negativi per gli uomini nel caso di possessioni demoniache. Platone, però, associa il fenomeno dell'entusiasmo soprattutto all'esperienza poetica, e gli esempi si sprecano. Parimenti nel proemio dell'*Odissea*, infatti, si legge: "Narrami o Musa [*Moûsa*], dell' eroe multiforme, che tanto vagò, dopo che distrusse la città sacra di Troia" (Omero, Odissea, I,1-2).

All'inizio dell'*Iliade*, una divinità femminile non meglio specificata viene subito legata a un tema, che è anche una passione: l'irrefrenabile 'rabbia' di Achille contro il sopruso del capo supremo Agamennone, il quale gli porta via la schiava preferita. Achille si ritira dal combattimento e i Greci cominciano a perdere. Poi, il troiano Ettore uccide in duello l'amico strettissimo di Achille, Patroclo. Allora, dimentico della propria ira, Achille ritorna nella battaglia. È preda, ora, di una furia sconfinata, cosmica (ancora 'rabbia',

Figure 1. Omero e la Diva.

ma adesso 'selvaggia'): combatte contro la natura e gli uomini, ammazza senza pietà, insegue sfida e batte Ettore: a lui morente, che lo implora di restituire il suo corpo ai genitori, dice che se gli bastassero l'animo e la rabbia (sempre 'rabbia'), lo sbranerebbe e lo divorerebbe crudo lui stesso. L'*Iliade* è il poema dell'Io collerico e la dea cui il poeta chiede l'ispirazione deve spirare fuoco.

Da dove proviene quest'ira oscura, ostinata, distruttiva? Come fa la Musa a cantarne? All'inizio c'è l'esaltazione, la passione, (la 'belva dell'amore', diceva Saffo), la follia: un'opera di poesia è davvero bella, sostiene Democrito, se composta con *enthusiasmós* e *hierón pnéuma*, 'spirito sacro'. Platone parla di invasamento e mania provenienti dalle Muse: "Impossessatesi di un'anima tenera e pura, la destano e la traggono fuori di sé nell'ispirazione bacchica in canti e altre poesie". Cicerone specificherà: 'Infiammazione dell'animo' e 'afflato di furore'. Dal *Fedro*, Platone ritorna sul tema nello *Ione* e fissa il tutto in un'immagine splendida: il poeta è attratto come fosse da un magnete, che è la Musa. Essa forma gli ispirati, che sono come baccanti: appena colgono un'armonia e un ritmo, si danno alla danza. Dalle fonti di miele che scorrono dalle valli selvose delle Muse, "portano a noi come api i loro canti, così, come api, a volo". Il poeta è infatti un essere leggero, alato, sacro, che non sa poetare se prima non sia stato ispirato dal dio "se prima non sia uscito di senno, e più non abbia in sé intelletto". Passione delle passioni! Anche la filosofia e la scienza hanno la loro Musa. Certo, sono diverse da quelle di un *Filottete*, di un'*Antigone*, di un *Edipo*. Chissà cosa ne avrebbe pensato il loro autore, Sofocle, il quale ha pur composto, pare, un dramma dedicato alle Muse? La prossimità di Muse e passioni ha un seguito eclatante: non solo dove Boccaccio parla del fervor all'origine della poesia, ma addirittura in Dante, il quale non si limita a invocare le Muse all'inizio dell'*Inferno* e del *Purgatorio*, ma dinanzi alla prova poetica suprema, quella del *Paradiso* chiede l'aiuto di Apollo in persona con parole infiammate: "Entra nel petto mio, e spira tue / sì come quando Marsia traesti / de la vagina de le membra sue". Ma veniamo ora a noi.

La primissima idea di un lavoro creativo (romanzo, racconto, poesia, ecc.) è appena una luce che si accende. È una prefigurazione che sarà inseguita tenacemente dallo scrittore nella speranza di avvicinarsi a quella intuizione mitica, assoluta, forse anche sbagliata. In quella intuizione sta il novanta per cento di tutta l'attività creativa di un artista. Se si potessero sommare insieme i momenti di creazione pura - conseguenza di una straordinaria inspirazione - in tutta l'esistenza di un artista (grande quanto si voglia), non si arriverebbe neanche a cinque minuti. Ecco perché Edison fu il coiner, il coniatore, dell'aforisma secondo il quale per portare a termine un opera d'arte occorre "one per cent inspiration, ninety-nine per cent perspiration". Tutto il resto è lavoro quotidiano, falegnameria, talvolta perfino routine. Quindi niente ispirazione perenne, ma casuale, sporadica illuminazione iniziale. La fatica comincia subito davanti alla pagina vuota. L'inizio è il luogo letterario per eccellenza, fuori c'è un mondo completamente diverso - il mondo non scritto - ma ora si deve entrare in un mondo verbale: occorre studiare bene le zone di confine dell'opera letteraria.

Gli antichi avevano una chiara coscienza dell'importanza di questo momento e perciò aprivano i loro poemi con l'invocazione alla Musa, giusto omaggio alla dea che custodisce e amministra il grande tesoro della memoria, di cui ogni mito, ogni epopea, ogni racconto fa parte. Bastava il fuggevole richiamo alla Musa,

Figura 2 Le Muse con Apollo.

Figura 3 Il poeta circondato dalle Muse.

un'invocazione che era anche un addio, un segno di intesa alla folla di eroi e all'intrico di imprese. Insomma, dire "Cantami o diva del Pelide Achille l'ira funesta…" sta a significare che il cantore è tale in quanto ha ricevuto per grazia divina gli insegnamenti degli dei. Omero ricorre alle Muse, perché sono le figlie di Zeus e della memoria (*Mnemosine*). Significa quindi anche non dimenticare gli altri cento episodi della guerra di Troia, oppure, se mi interessa il ritorno di Ulisse, non dimentico per questo il ritorno di tanti altri eroi.

Vediamo che i grandi autori dell'antichità continuavano a distinguere il genio dell'ispirazione dalla fatica di lavorare sodo per scrivere. Infatti, quattro secoli dopo Omero, quel rompiscatole di Aristotile nello scritto *Dell'anima* si faceva premura di distinguere l'ispirazione (*phantasie* dal verbo *phanèm*, mostrare) dalla sensazione e dalla riflessione, come quella facoltà capace di "creare un'immagine davanti agli occhi". Dopo tre secoli l'avvocato, quasi filosofo, Cicerone parla d'ispirazione come "accensione dell'anima". Per Dante, poi, l'ispirazione è un suggerimento dato da Dio per sua grazia. Venendo all'Ottocento, troviamo da una parte Balzac che con la sua *La commedia umana* sforna la bellezza di ottantacinque romanzi in circa vent'anni, un unico grande libro in cui è racchiusa tutta la civiltà nostra contemporanea (Gide chiamò il tutto "il San Gottardo del romanzo"). Dall'altra, c'è un Flaubert che soffrì contemporaneamente o di astenia (*Madame Bovary*) o di bulimia ispirativa (*Bouvard* e *Pecuchet*), in cui affermò che la raccolta dei suoi appunti era alta otto pollici, poco più di venti centimetri. Altri stakanovisti della scrittura furono Tolstoi (quattro anni per *Guerra e pace*, tre per *Anna Karenina*), Gogol (sei anni per la prima parte delle *Anime morte* senza riuscire a scrivere la seconda parte in altrettanti anni); però affermò: "Non conosco nessun genio, tranne quello del duro lavoro". Ma il più originale di tutti fu Rainer Maria Rilke che in *Del Poeta* rivoluzionò l'idea di inspirazione, giacché a suo dire: "l'opera si fa da sola, purché le si dia il tempo di maturare. Bisogna aspettare, lasciate maturare ogni sentimento nell'incosciente, nell'inesprimibile e attendere con tranquillità". E, forse aggiungiamo noi, solo per coloro che credono nell'immortalità.

Ora molti si chiederanno: se Omero (o chi per esso) sentiva il bisogno nel proemio dell'*Illiade* d'invocare l'aiuto di una delle ragazze-Muse (se non sbaglio Calliope), ciò vuol dire che sin dagli antichi aedi l'ispirazione era vitale nella pratica della scrittura. E allora ci chiediamo: «a chi dovrebbe rivolgersi un povero cristo che comincia a scrivere oggi, sapendo di non essere né Omero, né tanto meno Dante?». Rattristati - ma non troppo, c'è ben altro di cui rattristarsi - dalle scritture molto discutibili di varie categorie (professori, giornalisti, scrittori, ecc.) verrebbe da pensare che nell'epoca attuale le Muse scarseggino notevolmente. Tuttavia, seguendo il buon senso, la passione di scrivere soprattutto e se si conosce bene quello di cui si vuol scrivere, parrebbe che tre regole potrebbero essere utili a raddrizzare noi fanatici scrittorelli, oltre ai buoni esempi buoni da seguire.

Innanzitutto, bisogna impegnarsi: se si scrive bene un'e-mail o la lista della spesa, a maggior ragione si scriverà bene un argomento più impegnativo.

Inoltre, chi scrive per farsi capire, deve scrivere chiaramente.

La terza regola ce la fornisce il retore Catone: "*Rem tene, verba sequentur*", se conosci bene quello di cui vuoi scrivere, le parole verranno da sole. È come per un conferenziere o un professore: più conosce l'argomento e meglio lo spiega.

Bastano queste tre regolette per scrivere bene? Ovviamente, no, ma servono per aiutarci: se non siamo ben documentati, pensiamo a Catone; se non abbiamo molta voglia, pensiamo a chi si impegna anche nelle piccole cose; e, infine, al posto di dieci frasi complicate, usiamone due, pensando al mafioso (nella finzione) Silvio Dante – della serie televisiva *I Soprano* - il cui motto era: "Hai qualcosa da dire, e cavolo, dillo subito chiaramente!".

Meeting Calendar

WHEN	WHERE	WHAT	WHO TO CONTACT
		2024	
April 5-7	Pacifico Yokohama North (Japan)	The 64th Annual Meeting of Japanese Respiratory Society: "Pulmonology in the Post COVID-19 Era"	https://www.jrs.or.jp/jrs64/en/64jrs@jrs.or.jp
April 10-12	Mainz (Germany)	Course: "Interstitial Lung Diseases"	www.ersnet.org
April 11-13	Toronto (Canada)	Canadian Respiratory Conference 2024	https://cts-sct.ca/crc/
April 12-13	Matera (Italy)	Congress: "Basilicata 2024. Attualità e side future in Medicina Respiratoria: esperienze a confronto"	www.samacongressi.it
April 29 - May 2	Kyrena (Cyprus)	27th Annual National Congress Turkish Thoracic Society	https://www.toraks.org.tr/
May 2-3	Oxford (UK)	Course: "Thoracic ultrasound training programme"	www.ersnet.org
May 8-10	Tibilisi (Georgia)	IX European Congress on Asthma, COPD & Immunpathology	www.wipocis.org
May 9-11	Athens (Greece)	12th International Primary Care Respiratory Group World Conference	www.ipcrg2024.org
May 17-22	San Diego, CA (USA)	ATS 2024 International Conference	https://conference.thoracic.org/
May 31 - June 3	Valencia (Spain)	EAACI Congress 2024	https://eaaci.org/events/annual-congress/
June 5-8	Glasgow (UK)	47th European Cystic Fibrosis Conference	https://www.ecfs.eu/glasgow2024
June 5-8	Marseille (France)	Skills course: Rigid bronchoscopy	www.ersnet.org
June 6-8	Valencia (Spain)	Congreso Nacional SEPAR	https://www.congresosepar.com/separ2024
June 13-14	Bristol (UK)	Course: "Thoracic ultrasound training programme – part two"	www.ersnet.org
July 10-13	Santiago (Chile)	17° ALAT Congress	https://alatorax.org
July 29-31	Porto (Portugal)	Course: "Respiratory infections"	www.ersnet.org
September 7-10	San Diego, CA (USA)	2024 Lung Conference on Lung Cancer	https://wclc2024.iaslc.org/
September 7-11	Wien (Austria)	ERS Congress 2024	www.ersnet.org
September 30 - October 2	Naples (Italy)	Skills course: paediatric bronchoscopy	www.ersnet.org
October 6-9	Boston, MA (USA)	CHEST 2024 Annual Meeting	Chestnet.org
October 16-19	Marseille (France)	Skills course: Thoracoscopy and pleural techniques	www.ersnet.org
Novembre 7-9	Taormina, ME (Italy)	Pneumomeeting 2024	www.pneumomeeting.it
November 7-10	Hong Kong (Hong Khong)	APSR 2024- 28th Congress of the Asian Pacific Society of Respirology	https://www.apsr2024.hk/#
November 16-18	Milan (Italy)	XXV Congresso Nazionale della Pneumologia	www.sip2024.it

BRONCHO • MUNAL

OM-85 LISATO BATTERICO LIOFILIZZATO

Induce allenamento immunitario innato[1]

Aumenta la capacità di rilevare e rimuovere i patogeni (virus e batteri) e di regolare intensità e durata della risposta infiammatoria delle cellule immunitarie innate[1]

Adulti 7 mg | 30 capsule | € 29,00 | **CLASSE C - RR**

La capsula di **BRONCHO•MUNAL** può essere aperta e il suo contenuto può essere versato in una bevanda* prima della somministrazione**[2]

** acqua, succo di frutta, latte, ecc.*
*** in pazienti che hanno difficoltà a deglutire*

Bambini 3,5 mg
granulato, 30 bustine
€ 23,50
CLASSE C - RR

Bambini 3,5 mg
30 capsule
€ 23,00
CLASSE C - RR

POSOLOGIA

1 capsula o 1 bustina al giorno per 10 giorni consecutivi al mese per 3 mesi consecutivi. Il ciclo di trattamento profilattico può essere ripetuto, se necessario[2]

1. Troy NM, et al. J Allergy Clin Immunol 2022;S0091-6749(22)00040-9.
2. BRONCHO MUNAL, Riassunto delle caratteristiche del prodotto.

ABIOGEN PHARMA

Inquadrare il QRCode per consultare il RCP