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ORIGINAL ARTICLE

Evaluation of pulmonary tuberculosis diagnostic tests in children and adolescents at a pediatric reference center

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Tuberculosis;
Pediatric hospital;
Diagnosis;
Clinical study

Abstract
Introduction: This study evaluates the performance of individual and combinations tests used for pediatric tuberculosis diagnosis at a reference center.
Materials and Methods: Diagnostic test outcomes from children with presumed pulmonary tuberculosis evaluated from January 2005 - July 2010 were compared to a standard diagnosis made by an expert panel of physicians.
Results: Presence of at least one sign/symptom, history of contact, or abnormal chest X-ray (aCXR) individually showed the highest sensitivity (85.7%). While the combination of history of contact, at least one sign/symptom, positive tuberculin skin test, and aCXR had low sensitivity of 20%, but the specificity and a positive predictive value were 100%, respectively. The combination of tests used in the International Union Against Tuberculosis and Lung Disease and the Brazilian Ministry of Health systems showed sensitivity of 28.6% and 71.4% and specificity of 95.8% and 97.0%, respectively.

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Conclusions: In the absence of a gold standard, the combination of clinical history, tuberculin skin test, and aCXR, as well as the Brazilian scoring system serve as simple, low-cost approach that can be used for pediatric TB diagnosis by first-contact care providers.

Introduction

Tuberculosis (TB) remains a major global public health problem and according to the World Health Organization (WHO) in 2017, 10.0 million people developed TB disease, 1.0 million of which were children (aged <15 years). In cases of deaths caused by TB, (aged <15 years) 15% of total deaths and 10% of total deaths in HIV positive cases these values are higher than their share of estimated cases, suggesting poorer access to diagnosis and treatment.[1]

Many clinical and laboratory tests have been proposed for the diagnosis of pediatric TB, but a gold standard is lacking.[2] Currently, pediatric TB diagnosis is based on history of contact, clinical signs, chest radiography, tuberculin skin testing (TST), and microbiological examination. However, children with TB can present clinical signs and abnormalities on chest x-rays (aCXR) that are nonspecific. Moreover, respiratory specimens are difficult to collect and bacteriologic yield is low in pediatric patients, greatly reducing rates of bacteriological confirmation.[3,4]

There is a great need to identify diagnostic tests that are more sensitive and specific for the diagnosis of pulmonary TB in pediatric patients. A number of scoring systems have been proposed for the diagnosis of pediatric TB, though no single system has been adequately validated.[5–8] The Brazilian Ministry of Health (BMoH) system has been evaluated for its use in HIV-infected and uninfected children.[9] In 1998, the International Union Against Tuberculosis and Lung Disease (IUATLD) proposed a system[10] based on different scores according to the local TB epidemiology, which has yet to be validated in other settings.[7]

In this context the aim of this study was to evaluate the performance of single and combinations tests used in the diagnosis of pediatric TB, as well as two scoring systems in a Reference Center in Brazil.

Materials and methods

Study population

The study model was a descriptive, survey of a cohort in a low HIV prevalence setting. Study cohort included children of 14 years of age and under, evaluated for pulmonary TB between January 2005 and July 2010 at the Clinical Hospital of the Federal University of Paraná, the reference center for pediatric tuberculosis in Curitiba, Brazil.

Data collect

Data on epidemiological, clinical, laboratory, radiological and treatment outcomes were extracted from medical records using a standardized questionnaire. Medical records for all children fulfilling inclusion criteria in this time period were able to be recovered. However, patients were excluded if the record didn't contained key data for expert panel diagnosis, if they were transferred to another service or were lost to follow-up before the attending physician made the diagnosis.

Evaluation of diagnostic tests

For diagnostic test evaluation, a presumed pulmonary TB was considered if the subjects presented one of more of the following signs or symptoms: cough for two weeks or more, fever, sweating, pneumonia or wheezing with no improvement after treatment with antibiotics or bronchodilators, loss of appetite, adynamia, and loss or stabilization of weight. In children 2 years and under who had received BCG vaccination, TST greater than or equal to 10 mm was considered positive; in children over 2 years of age, independent of vaccination state, TST greater than or equal to 5 mm was considered positive.[9]

Evaluation of scoring systems

Data from subject medical records were also used to apply two common scoring systems used for diagnosis of pediatric tuberculosis, the IUATLD[10] and BMoH[9] systems. For the BMoH system, both a cutoff of 30 (including ''possible'' and ''very likely'' TB classifications) and a cutoff of 40 (only ''very likely TB'' subjects) were evaluated. As Curitiba City is classified as having low TB prevalence,[11] the IUATLD scoring system for areas of low prevalence was employed here. Additionally, because the IUATLD system does not include follow-up, we evaluated subjects at initial appointment (IUATLD I) and at the subsequent consultation when physician diagnosis was made (IUATLD S), as some subjects presented change in evaluation parameters after administration of non-tuberculosis treatments. For both IUALTD evaluations, a score of 9 or more was considered a TB case.

As a way of creating diagnostic groups for this study, a panel of experts (consisting of an infectious disease specialist and a pulmonologist, both specializing in pediatric TB) evaluated subject data and diagnosed them as a TB, latent TB, or no TB case. In cases where there was disagree-

ment in the diagnosis provided by the two-person panel, a third expert issued a final decision. Experts had access to all patients' data, including TB treatment outcome through a standardized form and classified cases according to their clinical experience.

All analyses were carried out in SAS v9.2. The statistical relationship of sociodemographic characteristics of the different childrenś groups suspected of pulmonary tuberculosis were evaluated by Pearsonś chi-squared and Pearsonś chi-squared with Yates correction and Mann-Whitney. Positive predictive value (PPV) and negative predictive value (NPV) of diagnostic tests were calculated using the prevalence of pediatric TB at the study site (11%), as well as rates found in other healthcare settings (1% and 5%).[9] To assess the degree of agreement between expert diagnoses, a Kappa statistic was calculated and interpreted according to the criteria of Landis and Koch.[12]

Results

From a total of 236 children with presumed pulmonary TB, 21.2% (50/236) were excluded from the study cohort for the following reasons: 24 lost to follow-up before diagnosis, 20 incomplete medical records, and 6 inconclusive diagnoses by expert panel.

Of the remaining 186 children, 34 (18.3%) were classified as not TB, 131 (70.4%) as latent TB and 21 (11.3%) as TB cases. Diagnostic agreement between experts varied from substantial to almost perfect (*Kappa* = 0.94, 0.75, 0.69).

The subjects were then divided into two groups for analysis: active TB group, including the 21 TB cases, and No TB (NTB) group including in this group the 131 latent TB infection and 34 not TB cases.

The Sociodemographic characteristics did not differ between the two groups and is important to highlight that the proportion of boys in the TB group was 52% and in the NTB group 50% ($p = 0.95$); white skin color ratio was 91.7% in the TB group and 79.8% in the NTB group ($p = 0.38$); the median age in year of TB group was 5.7 (0.7–13.9) and in NTB group was 5.8 (0.4–14.9) ($p = 0.94$) and finally the median number people living in a house was 5 (4–13) in TB group and 5 (3–10) in NTB group ($p = 0.13$).

Analysis of epidemiological history showed that 85% of the TB and 91.6% of NTB groups had history of contact with at least one index case. In both groups, a household contact was most common (70% of TB group, 79.3% of NTB group), with the greatest percentage of index cases being parents for both groups (27.7% TB group, 43.5% NTB group). In the TB group, 38.9% of children had contact with more than one adult TB case, which was significantly higher ($p = 0.02$) than the percentage of NTB cases with more than one contact (18.4%).

A significantly higher percentage of TB group *versus* NTB group was positive for all signs and symptoms evaluated, except for dry cough (Table 1) ($p < 0.001$).

To evaluate other potential diagnoses, 46% of subjects that presented at least one sign or symptom were initially treated for other conditions (e.g pneumonia, asthma) prior to final TB diagnosis (data not shown). TB group subjects had significantly less improvement after this initial non-TB treatment ($p < 0.01$). However, it is worth noting that 35% percent of TB group subjects improved clinically, and for these subjects the return of symptoms or the maintenance of altered radiological exams was critical to the later TB diagnosis. No significant difference was found between groups when analyzing co-morbidities that could interfere with the diagnosis of TB (28.6% TB and 24.4% NTB; $p = 0.78$), and only 2 subjects were HIV-positive, both in the TB group.

All subjects in the TB group had previously received the BCG vaccination, while 95.1% of the NTB group had been vaccinated ($p = 0.6$). The TST was positive in 82.4% of the TB group and 57.1% of the NTB group ($p < 0.001$), and the average diameter of positive responses was significantly larger in the TB group (TB group = 19.5 ± 5 mm. NTB group = 15.4 mm $\pm$ 5 mm; $p < 0.001$). aCXR was observed in 85.7% of the TB group and 7.9% of NTB group ($p < 0.001$). In the TB group, smear and culture positive was observed in 23.5% (n = 4/17) and 26.7% (n = 4/15), respectively. In the NTB group, all subjects evaluated were sputum smear (n = 0/44) and culture negative (n = 0/25).

When analyzing the accuracy of single tests for TB diagnosis, the presence of at least one sign or symptom (85.7%), history of adult contact (85.7%) and aCXR (85.7%) showed the highest sensitivity. Evaluating combinations of tests, we found that the BMoH system with a cut-off of 30 showed a higher sensitivity (95.2%) than any single or combined test. While alone, the aCXR showed high accuracy (91.4%), the combination of at least one sign/symptom, history of contact and aCXR increased accuracy (95.1%).

The sensitivity, specificity, and accuracy for individual and combinations of tests are described in Table 2. The sensitivity and accuracy provide useful information to compare performance of diagnostic tests, but not the positive predictive value (PPV) or negative predictive value (NPV).[13]

Therefore, we assessed these accuracy tests using the prevalence of our study cohort as well as simulating prevalence rates found in other healthcare settings (Table 3 and Table 4). Overall, single-test PPV was low. However, looking at test combinations, presence of at least one sign/symptom, history of contact, positive tuberculin skin test and aCXR had a PPV of 100%. Both BMoH and IUTLD systems showed higher NPV values, but lower PPV values, than this combination in all prevalence scenarios.

Discussion

In this study, an expert panel of physicians was employed to directly compare the performance of different tests used in the diagnosis of pediatric TB. We found that while the presence of one or more sign or symptom, history of TB contact, and aCXR had the highest single test sensitivities, the combination of these tests with TST showed highest accuracy and resulted in a PPV of 100% in TB prevalence rates varying from 1% to 11%.

Evaluating the two diagnostic scoring systems, our findings reaffirmed high sensitivity of the BMoH system with cut off of 30 and high specificity with a cut off 40, as well as an NPV above 95%.[14] Our study is the first to evaluate the IUATLD system in a Brazilian population, which was previously shown a range of sensitivity and specificity of this system in different populations.[10] In our cohort, this system showed low sensitivity and high specificity. aCXR was

Table 1 Signs and symptoms present in TB and Not TB groups.

Sign/Symptom	TB Group n = 21 %	Not TB Group n = 165 %	p-value
Cough	16 7	64 38.8%	0.001[a]
Length of cough (days)	21.0[d] 1 – 330[e]	60.0[d] 30 – 730[e]	<0.001[b]
Productive cough	14 66.7%	45 27.3%	<0.001[a]
Length productive cough (days)	21.0[d] 3 – 330[e]	60.0[d] 30 – 730[e]	<0.001[b]
Dry cough	2 9.5%	20 12.1%	1.00[a]
Length dry cough (days)	15.0[d] 1 – 180[e]	30.0[d] 30 – 30[e]	0.52[b]
Sweating	10 47.6%	26 15.8%	0.001[a]
Weight loss	11 52.4%	25 15.1%	<0.001[a]
Fever	9 42.9%	22 13.3%	0.002[a]
Anorexia	7 33.3%	14 8.5%	0.002[a]
Adynamia	5 23.8%	7 4.2%	0.003[a]
Altered auscultation[c]	7 33.3%	7 4.2%	<0.001[a]

[a] Fisher's exact test.
[b] Mann-Whitney.
[c] all reported presence of cough.
[d] Average of days.
[e] Variation of days; TB = tuberculosis.

the single diagnostic test that showed highest sensitivity, accuracy and PPV. While this strongly supports the use of CXR in diagnosis, it is important to note that the clinical implementation of this examination can be cumbersome, as good image quality and trained readers are required for reliable interpretation.[15] The IUATLD system was developed for low-resource settings and does not include CXR.[10] Compared to our analysis of combinations of tests excluding CXR, the IUATLD system had the highest PPV, confirming that this system can be useful as a TB diagnostic approach in regions where CXR is not available.

To further evaluate the tests as a point of care diagnosis approach, we also assessed performance in the absence of CXR and TST results. We found that—compared to the combination of signs/symptoms, history of contact, aCXR, and TST—signs/symptoms and history of contact alone showed a doubling in sensitivity and a reduction in specificity. Moreover, while PPV was greatly reduced, NPV increased in the absence of CXR and TST results. Together, these findings indicate that presence of signs/symptoms and history of contact are useful tests in point of care diagnosis for ruling out TB suspects.

The presence of at least one sign or symptom alone also showed high single test sensitivity, though each signs and symptoms evaluated individually had a much lower sensitivity. In previous studies, the individual sign or symptom with the best performance has varied.[16–20] Together with our data, this suggests it is important to consider all signs and symptoms rather than focus on a particular one when diagnosing pediatric patients. Further, many cases of pediatric TB may be asymptomatic.[21,22] Along with our findings showing the increased sensitivity, accuracy, and PPV of signs and symptoms in combination with other diagnostic tests, this indicates that signs and symptoms are best interpreted along with other diagnostic tests.

Pediatric TB may have high mortality if not detected and treated, though with proper treatment, outcomes are generally good and few adverse effects are observed.[23] Therefore, diagnostic tests should prioritize the avoidance of false negatives over false positives.[9] Therefore in this study we focused on identifying tests with high sensitivity and accuracy, rather than specificity.

In our cohort, a slightly larger percentage of NTB cases had history of TB contact, yet TB contact was part of the test combination that showed the highest accuracy. It has previously been shown that history of TB contact is an important risk factor for childhood TB in low-incidence settings, though it is less informative in high-incidence settings.[19,22,24] At our teaching hospital, the majority of pediatric patients evaluated for TB are contacts of adult TB cases, and thus it is

Table 2 Sensitivity, specificity, and accuracy of single and combinations of tests.

Test(s)	*Single Tests* Sensitivity	Specificity	Accuracy
Cough	76.2	61.2	62.9
Sweating	47.6	84.2	80.1
Weight loss	52.4	84.9	81.2
Fever	42.9	86.7	81.7
Anorexia	33.3	91.5	85.0
Adynamia	23.8	95.8	87.6
Altered auscultation	33.3	95.8	88.7
One or more sign or symptom (SS)	85.7	56.4	59.7
History of contact (HC)	85.7	7.9	16.7
Altered chest x-ray (aCXR)	85.7	91.1	91.4
Positive tuberculin skin test (TST)	60.0	17.6	22.2
Smear positive	23.5	100.0	69.1
Culture positive	26.7	100.0	67.7
Combinations of tests	Sensitivity	Specificity	Accuracy
Cough + weight loss + anorexia	14.3	98.8	89.2
Cough + sweating + anorexia	14.3	95.8	86.6
SS + HC	71.4	61.8	62.9
SS + HC + TST	35.0	72.1	68.1
SS + HC + aCXR	60.0	99.4	95.1
HC + TST + aCXR	35.0	97.0	90.3
SS + HC + TST + aCXR	20.0	100.0	91.4
BMoH: cutoff 30	95.2	91.5	91.9
BMoH: cutoff 40	71.4	97.0	94.1
IUATLD I	28.6	95.8	88.2
IUATLD S	23.8	98.8	90.3

Legend: BMoH: Brazilian Ministry of Health; IUATLD: International Union Against Tuberculosis and Lung Disease.

Table 3 Positive predictive value and negative predictive value for individual tests at various prevalence rates.

	Test(s)	Prevalence of tuberculosis in children 14 and under				
	1%		5%		11%	
	PPV	NPV	PPV	NPV	PPV	NPV
Cough	2.0	99.6	9.4	98.0	19.5	95.4
Sweating	3.0	99.4	13.7	96.8	27.2	92.9
Weight loss	3.4	99.4	15.4	97.1	29.9	93.5
Fever	3.2	99.3	14.5	96.7	28.4	92.5
Anorexia	3.8	99.3	17.1	96.3	32.7	91.7
Adynamia	5.4	99.2	22.8	96.0	41.0	91.1
Altered auscultation	7.4	99.3	4.7	91.3	10.3	81.7
One or more sign or symptom (SS)	2.0	99.8	9.8	96.7	19.5	97.0
History of contact (HC)	0.9	98.2	4.7	91.3	10.3	81.7
Altered chest X-ray (aCXR)	8.9	99.8	33.7	99.2	54.4	98.1
Positive tuberculin skin test (TST)	0.7	97.8	3.7	89.3	8.3	78.1
Smear positive	100.0	99.2	100.0	96.1	100.0	91.4
Culture positive	100.0	99.3	100.0	96.3	100.0	91.7

Legend: VPP:Positive Predictive Value; VPN: Negative Predictive Value.

not surprising that history of contact alone is insufficient for diagnosis. The TB cases had a significantly higher rate exposure to multiple contacts ($p = 0.02$), which may have led to a greater burden of exposure and illness. Thus, while TB contact is an important diagnostic test, our results indicate that it is best applied in combination with other tests. Thus, the use of diagnostic scores as auxiliary tools in the diagnosis of TB is favored, since in isolation both TST and contact

Table 4 Positive predictive value and negative predictive value for combinations of tests at various prevalence rates.

	Test(s)	Prevalence of tuberculosis in children 14 and under					
	1%		5%		11%		
	PPV	NPV	PPV	NPV	PPV	NPV	
SS + HC	1.9		99.5	9.0	97.6	18.8	94.6
SS + HC + TST	1.3		99.1	6.2	95.5	13.4	90.0
SS + HC + aCXR	49.8		99.6	83.8	97.9	92.4	95.3
HC + TST + aCXR	10.5		99.3	37.8	96.6	58.8	92.4
SS + HC + TST + aCXR	100.0		99.2	100.0	95.7	100.0	91.0
BMoH: cutoff 30	10.2		100.0	37.2	99.7	58.1	99.4
BMoH: cutoff 40	19.2		99.7	55.4	98.5	74.5	96.5
IUATLD I	6.4		99.3	26.3	96.2	45.6	91.6
IUATLD S	16.6		99.2	50.9	96.1	70.9	91.3

Legend: VPP: Positive Predictive Value; VPN: Negative Predictive Value; SS: One or more sign or symptom; HC: History of contact; TST: Positive tuberculin skin test; aCXR: Altered chest X-ray; BMoH: Brazilian Ministry of Health; IUATLD: International Union Against Tuberculosis and Lung Disease.

history are little help in the diagnosis, especially in places of high incidence of TB.

Others potential limitations of our study is that TST was conducted and read at different locations prior to patient arrival at the hospital. However, in Brazil these tests can only be conducted, in the public health system, by a trained health official using standardized tool. Thus, we believe variability in interpretation to be low. Additionally, chest radiographs were read by the attending physician of each subject, and therefore also may vary in their interpretation. BMoH, since its first publication has undergone some changes, especially related to the TST, the last change was in 2019. This score should still be validated with the current data.

Conclusion

In conclusion, using an expert panel to define the gold standard for TB diagnosis, we were able to compare the performance of individual and combinations of pediatric diagnostic tests. These are simple, low-cost triage tests that can be used as a rule-out diagnostic by first-contact care providers, including physicians and community health workers, as recommended by WHO. Moreover, the BMoH system also performed well in our cohort. Thus, it should continue to be widely used in Brazil in settings with low HIV prevalence.

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Ethical approval

This study was approved by the Ethics Committee of the Clinical Hospital of the Federal University of Paraná (CAAEE 0126.0208.000-08. 26/06/2008).

Conflicts of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Epidemiology, ventilation management and outcome in patients receiving intensive care after non—thoracic surgery — Insights from the LAS VEGAS study

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PPC

Abstract
Introduction and objectives: Information about epidemiology, ventilation management and outcome in postoperative intensive care unit (ICU) patients remains scarce. The objective was to test whether postoperative ventilation differs from that in the operation room.
Material and methods: This was a substudy of the worldwide observational LAS VEGAS study, including patients undergoing non—thoracic surgeries. Of 146 study sites participating in the LAS VEGAS study, 117 (80%) sites reported on the postoperative ICU course, including ventilation and complications. The coprimary outcomes were two key elements of ventilator management, i.e., tidal volume (V_T) and positive end—expiratory pressure (PEEP). Secondary outcomes included the proportion of patients receiving low V_T ventilation (LTVV, defined as ventilation with a median V_T < 8.0 ml/kg PBW), and the proportion of patients developing postoperative

Abbreviations: ARDS, acute respiratory distress syndrome; ARISCAT, assess respiratory risk in surgical patients in Catalonia risk score; CPAP, continuous positive airway pressure; FiO_2, fraction of oxygen in inspired air; ICU, intensive care unit; IRB, institutional review board; LAS VEGAS, Local ASsessment of VEntilatory management during General Anesthesia for Surgery study; NIV, noninvasive ventilation; OR, odds ratio; PBW, predicted body weight; PEEP, positive end—expiratory pressure; PPC, postoperative pulmonary complications; Pplat, plateau pressure; RR, respiratory rate; V_T, tidal volume.

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pulmonary complications (PPC), including ARDS, pneumothorax, pneumonia and need for escalation of ventilatory support, ICU and hospital length of stay, and mortality at day 28.
Results: Of 653 patients who were admitted to the ICU after surgery, 274 (42%) patients received invasive postoperative ventilation. Median postoperative V_T was 8.4 [7.3—9.8] ml/kg predicted body weight (PBW), PEEP was 5 [5—5] cm H_2O, statistically significant but not meaningfully different from median intraoperative V_T (8.1 [7.3—8.9] ml/kg PBW; $P < 0.001$) and PEEP (4 [2—5] cm H_2O; $P < 0.001$). The proportion of patients receiving LTVV after surgery was 41%. The PPC rate was 10%. Length of stay in ICU and hospital was independent of development of a PPC, but hospital mortality was higher in patients who developed a PPC (24 versus 4%; $P < 0.001$).
Conclusions: In this observational study of patients undergoing non—thoracic surgeries, postoperative ventilation was not meaningfully different from that in the operating room. Like in the operating room, there is room for improved use of LTVV. Development of PPC is associated with mortality.

Introduction

Unsafe ventilator settings affect outcomes in critically ill patients with or without preexisting lung damage.[1] Two worldwide observational studies of ventilation management in intensive care units (ICUs), one in patients with acute respiratory distress syndrome (ARDS)[2] and one in patients at risk for ARDS,[3] showed that a substantial proportion of patients does not receive lung—protective ventilation. One worldwide observational study of ventilation management in the operating room (OR), showed a comparable underuse of lung—protective ventilation.[4]

Postoperative pulmonary complications (PPC), like ARDS, pneumothorax, pneumonia and escalation of ventilatory support are associated with postoperative outcomes.[5] Use of intraoperative protective ventilation has the potential to prevent these complications.[6—8] Protective ventilation at least includes the use of a low V_T,[9] and a low driving pressure.[10] The role of PEEP is much less certain, but changes in PEEP that result in a lower driving pressure may reduce postoperative pulmonary complications.[11] There is much less information on the effects of postoperative protective ventilation on outcomes. In cardiac surgery patients, postoperative ventilation with a low V_T has an association with less organ dysfunctions and a shorter intensive care unit (ICU) length of stay.[12] In hypoxemic cardiac surgery patients, postoperative ventilation with higher positive end—expiratory pressure (PEEP) reduces the severity of postoperative complications and shortens ICU and hospital stay.[13]

It is uncertain whether postoperative ventilation management as provided in the ICU, has associations with outcome alike intraoperative ventilation in the operating room has with the occurrence of postoperative pulmonary complications. We performed a substudy of the LAS VEGAS trial[4] in which we tested the hypotheses that postoperative ventilation in the ICU differs from that in the operating room, and that postoperative ventilation settings have associations with postoperative outcomes.

Methods

Study design and ethical concerns

This was a substudy of the LAS VEGAS study,[4] the protocol of the study was first approved by the appropriate Institutional Review Board (IRB) of the Amsterdam University Medical Centers, location 'Academic Medical Center' in Amsterdam, The Netherlands (W12_190#12.17.0227). The protocol of this substudy was not prepublished, but previously announced.[14] This substudy ran in centers that expressed interest in this part of the protocol, and only if it was possible to collect granular ICU data. The results of the substudy have not been reported before.

Each site was requested to seek approval to implement the study protocol from their respective institutional review boards. If required, written informed consent was obtained from patients. The parent study was registered at clinicaltrials.gov (study identifier NCT01601223).

Participants

The LAS VEGAS study included adult patients receiving invasive ventilation via either an endotracheal tube or supraglottic device during general anesthesia for elective or non—elective surgery. Patients were excluded if aged less than 18 years of age, or scheduled for pregnancy—related surgery. Additional exclusion criteria of the current analysis were mechanical ventilation in the week before index surgery, surgery involving intrathoracic procedures (i.e., cardiac or lung surgery), and procedures requiring intraoperative one—lung ventilation. Procedures outside the operating room and patients who required cardiopulmonary bypass were also excluded.

Patients were eligible for participation in this substudy if they were admitted at the ICU directly after surgery——-whether planned or unplanned. Patients admitted to an ICU at a later time point, i.e., if first transferred to the ward and then admitted at the ICU, were also not included.

Data collection

The data collected in the LAS VEGAS study included patient baseline characteristics, and the preoperative risk factors for PPC included in the 'Assess Respiratory Risk in Surgical Patients in Catalonia risk score' (ARISCAT risk score) for PPC.[15,16] During the intraoperative period, ventilation settings were collected hourly, including V_T, PEEP, plateau pressure (Pplat), respiratory rate (RR) and fraction of oxygen in inspired air (FiO_2). During the postoperative period, the highest and lowest daily value of these ventilation variables. In addition, occurrence of PPC was scored up to

postoperative day 5, or up to ICU−discharge, whichever occurred first. Life status was collected up to day 28, or up to hospital−discharge, whichever occurred first.

Outcomes

The coprimary endpoints were V_T and PEEP during intraoperative and postoperative ventilation. Secondary endpoints were the proportion of patients receiving low V_T ventilation (LTVV) in the OR and in the ICU, and other ventilation variables like Pplat, RR and FiO_2, occurrence of PPC, and ICU and hospital length of stay (LOS) and day−28 in−hospital mortality.

Definitions

Low V_T ventilation (LTVV) was defined as ventilation with a median $V_T \leq 8$ ml/kg PBW; ARDS was defined according to the Berlin definition for ARDS;[17] pneumothorax was scored if it was seen on clinically indicated chest X−ray; pneumonia was diagnosed if a new or progressive infiltrate was seen on a postoperative chest X−ray, and if at least two of the following three following features were present−fever ($> 38.0^{\circ}C$), leukocytosis or leukopenia (white blood cell count $> 12 \times 10^9$/ml or $< 4 \times 10^9$/ml) and purulent secretions. Escalation of ventilatory support was defined as any increase in ventilatory support on a subsequent day−from 'simple oxygen administration' (i.e., through a nasal prong, or non−rebreather mask) to 'continuous positive airway pressure' (CPAP), to 'noninvasive ventilation' (NIV) or to 'invasive ventilation'. For example, escalation of ventilation was scored when a patient was on CPAP on day 1, but needed NIV on day 2, and also if a patient received NIV on day 1, but needed 'invasive ventilation' on day 2, etc.

Analysis plan

Descriptive statistics are used to study patient characteristics, ventilation parameters and outcomes. Continuous variables are compared using the Wilcoxon Rank−Sum Test or the Wilcoxon signed−rank test, where appropriate; proportions are compared using the chi−squared test or Fisher exact test. Effects are shown as the average odds ratio with its 95% confidence interval (95% CI).

V_T is reported in absolute volume as well as normalized for PBW. PBW was calculated as 50 + 0.91 x (centimeters of height − 152.4) for males and 45.5 + 0.91 x (centimeters of height − 152.4) for females.[18]

To compare intraoperative with postoperative ventilation, distribution plots are constructed for V_T, PEEP, Pplat and RR. These plots used cutoffs that represent widely accepted values of each parameter and are used in most daily practices; V_T size of 8 ml/kg PBW, RR of 15 breaths per minute, PEEP of 5 cm H_2O and 25 cm H_2O for Pplat to form the matrices. For FiO_2 a cutoff of 40% was used.

Nearly all PPC needed a chest X−ray for confirmation; if a X−ray was not obtained, ARDS, pneumothorax and pneumonia was deemed not present. In one posthoc analysis, patients with a planned postoperative ICU admission are compared to patients with an unplanned admission. Kaplan−Meier graphs are used to compare occurrence of PPC, LOS and mortality in ICU and hospital.

All analyses were performed with R version 3.1 (http://www. R-project.org/). A P value < 0.05 was considered significant.

Results

Participating centers and patients

Among the 146 sites that participated in the LAS VEGAS study, 117 (80%) took part in this substudy in the ICU. The hospital characteristics of sites that did and did not participate are presented in **eTable 1**. Participating hospitals were more often teaching hospitals, with a higher number of ICU beds and hospital beds. Patient flow is presented in Fig. 1. Of 9,185 patients undergoing surgery in hospitals

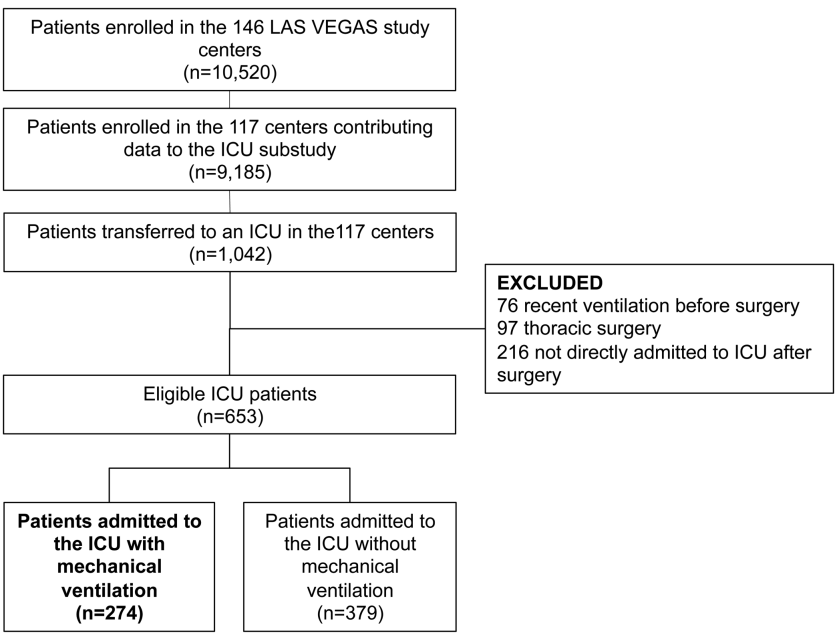

Fig. 1 Flowchart of patients.

participating in this substudy, 1,042 were admitted to an ICU−−0.3 patients per ICU bed over a 1−week period. After exclusion of patients with invasive ventilation before surgery, ICU admission not immediately following the surgical procedure, and patients who underwent thoracic surgery, we were left with 653 fully analyzable patients−−494 patients (76%) with a planned ICU admission, and 274 patients (42%) who continued with invasive ventilation in the ICU. Baseline characteristics of patients are presented in Table 1.

Primary outcome

Ventilation management is presented in Fig. 2 and Table 2. Median duration of postoperative invasive ventilation was 3 [2−7] hours; median duration of controlled ventilation was 1 [0−4] hours, after which patients continued with assisted ventilation until tracheal extubation.

Median V_T in the ICU was 8.4 [7.3−9.8] ml/kg PBW and PEEP was 5 [5−5] cm H_2O, statistically significant but not meaningfully different from V_T (8.1 [7.3−8.9] ml/kg PBW; $P < 0.001$) and PEEP in the OR (4 [2−5] cm H_2O; $P < 0.001$). The proportion of patients receiving LTVV in the ICU was 47%, similar to that in the OR (41%; $P = 0.13$). The proportion of patients receiving a median $V_T > 10$ ml/kg PBW was 21%, higher than that in the OR (10%, $P < 0.001$). The proportion of patients with median PEEP $>$ 5 cm H_2O in the ICU was 23%, higher than that in the OR (14% $<$ 0.001)

Secondary outcomes

Occurrence of PPC was 10%. Six patients (1%) developed ARDS, 13 patients (2%) were diagnosed with a pneumothorax, and 20 patients (3%) developed pneumonia. The most frequent PPC was escalation of ventilatory support−−of 39 patients (6% of total) who developed this PPC, 33 (85%) needed a step up to invasive ventilation (Table 3).

In patients who developed one or more PPCs median length of stay in the ICU and hospital was 3 [1−5] days and 9 [6−18] days, compared to 1 [1−2] days and 8 [5−13] days in patients who did not develop any PPC ($P = >0.01$ and $P = 0.09$). Hospital mortality was 24 and 4% ($P = <0.001$) in patients who did develop one or more PPCs versus patients who did not develop any PPC. Kaplan−Meier curves are presented in Fig. 3. Length of ICU and hospital stay was shorter for patients who did not develop any PPC. When comparing the composite outcome of PPC patients who developed ARDS, pneumothorax or pneumonia to patients who needed escalation of ventilation, patients with a PPC were discharged earlier from the ICU. Of note, as shown in Table 3, patients who developed ARDS or pneumothorax spent the longest time in the hospital. Mortality at day 28 was highest for patients who developed ARDS, and higher for patients who needed escalation of ventilation, compared to patients who developed pneumothorax or pneumonia and lowest for patients with no PPC.

Posthoc analysis

Median length of stay in the ICU and hospital was 1 [1−2] days and 7 [5−9] days, not different between planned and unplanned ICU admissions. Mortality was 6 and 3% ($P = 0.25$), for planned and unplanned ICU admissions.

Table 1 Baseline characteristics.

	All patients N= 653	
Age, Median [IQR]	61	[48.8-72]
ARISCAT score, Median [IQR]	47	[40-51]
Gender, male, N (%)	347	(53.1)
Ethnicity, N (%)		
Asian	17	(2.6)
Black ethnicity	4	(0.6)
Caucasian	561	(85.9)
Hispanic	9	(1.4)
Other	55	(8.4)
Reason for critical care admission, N (%)		
Respiratory failure	73	(11.2)
Intensive monitoring	401	(61.4)
Circulatory failure	86	(13.2)
Routine care (planned)	494	(75.7)
Airway protection	146	(22.4)
Reason for invasive ventilation, N (%)		
Respiratory failure	67	(10.3)
Pneumonia	15	(2.3)
Aspiration	5	(0.8)
Cardiac overload	16	(2.5)
Airway protection	137	(21)
Fatigue	40	(6.1)
Coma	22	(3.4)
Postoperative ventilation	319	(48.9)
Surgical procedure, N (%)		
Lower GI	116	(17.8)
Upper GI, hepatobiliary and pancreas	139	(21.3)
Vascular	30	(4.6)
Aortic	30	(4.6)
Neurosurgery, head and neck	174	(26.6)
Urological and kidney	59	(9)
Gynaecological	46	(7)
Endocrine surgery	6	(0.9)
Transplant	10	(1.5)
Plastic, cutaneous and breast	16	(2.5)
Bone, joint, trauma and spine	47	(7.2)
Other	28	(4.3)
Comorbidity, N (%)		
Liver cirrhosis	15	(2.3)
Metastatic cancer	84	(12.9)
Chronic kidney failure	40	(6.1)
COPD	100	(15.3)
Heart failure	93	(14.2)
Obstructive sleep apnea	26	(4)
Neuromuscular disease	5	(0.8)

Abbreviations: ARISCAT Assess Respiratory Risk in Surgical Patients in Catalonia; IQR interquartile range; GI gastro-intestinal; COPD chronic obstructive pulmonary disease.

Discussion

The findings of this substudy of a worldwide international 1−week observational study in non−thoracic surgery patients can be summarized as follows: (1) approximately 10% of patients is admitted to ICU after surgery, (2) but less than a third of these patients receive postoperative

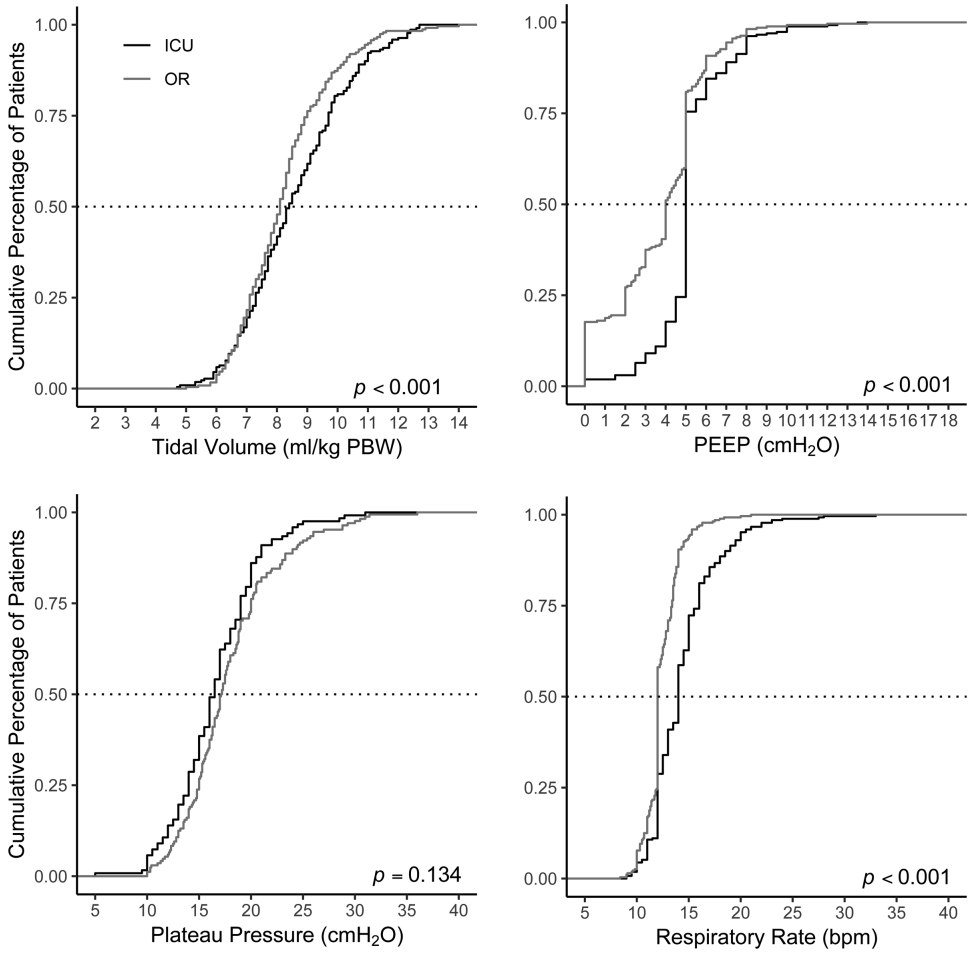

Fig. 2 Ventilation parameters in the operating room vs. in the intensive care unit. Cumulative frequency distribution of tidal volume (top left); positive end−expiratory pressure (top right); plateau pressure (bottom left); and respiratory rate (bottom right).

Table 2 Ventilatory parameters in OR compared to ICU.

Ventilatory parameters	In OR N= 653		In ICU N= 274*		P-value
$V_{T,}$ ml	510	[465-575]	525	[475-600]	0.053
V_T, ml/kg PBW	8.1	[7.3-8.9]	8.4	[7.3-9.8]	0.002
≤ 8	244/516	(47)	92/224	(41)	0.133
> 8	272/516	(53)	132/224	(59)	0.133
≤ 10	466/516	(90)	178/224	(79)	<0.001
> 10	50/516	(10)	46/224	(21)	<0.001
PEEP, cm H_2O	4	[2-5]	5	[5-5]	<0.001
≤ 5	551/645	(84)	200/265	(73)	<0.001
> 5	94/645	(14)	65/265	(23)	<0.001
Ppeak, cm H_2O	18.4	[15.7-21.5]	21	[20-23]	<0.001
Pplat, cm H_2O	16.8	[14.3-19.2]	16.5	[14-19]	0.344
RR, bpm	12	[11.7-13.2]	14	[12-16]	<0.001
FiO_2	56	[47.6-65]	42	[40-50]	<0.001

Data are presented as median [interquartile range] or number (percentage).
OR operation room; ICU intensive care unit; V_T tidal volume; PBW predicted bodyweight; PEEP positive end-expiratory pressure; RR respiratory rate; bpm breaths per minute.
Percentages are calculated on the amount of available values.
*of 653 patients transferred to ICU, 274 patients were on invasive ventilation on day 1.

Table 3 Patient centered outcomes separated for development of PPC.

Outcome parameters	No PPC N = 586		ARDS N = 6		Pneumonia N=20		Pneumothorax N = 9		Escalation of ventilatory support N = 33		P-value
ICU LOS	1	[1-2]	3	[1-5]	2.5	[1-5]	1	[0-4]	3	[2-5]	< 0.001
Hospital LOS	8	[5-13]	16	[11-26]	7	[5.5-17.5]	12	[6-21]	8.5	[6-14]	0.181
ICU death	7	(1.2)	0	0	0	0	1	(11)	3	(9)	0.028
Hospital death	20	(3.4)	3	(50)	2	(10)	1	(11)	10	(30)	< 0.001

Data are presented as median [interquartile range] or number (percentage).
ICU intensive care unit; LOS length of stay; IQR interquartile range; MV mechanical ventilation.
Patients are only counted once, i.e., when a patient scored for ARDS, he is no longer counted for another PPC - from left to right.

ventilation; and (3) duration of postoperative ventilation in the ICU is short. In addition, (4) postoperative ventilation management mirrors management of intraoperative ventilation with regard to V_T and PEEP settings; (5) one in every ten patients develops a PPC, not different in planned and unplanned admissions, and (6) development of a PPC is associated with mortality.

Strengths of this study are its prospective data collection and sample size; this was the largest prospective cohort to date describing postoperative ventilation in non—thoracic surgery patients. This is also the first study comparing intraoperative to postoperative ventilation, and reporting the occurrence of PPCs after surgery in patients who need postoperative care in an ICU. We included a yet non—standard pulmonary complication, named 'escalation of ventilation'. This complication has been proposed before, as it represents respiratory failure other than that caused by ARDS, pneumonia of pneumothorax.[5] We believe this is a strength as it shows a group of patients with worse outcome that would otherwise not have been captured. The short inclusion window of one week for the LAS VEGAS study decreases the influence of changes in care over time. The international, multicenter character of this study likely makes the findings generalizable.

Three large prospective observational studies have showed that there is room for improvement in invasive ventilation practice, in ICU patients with ARDS,[2] in ICU patients at risk for ARDS,[3] and in patients receiving intraoperative ventilation during general anesthesia for surgery.[4] The same is true for acutely ill patients receiving invasive ventilation before admission to a hospital, and in the emergency room.[19,20] The findings of the current study are in line with the findings of those studies. Indeed, a large proportion of patients did not receive postoperative LTVV. Our findings are important, as a substantial number of patients need postoperative ventilation in the ICU. At a global scale, this means that improvements in this practice can have enormous effects.

PEEP during ventilation in the ICU was largely the same as during intraoperative ventilation, and PEEP was low in both settings. This may seem in line with recent findings that suggest that most benefit comes from V_T limitation, and absence of benefit of high PEEP when a low V_T is used.[21,22] Ventilation with high PEEP also increases the risk for hypotension, thus may increase the need for vasopressors.[21,22] The finding that practice of postoperative ventilation mirrors intraoperative ventilation may suggest that caregivers probably do not change ventilator settings when a patient arrives at the ICU after surgery. A rise in PEEP may only be beneficial in patients who present with postoperative hypoxemia.[13]

PPCs are common and strongly associated with poor outcomes.[4,15] The proportion of patients developing PPCs in the parent LAS VEGAS study[4] and the current substudy are notably different (2.8 *vs* 10.4%). Compared to the general postoperative population, patients who are transferred directly from the OR to the ICU usually have more comorbidities, and this is indeed reflected by higher ARISCAT risk scores (47 [40—57] in the current cohort versus 15 [3—26] in the full LAS VEGAS study cohort). Higher ARISCAT scores are associated with more frequent development of PPC and worse outcomes,[4,16] which is affirmed by the current findings.

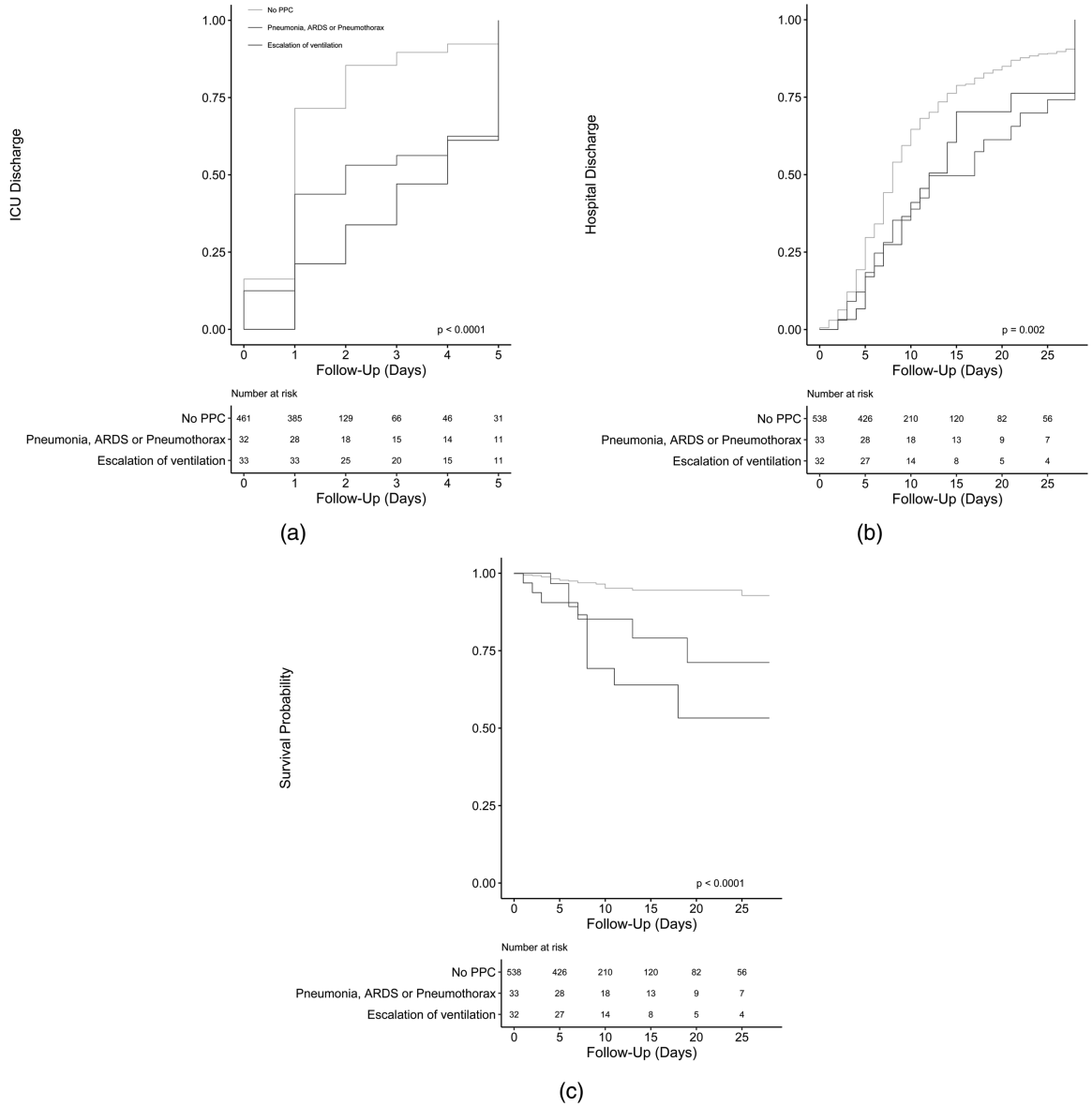

Fig. 3 Kaplan—Meier curves showing outcome in patients who did or did not develop a PPC, split up for no PPC vs pneumothorax, pneumonia and ARDS vs escalation of ventilatory support for (A) probability of ICU discharge; (B) probability of hospital discharge; (C) probability of in—hospital mortality.

This study has limitations. Compared to the large number of patients in the parent study, the number of patients in this substudy was small as we had only access to ventilation data in the ICU of 274 patients, representing 2,6% of the number of patients in the parent study (10,520 patients). Assuming that the incidence of postoperative ventilation in the ICU in the current cohort is representative for the overall cohort, there could still be reporting bias due to the fact that participation in this substudy was voluntary, and participation could have been rejected because of other reasons than a lack of time or access to the data. This limits the generalizability. Selection bias may have been introduced by two factors. First, a number of hospitals that participated in the parent study did not take part in this substudy. Second, patients with a delayed admission to the ICU, i.e., patients that went to the normal ward after surgery and then were admitted to the ICU for escalation of care, were excluded from this study. Thus, the findings of this analysis may not be generalizable. However, the latter may also explain why the proportion of patients developing PPC was lower than what would have been expected based on the ARISCAT score, as these patients may need escalation of care after having stayed in the normal ward. Nevertheless, the incidence of PPC was relatively high in comparison to the parent trial. Another important limitation is that duration of ventilation seems relatively short, i.e., median 3 [2—7] hours, but this is not surprising for this category of patients——in the majority of patients it was simple postoperative ventilation. Also, most patients were under controlled ventilation at the moment of collection of ventilation data. Due to the study design, we were not able to define whether or not a patient was having spontaneous breathing activity, and it could also

be that some patients were at a spontaneous ventilation mode at the latest time point ventilation data were captured. In addition, due to the short duration of ventilation in the ICU, biologically plausible relationships could be harder to determine. Nevertheless, the current findings are in line with what has been described over recent years. For instance, duration of ventilation in the ICU was longer than ventilation in the operating room in these patients, and clear associations have been found between intraoperative ventilation settings and postoperative complications. Lastly, using a relatively new and yet unstudied variable, 'escalation of ventilatory support', introduces uncertainty.

Conclusions

Non—thoracic surgery patients seldom need postoperative ICU admission and among those who do, less than half require postoperative ventilation. Intraoperative and postoperative mechanical ventilation settings are comparable, but there is room for improved use of LTVV. PPCs develop as frequent in planned as in unplanned admission, and their occurrence impacts outcome.

Assistance with the article

The members of the Steering Committee of the 'Local ASsessment of VEntilatory management during General Anesthesia for Surgery study' (LAS VEGAS) designed and overviewed conduct of the parent study, and all substudies. LAS VEGAS collaborators for the ICU substudy of LAS VEGAS, consisting of National — and Local Investigators, collected the data. Sabrine N. Hemmes was the overall LAS VEGAS coordinator. The substudy was proposed by Sharon Einav, Sabrine N. Hemmes and Marcus J. Schultz, and lead by Fabienne D. Simonis and Sharon Einav.

Members of the LAS VEGAS steering committee

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The LAS VEGAS network collaborators

Collaborators are listed in the Supplemental digital content (pp. 9—18).

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Author contributions

Conception and design: Sabrine N. Hemmes, Marcus J. Schultz, Marcelo Gama de Abreu, Paolo Pelosi; Administrative support: Sabrine N. Hemmes; Provision of study materials or patients: Sabrine N. Hemmes, Marcus J. Schultz; Collection and assembly of data: Sabrine N. Hemmes; Marcelo Gama de Abreu; Paolo Pelosi; and Marcus J. Schultz; Data analysis and interpretation: Fabienne D. Simonis, Ary Serpa Neto and Marcus J. Schultz; Manuscript writing: Fabienne D. Simonis and Sharon Einav, supported by all other authors; Final approval of manuscript: All authors

LAS VEGAS Writing committee & study collaborators

The LAS VEGAS Steering Committee members & Writing Committee members are listed in the acknowledgements section. Collaborators are listed in the Supplemental Digital Content (pp. 9-18)

Trial registration

Clinicaltrials.gov (study identifier NCT01601223)

Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2021.10.004.

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SPECIAL ARTICLE

Home mechanical ventilation: the Dutch approach

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Abstract In the Netherlands we have an unique organisation of only 4 centres being responsible for all patients who need Home Mechanical ventilation(HMV). Nationwide criteria for referral and initiation of HMV are stated in our national guideline and recently a unique national learning management system (LMS) for all caregivers and professionals was developed. A nationwide multi-centric research program is running and every centre is participating. In this paper we provide information about the evolution of HMV in the Netherlands during the last 30 years, including details about the number of patients, different diagnose groups, residence and the type of ventilators.

Introduction

Home mechanical ventilation (HMV) was first initiated in Europe in the sixties during the polio epidemic to offer the possibility of maintaining chronic ventilatory support outside the hospital. While patients with a neuromuscular disease were the first to be considered, many others with different diagnoses followed afterwards. Over the following years, it was observed by the Dutch government that the care of these patients was poorly organized; therefore, they chose to centralize HMV in 1992 and divided the Netherlands into four regions each with their own HMV center.[1] In addition, it was mandated that all centers had to be associated with a University hospital (Fig. 1). As we believe that this is a very well-functioning approach, we will describe the individual elements necessary to build such a unique system with focus on the following topics: 1) organization of HMV, 2) training

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Fig. 1 Distribution of the 4 HMV regions.

of caregivers and health-care professionals, 3) research, and 4) associated financial aspects. Furthermore, we will present detailed data obtained over the last 30 years from our national HMV registry, including number of patients, underlying diseases, use of invasive versus non-invasive intervention, and, most importantly, the residence of the patients.

Organization of HMV in the Netherlands

Each HMV center organizes patient care in their specific region with a team consisting of pulmonologists, specialized nurses and technicians. After the indication for HMV is determined by the pulmonologist, the specialized nurse will take over and start HMV. Currently, this still takes place in an inpatient setting but it is our goal to start HMV at home more often, as it has been shown to be safe, effective and cost-effecient.[2–4] During this process, the patient, family and caregivers are instructed and trained on site. Our team is also responsible for the follow-up with HMV patients, which means that the same group of nurses will visit the patient at home at least once every year and the patient will visit the outpatient clinic for scheduled intermittent evaluations. Technical aspects of the intervention, including analysis of the ventilator files, measurements of transcutaneous carbon dioxide and oxygen saturation, and (on indication) polygraphy, are addressed at home by the nurses, who are authorized to change settings accordingly. Patients can always contact their HMV center in case of problems as the nurses are on call 24/7. The Homecare provider is only involved in periodic and ad hoc maintenance of the ventilators. All the above is incorporated into the Dutch guidelines for Home Mechanical Ventilation (2012), which were collectively developed by all HMV centers to improve the communication in the care chain. Implementation of these guidelines led to a further increasing awareness in the care chain and standardized the roles of those involved. Safety criteria were standardized not only for the hospital, but also for private homes and other care facilities. Furthermore, it set a number of standards regarding expertise, minimum number of new patients treated per year, and number of specialized nurses required per patient for regular follow-up. As we try to create a safe environment for our HMV patients, the guidelines also include, for example, a protocol applicable in case of power failure; thus, how evacuation should be efficiently executed, which is particularly important for more dependent patients.

As our common standard guidelines are not suited for children, a special Dutch edition for children was developed.[5] Finally, to ensure proper communication between all parties in the field, which is crucially important for the success of a care system, the Dutch association of patients and professionals involved in chronic ventilatory support was established more than 30 years ago. It serves as a national mediator and information provider for patients, voluntary and professional caregivers, health insurance companies, and policy makers.

Education and training of caregivers and health-care professionals

In 2019, a unique national training program for caregivers of chronically ventilated patients was launched.[6] Protocols among the 4 HMV centers were unified and a blended learning experience was developed for both voluntary and professional caregivers. Whereas e-learning is used to provide the necessary knowledge, practical training will be given at our skills center and in specific patient-related situations. After completion of the training, an assessment consisting of a theoretical exam and a practical test will follow. The practical exam will contain all restricted and high-risk procedures,

testing the acquired knowledge of the necessary equipment, and assess how caregivers handle acute situations. The professional caregivers will be awarded with credits for their specific accreditation register. One of the main advantages of this training approach is that all voluntary and professional caregivers working in the field of HMV are trained in the same way across the entire country. To date, we have almost reached 10.000 registered individuals who have followed this learning program.

Research

In line with the aforementioned forms of collaboration regarding training, efforts are being directed toward optimally benefitting from research endeavors on a national level. For example, a recent study involving patients with neuromuscular diseases, showed similar results for HMV initiation at home and in the hospital in addition to substantial savings when initiating the process at home.[4] These study will impact our national guidelines regarding the place of initiation of HMV in specific patient groups. Further collaborative studies in COPD (NCT03053973), myotonic dystrophy (NL7972) patients and ALS patients (NCT05033951) are currently ongoing.

Telemonitoring

While we got more experience in telemonitoring during initiation and supervising patients at home, this was solely in a study environment and we find now that implementing it in daily care is more difficult. The challenges we have to deal with are privacy and security issues on the one hand and getting reliable signals of both ventilators and transcutaneous monitors. Nevertheless also on this important topic the 4 HMV centers have the same goal and it is foreseen to have a uniform pathway by 2022.

Financial aspects

The Dutch Healthcare authority dictates that HMV treatment will only be reimbursed if one of the 4 centers is involved. This means that all Dutch patients qualifying for HMV have to be referred to one of these centers. In 2017, a task force entrusted to look for alignment of disposables within the 4 different centers was assigned. The first national tender for the purchase of disposables needed for the care of HMV patients was completed, which will lead to a cost reduction. Plans are currently being conceptualized for joint procurement and maintenance of ventilators.

National registry on HMV

All patients treated over the last 30 years in any of the 4 Dutch HMV centers were included in the national registry for HMV.

Data collection

The data are collected in every center on the 1st of January every year and sent to the registry.

These data contain information regarding gender, sex, age, diagnosis leading to HMV, types of ventilation, and type of residence.

Diagnostic categories

Patients are divided into 5 main categories: neuromuscular disease, thoracic cage disorder, lung disease, sleep-related breathing disorder, and various (not belonging to the other 4 groups). The sleep-related breathing disorder group represents those patients who need ventilatory support (i.e., pressure support) if CPAP is not effective.

Age distribution

Patients are divided in 4 age categories: 0-18, 19-40, 41-60 and >61 years of age.

Types of HMV

HMV is divided into 3 types: non-invasive ventilation (NIV), invasive ventilation (IV) and negative pressure ventilation by Cuirass (a shell around thorax and abdomen).

Types of residence

We define 3 main types of residence: 'home', a private accommodation in which the patient or partner has full control, while care can be provided by themselves or by caregivers; 'nursing home', defined as institutions where patients live permanently because they need professional care facilities; 'other', comprising places of residence other than a nursing home where care is organized under certain individual conditions.

Fig. 2 shows the steady and marked growth of the number of patients and indicates that patients with neuromuscular disorders have consistently represented the largest group. As for all other groups, the number of HMV patients with thoracic disorders or lung disease steadily increased but remained similar relative to the total patient number. Interestingly, a modest increase in the relative number of HMV patients with sleep-related disorders appeared to be evident over the past 5 years.

When evaluating the dynamics of age distribution, we see a shift from younger patients who are in the age groups 0-18 and 19-39 years to more senior patients (>61 years of age) as being the predominant group relying on HMV. Even the middle aged group (40-60) was dominant in the first 20 years, but lost share in the last decade in favor of the senior group **(Fig. 3).**

While 30 years ago, patients almost exclusively were ventilated invasively, nowadays, the majority of patients undergo a non-invasive approach **(Fig. 4).**

Fig. 5 shows that the vast majority of HMV patients' lives at home and that the number of patients in nursing homes decreased from roughly 37% in 1991 to 4% in 2020.

Discussion

This paper outlines the unique organization of HMV in the Netherlands: an example of how knowledge and experience in the area of HMV can be efficiently centralized. The national registry provides a valuable source of information of trends in HMV in the Netherlands over the last 30 years. Carefully consulting this registry has led to a national guideline that defines what it entails to function as an effective HMV center. This contributed to a uniform set up and improved management of HMV as well as an updated reimbursement policy.

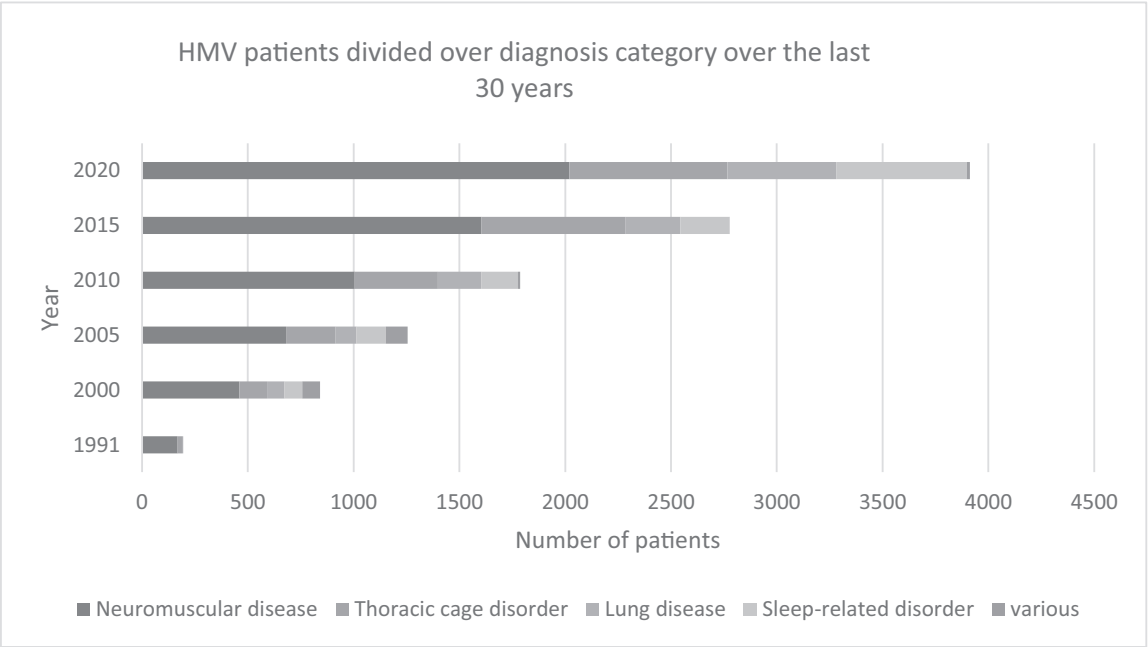

Fig. 2 The number of patients from all 4 Dutch HMV centers combined, categorized based on diagnosis.

Building on the strong cooperation among centers, a national education program fostering uniformity in high-risk procedures in the entire country was developed. In addition, a national research program with focus on both COPD and neuromuscular diseases has been launched. Currently, we are working on updating our guidelines to further improve our unique organization, with the end-goal of optimizing the care of HMV patients. We strongly agree with a recent editorial by Schwarz and Windisch in which they embraced our organization and suggested that the Dutch system might serve as a blueprint for other countries.[7]

The number of HMV patients in the Netherlands has considerably increased over the past 30 years (Fig. 2). In 2001/2002, at the time of the Eurovent study, the relative HMV use on a population-level was 5.6/100.000 in the Netherlands, while the average use amounted to 6.6/100.000 in Europe (with the exclusion of patients with OSA[8]). In 2020, 22 out of 100,000 people rely on HMV in our country; this number excludes patients with standard CPAP. While there is no recent update available of the Eurovent study, a much higher prevalence was recently reported in the Geneva district area (37.9/100.000) and the Italian region Lombardy (63 / 100.000).[9,10] Although it is evident that the Dutch

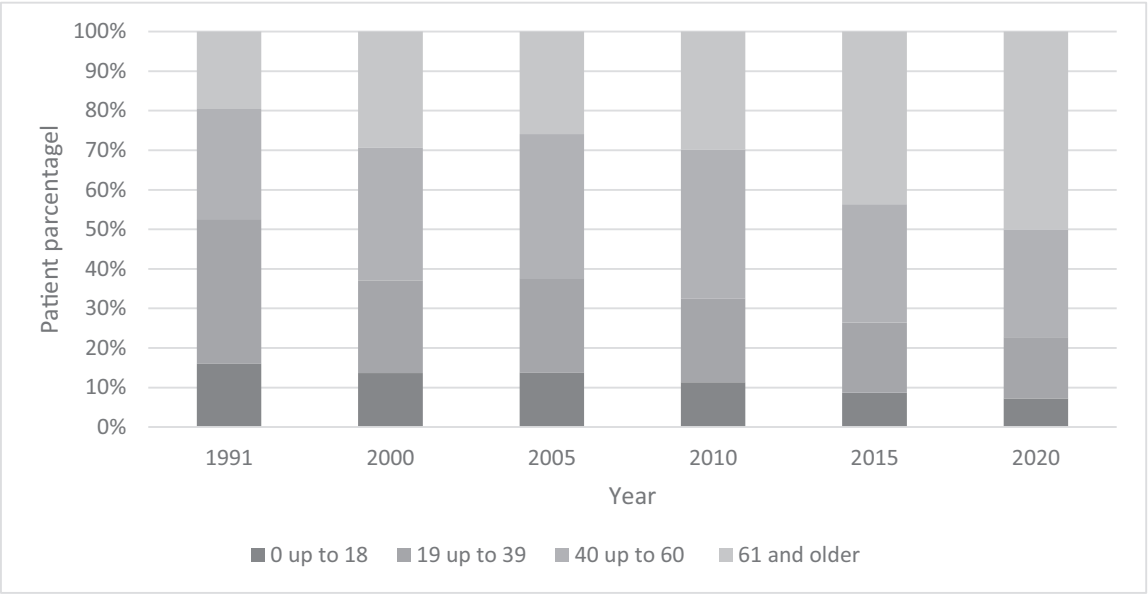

Fig. 3 Distribution of age groups of all Dutch HMV patients over the last 30 years. Percentages represent patients from all 4 HMV centers combined.

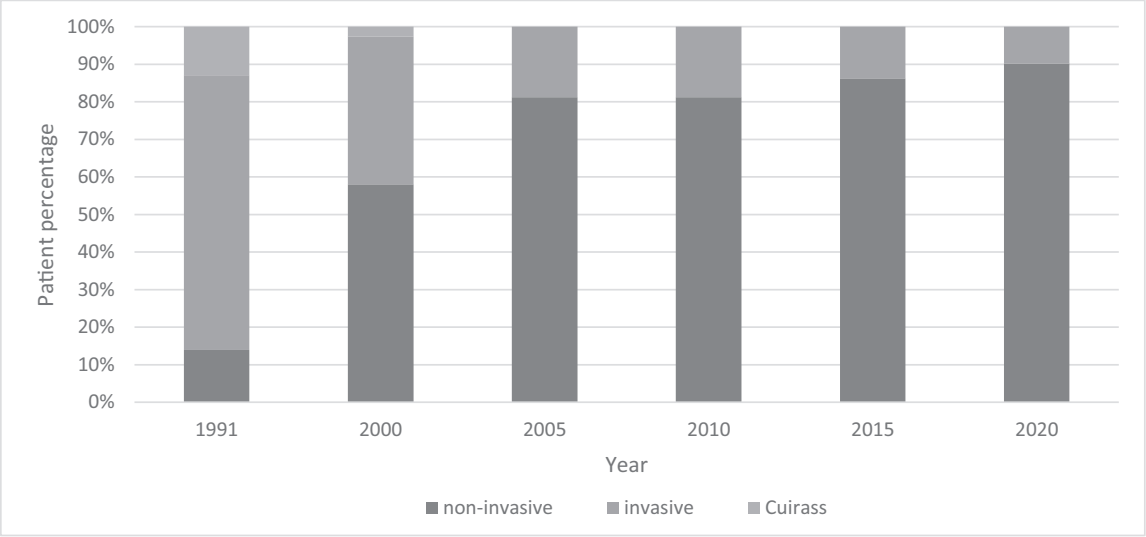

Fig. 4 Types of HMV over the last 30 years. Percentages represent patients from all 4 HMV centers combined.

prevalence of HMV users increased considerably over the last decade, it is still lower compared to other western countries. One of the reasons is that, due to our system, we are very restrictive in prescribing HMV. The Dutch uniform and strict guidelines used by all 4 centers ensure that only patients meeting certain criteria can start HMV. As mentioned before, patients that need HMV must be referred to one of the 4 centers; otherwise, HMV is not possible in the Netherlands. Not all patients might be motivated to travel to one of these centers leading to a lower number of patients on HMV. Another reason potentially underlying the relatively low prevalence in the Netherlands is that, in contrast to Italy and other south European countries, COPD was previously not considered an indication for HMV as we were not convinced of the (beneficial) effects of HMV treatment in COPD patients. This was highlighted and confirmed in a study by Crimi et al. (2016) showing that the Netherlands had the lowest percentage of COPD patients on HMV.[11] However, this perspective changed after publications by Kohnlein and Murphy demonstrating that chronic NIV is beneficial in COPD patients with chronic hypercapnic respiratory failure.[12,13] Nowadays, COPD patients with chronic hypercapnia do qualify for NIV in the Netherlands, preferably in combination with pulmonary rehabilitation.

Despite the policy change of prescribing NIV to specific COPD patients, this is still the smallest group of HMV patients in the Netherlands, in contrast to the situation in Switzerland, where COPD patients constitute the predominant HMV group.[9]

Remarkably, patients $>$ 60 years of age have become the largest group of HMV users in the Netherlands over the past decade (**Fig. 3**). A similar but even more extreme trend was observed in a Swiss study where the median age of HMV patients was 71 years and only 25% of the patient population was under the age of 59.[9] The exact reason for this is unclear; however, more knowledge and a better

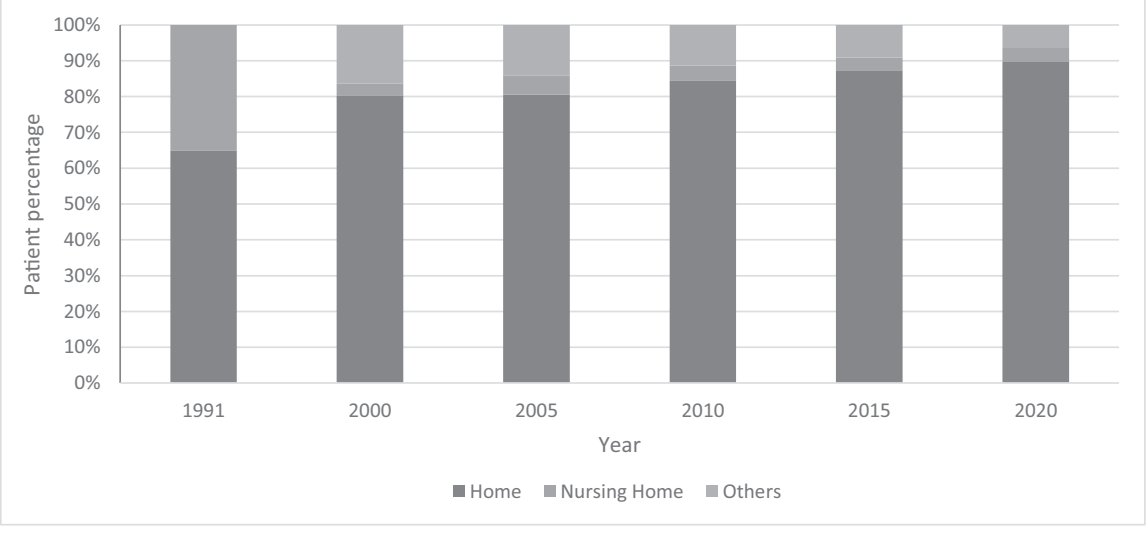

Fig. 5 Residence of HMV patients over the last 30 years. Percentages represent patients from all 4 HMV centers combined.

understanding of the possible benefits of HMV in this group might drive the increased demand among more senior patients.

As indicated by several studies, chronic ventilatory support shifted from invasive towards non-invasive ventilation over the last years. At present, we only apply invasive ventilation in ~10% of all our HMV patients in the Netherlands, which is similar to the 10.4% invasive ventilated patients reported in a 2018 Hungarian study.[14] The reason for this shift is the availability of more sophisticated ventilators with a wide range of masks and the possibility of adding mouthpiece ventilation. This means that in almost all patients an effective set up of non-invasive ventilation is possible. However, probably the most important contributing factor is the increased use of assist coughing techniques like air stacking and mechanical in- and exsufflation.[15] Sputum can be mobilized more effectively and there is no need to change to invasive ventilation. Finally, we are proud that 90% of the patients is still living at home probably partly due to the fact that ventilatory support is provided non-invasively. The care associated with NIV is less complex and less intense for caregivers than with invasive ventilation. Moreover, the use of ventilators in general has been simplified enormously. Another reason for the success of HMV is the blended learning program; ongoing evaluation indicates this initiative (in combinations with the nationwide protocols) is a supportive tool in daily practice for implementing home care.

In conclusion, this paper presents the unique organization of HMV in the Netherlands. The centralization of HMV care demonstrated to be effective in providing a uniform treatment to all patients with chronic respiratory failure based on a nationwide training system. Undoubtedly, continued collaborative research by the 4 HMV centers will further improve our standard of care.

Conflict of Interest

Dr. van den Biggelaar reports personal fees from Philips, personal fees from Westfalen Medical B.V., outside the submitted work. Dr. Hazenberg has nothing to disclose. Dr. Cobben has nothing to disclose. Dr. Gaytant has nothing to disclose. Dr. Gommers has nothing to disclose. Dr. Wijkstra reports grants from ZONMW, grants from VIVISOL, during the conduct of the study; grants and personal fees from Philips, grants and personal fees from RESMED, grants from Goedegebuure, grants from vital air, personal fees from Bresotec, personal fees from synapse, outside the submitted work.

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ORIGINAL ARTICLE

Correlation between levels of adipokines and inflammatory mediators with spirometric parameters in individuals with obesity and symptoms of asthma: Cross-sectional study

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Obesity;
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Inflammation;
Spirometry

Abstract
Introduction: The adipose tissue secretes adipokines and influences the release of inflammatory mediators contributing to a state of low-grade systemic inflammation that may change lung function.
Objective: To correlate levels of adipokines and inflammatory mediators with lung function in individuals with obesity and bronchial asthma symptoms.
Materials and methods: A cross-sectional study, including women with obesity (grade II and III) with symptoms and clinical diagnosis of asthma. Anthropometric measurements (weight, height, BMI), pulmonary function test (spirometry), asthma control test questionnaire, collection of systemic inflammatory markers (blood collection) and pulmonary markers (sputum collection) were collected and were analyzed: IL-6, IL-8, TNF-α, adiponectin, resistin, leptin and C-reactive protein (CRP). The patients were stratified into two groups according to asthma control.
Results: 80 women were analyzed and 40% had an ACT score greater than or equal to 18 and were classified as ''controlled asthma''. More than half of the patients of ACT < 18 score obtaining measures of FEV1, PEF and FEF25–75% below and 80% of predicted. There was a significant and negative correlation between IL-6 in the sputum with FVC and FEF25–75% in the group ACT < 18 and with FVC and FEV1 in the group ACT $\geq$ 18.

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Conclusions: Therefore, we concluded that the increase of interleukin-6 in the sputum is related to worse pulmonary function even in patients with controlled asthma, especially in the translate airway permeability measures.

Introduction

The Brazilian Ministry of Health[1] research shows that 54% of the Brazilian population over 18 years old are overweight, 57.3% of men and 51.2% of women. The World Health Organization[2] shows that in 2016 more than 1.9 billion adults (39%) were overweight and more than 650 million (13%) were obese.

The adipose tissue, being an endocrine organ, secretes adipokines and influences the release of inflammatory mediators and such substances contribute to a low grade systemic inflammation state and can promote directly or systemically changes in pulmonary function.[3–5] Increased adipose tissue may also influence the susceptibility to lung infections, increased lung inflammation with environmental exposure, and airway obstruction exacerbation in preexisting lung diseases.[6]

Beuther et al.[7] observed in a meta-analysis that the obese individual is more likely to develop asthma in comparison to eutrophic, and in Melo et al.[8] study, asthma prevalence in the obese population was 18.5% in a sample of 363 obese, and in Baltieri et al.[9] study, asthma prevalence was 4.6% in a sample of 4791 obese.

In view of the vast metabolic and inflammatory changes that accompany the obese individual, altered pulmonary function is evident in many studies, both by inflammatory and mechanical origin. Studies have therefore shown lung function alteration in the obese individuals without associated prior disease, such as the mechanical changes caused by adipose tissue deposition around the thorax and abdomen, which include reduction of Expiratory Reserve Volume (ERV),[10] and may cause areas of atelectasis, especially in the pulmonary bases.[11,12] In addition to inflammatory alterations, inflammatory cytokines act on the lung which causes lung function impairment. Such changes are evidenced in the literature by the reduction of Forced Expiratory Volume in the First Second (FEV_1), Functional Residual Capacity (FRC), Forced Expiratory Flow in 25–75% (FEF25–75%) and increase in FEV_1/FVC (Forced Vital Capacity) ratio.[5,13,14]

Thus, the aim of the present study was to correlate adipokines levels and inflammatory mediators with lung function in individuals with obesity and bronchial asthma symptoms.

Method

This is a cross-sectional study conducted at a training hospital, approved by the Research Ethics Committee, registered in the Brazil Platform and with Research Support from the Foundation for Research Support of the State of São Paulo (FAPESP).

Sampling

The study population was included provided they fulfilled the following criteria:

Inclusion criteria

- Obesity grade II and III (BMI $\geq 35\,kg/m^2$)
- Feminine gender
- Initiating multiprofessional follow-up at the Institution's Ambulatory Surgery
- Manifestation of asthma symptoms and clinical diagnosis according to the Global Initiative for Asthma[15] and the Guidelines of the Brazilian Society of Pulmonology and Phthisiology (SBPT) for Asthma Management.[16]

Exclusion Criteria

- Smoking
- Cognitive limitations that prevent the understanding of the tests or belonging to the vulnerable groups
- Chronic or acute inflammatory diseases, with asthma exception.

Outcome measures

1. Pulmonary function test

Spirometry was performed at the Pulmonary Function Laboratory of the institution by trained technicians. Easy-One equipment was used and followed the standards of the American Thoracic Society – ATS and European Respiratory Society – ERS.[17] Two maneuvers were performed to assess the pulmonary volume and flow measurements: slow vital capacity (SVC) and forced vital capacity (FVC). The maneuvers were performed until three acceptable and two reproducible curves were obtained, with no more than eight attempts. The values extracted from each maneuver were selected according to Pereira.[18] To calculate the predicted values, the equation proposed by Pereira et al.[19] for the Brazilian population.

The volunteers were rested for 10 min prior to the test and were properly guided in performing the maneuvers.2. Collection and processing of systemic inflammatory profile markers

With the patient at 12 h of fasting, the blood was collected in a vacuum collection system (Vacuette®), two dry tubes (9 ml) for the serum use.

Table 1 Sample characteristics ($n = 80$).

	ACT ≥ 18 ($n = 32$)		ACT < 18 ($n = 48$)	
	Mean ± SD	Range (min–max)	Mean ± SD	Range (min–max)
Age (years)	36.90 ± 8.36	22–57	40.97 ± 9.95	28–64
Weight (kg)	119.9 ± 17.9	88–155	114.5 ± 18.79	82–194
Height (cm)	163.7 ± 5.55	150–179	159.25 ± 5.59	148–171
BMI (kg/m^2)	44.8 ± 5.81	35–55	45.2 ± 7.25	34–82

ACT: asthma control test; SD: standard deviation.

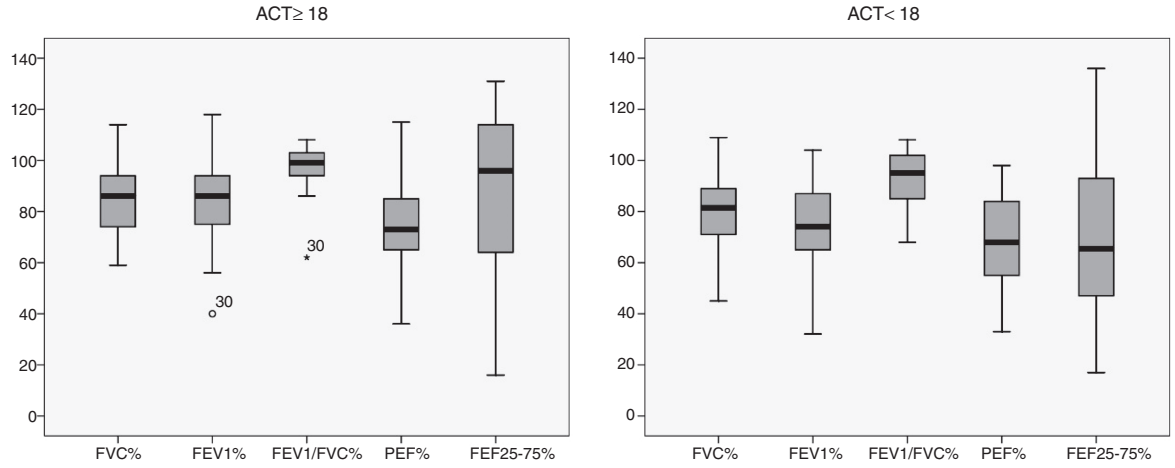

Figure 1 Box plot of spirometric variables in percent of predicted of each group based on the ACT score.

The collected blood was immediately processed in a centrifuge (Eppendorf® brand – model 5804R) with a rotation of 4500 rpm for 20 min at 4 °C. Serum was stored in a freezer for analysis of adipokines and inflammatory mediators.

3. Collection and processing of local inflammatory profile markers

For patient safety the procedure was performed in a hospital environment and accompanied by a pulmonologist with medication and emergency material available.

First, patients underwent spirometry to determine baseline FEV_1. Patients, as long as they were not in asthma exacerbation crises, underwent the sputum induction procedure by administering 10 ml of 3% saline solution for 12 min with an Ultrasonic Nebulizer Inhaler (Pulmosonic Star – Soniclear® – São Paulo, Brazil – Registration in the MS/ANVISA: 80023140008).

Patients were advised, when they felt the need, to cough and expectorate in available Falcon Tube, having rinsed the mouth earlier. If there was no sputum production the above procedure was repeated with 4% and 5% saline solution. Patients were monitored with pulse oximetry to check for peripheral oxygen saturation and pulmonary auscultation to verify bronchospasm presence and, if necessary, at intervals of each inhalation increment, FEV_1 was measured as a safety procedure, and if between 10% and 20%, the previous inhalation was repeated; if there was a fall in $FEV_1 > 20\%$ the collection was interrupted. If there was a fall in $FEV_1 < 10\%$, sputum induction was continued[20].

If there were no intercurrences, the procedure was interrupted as soon as sufficient sputum sample was available for processing.

The obtained sputum sample was processed immediately using DTT and PBS usually in a ratio of 1:1, up to four times the dilution, vortexed and carried in the bain-marie at 37 °C with manual shaking with a pipette for 15–20 min. The sample was then centrifuged (Thermo Scientific, Legend Mach 1.6R Centrifuge) with rotation of 1800 rpm, temperature of 5 °C for 10 min. The supernatant was stored in a freezer at −80 °C for the analysis of adipokines and inflammatory mediators.

Dosage of inflammatory mediators in the blood and sputum

The levels of IL-6, IL-8, TNF-α, adiponectin, resistin, leptin and C-reactive protein (CRP) were measured following the manufacturer's recommendations by the ELISA method (R&D Systems, CA, USA). The reading was performed on a multiplate reader (SpectraMax i3, Molecular Devices, CA, USA) at a wavelength of 540 nm.

Asthma control test (ACT)

The ACT[21–23] was applied to verify asthma control. It is a self-administered questionnaire and has five items related to the symptom, use of relief medication and asthma impact in daily activities. Each question includes a score between 1 and 5, with 25 total points representing total control of asthma or remission of symptoms, with a score ≥18 being

Table 2 Spearman correlation between adipokine levels and inflammatory blood and pulmonary sputum mediators with spirometric variables of group classified as ''controlled asthma'' (ACT $\geq$ 18); values expressed in Spearman correlation coefficient (*r*).

Variables	Blood				
	FVC	FEV_1	FEV_1/FVC	PEF	$FEF_{25-75\%}$
Adiponectin	−0.077	0.032	0.261	0.148	0.201
IL-6	−0.290	−0.235	−0.006	−0.154	−0.126
IL-8	−0.374	−0.283	−0.022	−0.497*	−0.127
Leptin	−0.201	−0.212	−0.003	0.108	−0.098
Resistin	0.271	0.262	0.110	0.296	0.244
TNF-α	−0.049	−0.099	−0.177	−0.050	−0.204
CRP	0.080	0.205	0.400*	0.254	0.324
Variables	Sputum				
	FVC	FEV_1	FEV_1/FVC	PEF	$FEF_{25-75\%}$
Adiponectin	−0.026	−0.038	−0.057	0.123	−0.033
IL-6	−0.425*	−0.423*	−0.283	−0.167	−0.339
IL-8	−0.179	−0.132	0.081	0.018	0.048
Leptin	−0.119	−0.094	0.017	0.101	−0.024
Resistin	−0.097	−0.078	−0.005	0.225	0.007
TNF-α	0.167	0.113	−0.023	0.122	0.041
CRP	0.123	0.053	−0.242	−0.130	−0.086

FVC: forced vital capacity; FEV_1: forced expiratory volume in the 1st second; PEF: peak expiratory flow; FEF25–75%: forced expiratory flow between 25 and 75% of the FVC curve.
*p-value statistically significant with blood CRP × FEV1/FVC p-value = 0.039; blood IL-8 × PEF p-value = 0.008.
**p-value statistically significant with sputum IL-6 × FVC p-value = 0.027; sputum IL-6 × FEV1 p-value = 0.028.

Table 3 Spearman correlation between adipokine levels and inflammatory blood and pulmonary sputum mediators with spirometric variables of group classified as ''non-controlled asthma'' (ACT < 18); values expressed in Spearman correlation coefficient (*r*).

Variables	Blood				
	FVC	FEV_1	FEV_1/FVC	PEF	$FEF_{25-75\%}$
Adiponectin	−0.095	−0.131	−0.228	−0.185	−0.188
IL-6	0.015	0.042	0.157	0.048	0.092
IL-8	−0.113	−0.037	0.236	0.134	0.107
Leptin	−0.062	0.022	0.044	−0.124	0.044
Resistin	−0.130	−0.049	0.116	−0.068	0.045
TNF-α	−0.075	0.007	0.182	−0.021	0.079
CRP	−0.231	−0.250	−0.079	−0.131	−0.181
Variables	Sputum				
	FVC	FEV_1	FEV_1/FVC	PEF	$FEF_{25-75\%}$
Adiponectin	0.235	0.200	−0.027	0.140	0.097
IL-6	−0.227	−0.358*	−0.323	−0.247	−0.354*
IL-8	−0.160	−0.201	−0.086	−0.019	−0.171
Leptin	−0.096	−0.078	−0.096	0.003	−0.067
Resistin	0.150	0.050	−0.110	0.008	−0.039
TNF-α	0.315*	0.205	−0.086	0.038	0.043
CRP	0.107	0.088	0.042	−0.029	0.038

FVC: forced vital capacity; FEV_1: forced expiratory volume in the 1st second; PEF: peak expiratory flow; FEF25–75%: forced expiratory flow between 25 and 75% of the FVC curve.
*p-value statistically significant with sputum TNF-α × FVC p-value = 0.045; sputum IL-6 × FEV1 p-value = 0.034; sputum IL-6 × FEF25–75% p-value = 0.037.

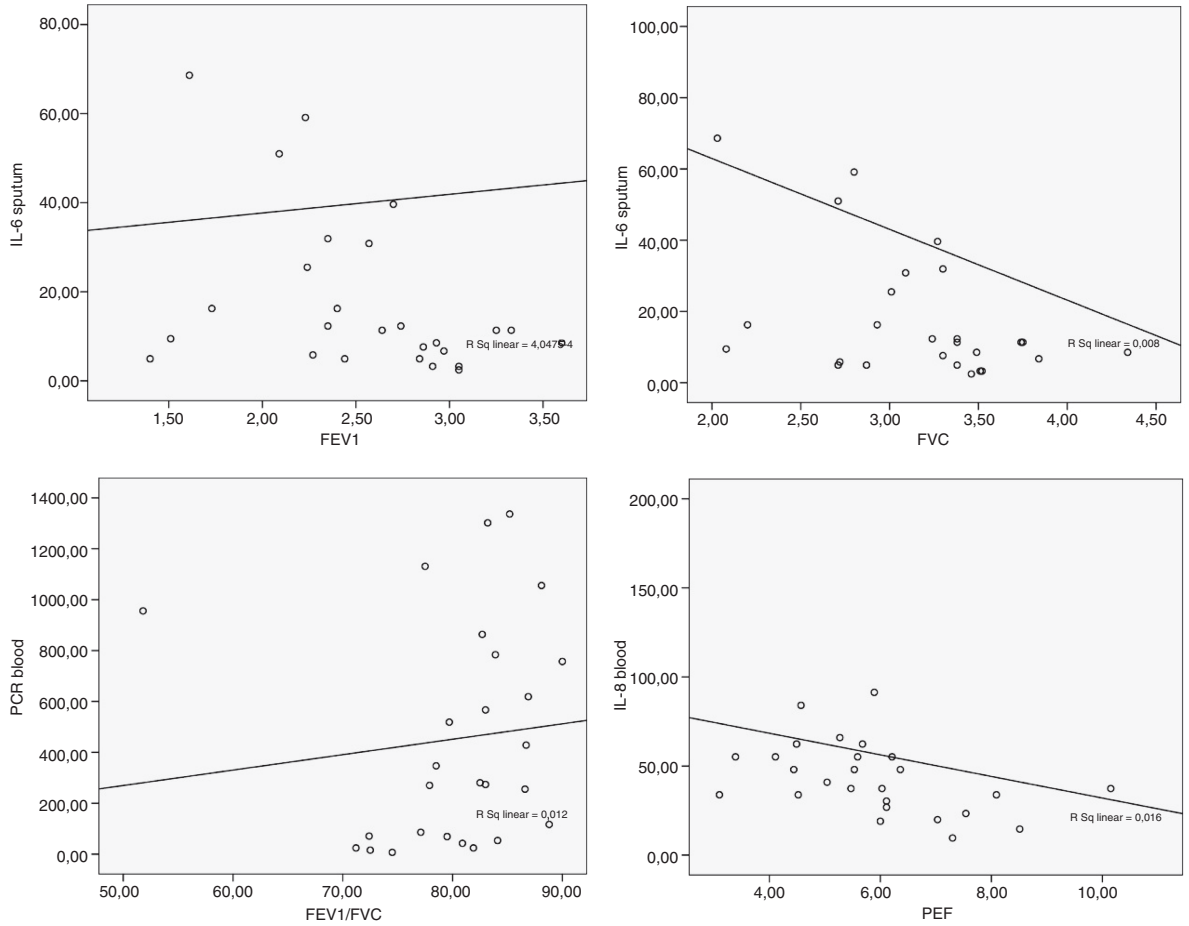

Figure 2 Group classified as ''controlled asthma'' (ACT $\geq$ 18): Scatter plot between sputum IL-6 $\times$ FVC ($r = -0.425$; p-value = 0.027); sputum IL-6 $\times$ FEV1 ($r = -0.423$; p-value = 0.028); and between blood CRP $\times$ FEV1/FVC ($r = 0.400$; p-value = 0.039); blood IL-8 $\times$ PEF ($r = -0.497$; p-value = 0.008).

defined as ''controlled asthma''. Although the international validation[22] considers a cutoff point greater than or equal to 20, the ACT validation in Brazil[23] found a cutoff point of 18 or more to categorize ''controlled asthma'', therefore, because it is a study in a Brazilian population, we consider the respective cutoff point. The questionnaire was used as a way of describing the stage of disease control.

Statistical analysis

The data were computed in the SPSS program (Statistical Package for Social Science) v13.0 and to describe the sample profile of the variables the means, standard deviation, minimum and maximum values were extracted. The patients were stratified into two groups according to asthma control, one group with an ACT questionnaire score greater than or equal to 18 (controlled asthma) and another group with an ACT score less than 18 (non-controlled asthma).

To compare the variables of adipokines and inflammatory mediators with the spirometric variables, the Spearman Correlation test was performed and the Coefficient r value was presented. The level of significance adopted for this study was 5%.

Results

We analyzed 80 women who entered the program and the patients who answered the ACT questionnaire to check asthma control 40% had a score greater than or equal to 18 and were classified as ''controlled asthma''. The data of the characteristics of each group based on the ACT score are described in Table 1. Of the patients studied, 19.1% had grade II obesity and 80.9% had grade III obesity.

Fig. 1 characterizes the values obtained from the pulmonary function variables of the sample studied, described as a percentage of the predicted value in the literature of each group based on the ACT score. For the group classified as ''controlled asthma'' (ACT $\geq$ 18) 56.25% of the patients obtained values above 80% of that predicted in FVC versus 50% of the group classified as ''non-controlled asthma'' (ACT < 18). For FEV1, 53.1% vs. 37.5%; FEV1/FVC 87.5% vs. 72.9%, PEF 34.3% vs. 22.9% and FEF25–75% 56.2% vs. 29.12% respectively.

The data obtained from the Spearman correlation between adipokine levels and inflammatory blood and pulmonary sputum mediators with spirometric variables of group classified as ''controlled asthma'' (ACT $\geq$ 18) are expressed in Table 2 and Fig. 2. And between adipokine

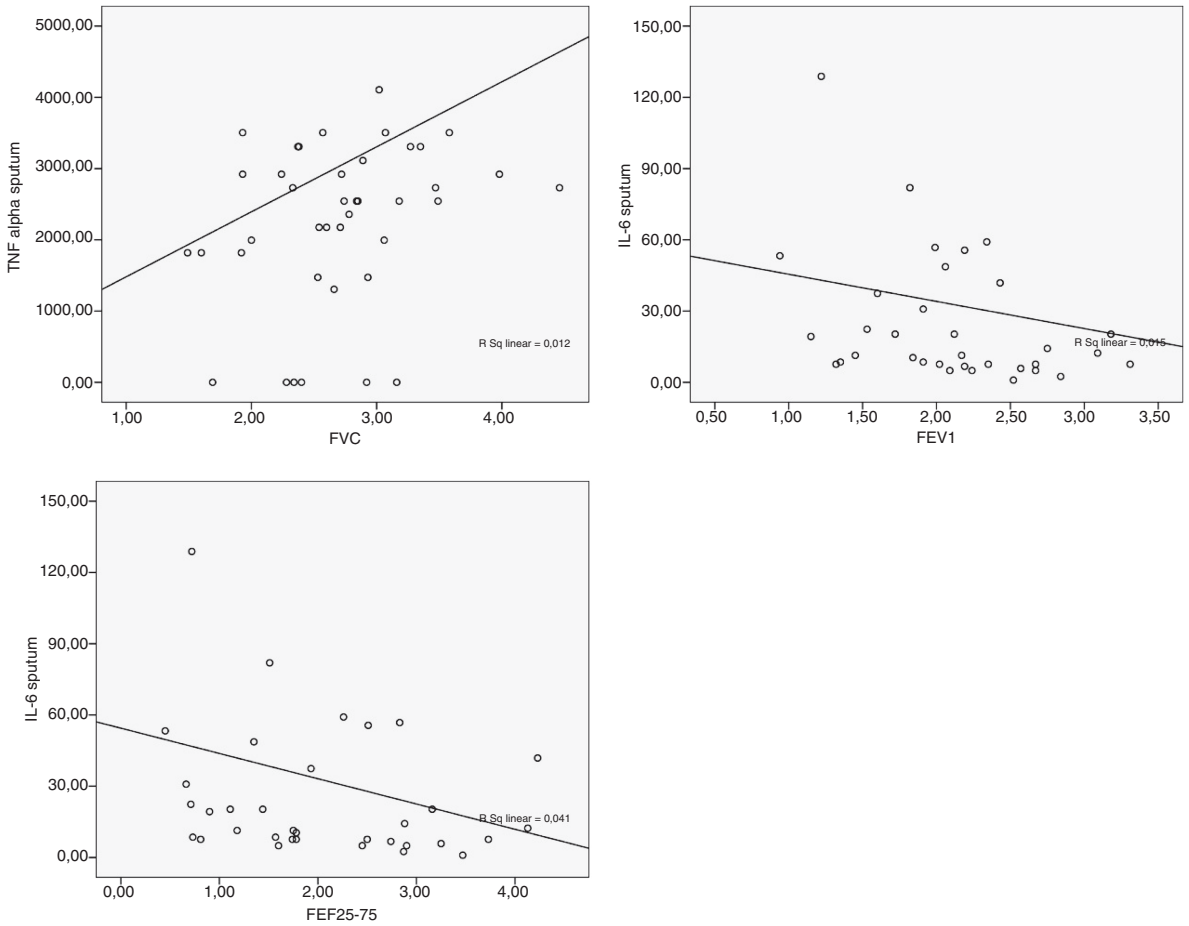

Figure 3 Group classified as ''non-controlled asthma'' (ACT < 18): Scatter plot between sputum TNF-α × FVC ($r = 0.315$; p-value = 0.045); sputum IL-6 × FEV1 ($r = -0.358$; p-value = 0.034); sputum IL-6 × FEF25−75% ($r = -0.354$; p-value = 0.037).

levels and inflammatory blood and pulmonary sputum mediators with spirometric variables of group classified as ''non-controlled asthma'' (ACT < 18) are expressed in Table 3 and Fig. 3.

Discussion

We observed that 60% of the patients did not have controlled asthma in relation to symptoms, medication use and impact on daily activities, directly reflecting on the pulmonary function measurements, with more than half of the patients in this group obtaining measures of FEV1, PEF and FEF25−75% below and 80% of predicted levels. Such measures represents the permeability of small pathways[24] and the examination of lung function together with patient's symptomatology and a good clinical evaluation contributes to the pulmonary diseases diagnosis, such as asthma. Epidemiologically, about 300 million individuals are affected by asthma in the world. According to the World Health Organization,[25] it is estimated that 235 million people worldwide suffer from asthma. It is a global public health problem, but more than 80% of deaths occur in low and middle-income countries.

The presence of asthma symptoms can cause quality of life impairments, mainly related to environmental stimuli and activity limitation and worse classifications of quality of life is associated with worse FEF25−75%.[26]

Since adipose tissue is an endocrine organ, the obese individual may present a low-grade systemic inflammatory condition that can affect several organs, including the lungs. Such inflammation may lead to narrowing, airflow obstruction, and premature closure of small airways,[3–5,27] causing asthma symptoms.

Bronchial hyperresponsiveness to an inhaled antigen can lead to an inflammatory cascade of airways and degranulation of mast cells, activation of T cells and alveolar macrophages, cytokine production, and recruitment and activation of eosinophils in the airway, resulting in epithelial scaling.[28] In view of this, all mechanical and inflammatory changes in the lungs of morbidly obese individuals may lead to changes in the permeability of the smaller airways, reflecting FEV_1, PEF and FEF25−75%.[13]

Thus, the treatment of these patients should involve therapy for weight loss and symptomatic respiratory improvement. There is evidence that weight loss improves levels of inflammatory mediators and adipokines in individuals with grade II and III obesity culminating in better asthma control.[9]

Most of the studies evaluated by Gupta et al.[29] study adipokines, such as adiponectin and leptin, as triggers of the

inflammatory alterations found in obese individuals, and the proinflammatory action of leptin is structurally homologous to IL-6 and increases chemotaxis and phagocytosis, leads to cell proliferation T that modulates cytokines and favors the Th1 response rather than Th2. Leptin levels increase in proportion to the increase in BMI.[30] On the other hand, adiponectin has anti-inflammatory action and inhibits the production of some inflammatory cytokines such as IL-6 and TNF-α.[29]

In the present study, there was a significant negative correlation between IL-6 in the sputum with FVC and FEF25-75% in the group ACT < 18 and with FVC and FEV1 in the group ACT $\geq$ 18. The higher the number of pulmonary IL-6, the worse the spirometric values were. The Peters et al.[31] study suggests a role for plasma IL-6 in systemic inflammation as a measure of disease severity in an asthmatic patients, as well as an association between increased IL-6 and worse FEV_1 in obese individuals.

There is evidence that IL-6 is also related to visceral obesity and adiponectin with subcutaneous obesity in asthmatic women. Visceral obesity is associated with poorly controlled asthma and poor lung function, as well as increased levels of IL-6.[32]

The present study also found a negative, significant correlation between the blood concentration of IL-8 with PEF in ACT $\geq$ 18 group. Alveolar macrophages of obese subjects with asthma produce higher amounts of IL-8 and TNF-α after leptin stimulation than macrophages of non-asthmatic obese or eutrophic individuals.[33] IL-8 stimulates inflammation by having a pro-inflammatory action and is related to the extent of neutrophilic inflammation due to chemotactic action for neutrophils.[34] In addition, obesity alone can promote reduction of lung volumes such as FVC and expiratory reserve volume (EVR)[10,35] due to the increase of adipose tissue in the abdominal and thoracic regions causing a restrictive disorder.

Finally, establishing a relationship between the inflammatory aspects of the individual with obesity and their pulmonary function is of great importance in clinical practice in the identification of the symptomatic cause and establishment of effective treatment, such as managing the asthma treatment in the obese in order to improve the profile especially related to interleukin-6 and weight loss as suggested recently.[9]

Conclusion

It was concluded that the lack of control of asthma symptoms, use of relief medication and interference in daily activities was related to worse lung function, in addition to the increase in pulmonary interleukin-6 being associated with worse lung function even in patients with controlled asthma, especially in the translate airway permeability measures. However, the lack of a control group and the cross-sectional design of this study limit the results extrapolation.

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ORIGINAL ARTICLE

Connective tissue disease-associated interstitial lung disease

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KEYWORDS
Connective tissue disease;
Interstitial lung disease;
Rheumatoid arthritis;
Systemic sclerosis;
Tocilizumab;
Nintedanib

Abstract
Background: Connective tissue diseases (CTD) are frequently associated with interstitial lung disease (ILD), significantly impacting their morbidity and mortality.
Aim: Analyze the experience of an autoimmune specialized unit on treating CTD-ILD and characterize the population based on most frequent diseases, imaging patterns, lung function tests results, serology and treatment. Assess mortality and mortality predictors in these patients.
Methods: Retrospective, descriptive and statistical analysis of the CTD-ILD patients followed up at an autoimmune diseases unit during a 6-year period.
Results: Over the study period, 75 patients with CTD-ILD were treated with a mean follow-up of 49 ± 31 months.

The most frequent CTD were systemic sclerosis and rheumatoid arthritis. ILD was diagnosed prior to CTD in 8% of patients and concomitantly in 35%. Nonspecific interstitial pneumonia was the CT pattern in 60% and 35% had an isolated diminished DLCO on lung function tests. Pulmonary hypertension was present in 12% and it was the single most important mortality predictor (OR 14.41, $p = 0.006$). Corticosteroids are the mainstay of treatment but biologics were prescribed in 39% of the patients (mostly tocilizumab and rituximab). Two scleroderma patients were recently treated with nintedanib.
Conclusions: ILD is a potential complication of every CTD and can impose a dramatic burden on these patients. The clinical relevance of ILD together with their early expression in the course of the disease underlines the importance of the presence of chest physicians in these units.

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Introduction

Connective tissue diseases (CTD) are a group of diseases with heterogeneous systemic features and immune-mediated multi-organ disfunction. The respiratory tract can be targeted in virtually every CTD and with a multitude of manifestations, bringing important implications to the diagnosis, follow-up, treatment and prognosis of these patients.[1,2] Lung involvement is a decisive contributor to the mortality in CTD, and is now the leading cause of death in systemic sclerosis (SSc)[3] and an increasing cause of death in rheumatoid arthritis (RA), even as the overall mortality rates are falling.[4]

Interstitial lung disease (ILD) is frequently present in patients with autoimmune myopathies, SSc, Sjögren's syndrome, RA and systemic lupus erythematosus (SLE), with estimated prevalences of 40%, 30–40%, 40%, 10% and 12%, respectively.[5] It is important to keep in mind that ILD may be the only manifestation of a yet-to-be diagnosed CTD.[6]

High-resolution computed tomography (HRCT) and pulmonary function tests (PFT) are the best tools to evaluate lung involvement and have prognostic value.[7–9]

While there are no definitive serum biomarkers for CTD-ILD, the presence of some disease-specific markers can lead to a better screening and risk-stratifying of patients.[10]

Pulmonary hypertension (PH) is a common finding in CTD-ILD patients and adds significant impact to the morbidity and mortality of these patients.[11]

Development of lung disease, and its associated symptoms like dyspnea and cough, provides extra burden on a group of diseases already highly impactful on quality of life.[12]

Even though ILD is a common complication of CTD, the definitive guidance on how to treat these patients is scarce. Corticosteroids still represent the mainstay of treatment.[13] In the context of SSc, there is also an increasing body of evidence for biologics, such as tocilizumab[14] and rituximab,[15] and renewed enthusiasm for new therapeutical targets, such as antifibrotic drugs.[16,17]

Due to the sheer complexity and systemic involvement of these diseases, a multidisciplinary approach should be the gold-standard when treating these patients.[18] This paper aims to compile, analyze and discuss the experience of our unit in the management of CTD-ILD.

Methods

The authors conducted a retrospective, descriptive analysis of patients older than 18 years diagnosed with CTD-ILD followed up at an autoimmune diseases outpatient clinic between January of 2013 and December of 2018.

The diagnosis of CTD was based on clinical and serologic criteria according to the most recent EULAR recommendations and the diagnosis of ILD was made on the basis of HRCT findings. All patients were discussed in a weekly autoimmune diseases multidisciplinary team meeting. Cases were further discussed with pulmonology and radiology on a case-by-case basis.

HRCT scans and PFT results shown are the ones done at the ILD diagnosis. HRCT scans were obtained with 1–1.5 mm thick slices. PFT were carried out according to a standardized protocol in the respiratory medicine department. Static lung volumes were measured using the plethysmography method, and the lung diffusion capacity of CO (DLCO) using the single breath-hold method. Antibodies were tested with the following techniques: ANA, ANCA – indirect immunofluorescence assay; Anti-SSA, anti-SSB, anti-Sm – Immunoblot assay; anti-dsDNA, anti-CCP – fluorescence enzyme immunoassay (FEIA); Rheumatoid factor – turbidimetry.

Data was collected from hospital records and handled in an anonymous and population-based fashion. Normally distributed variables are presented as mean and standard deviation and non-normal variables are presented as median and interquartile range. Differences in baseline variables were tested with t-tests for continuous variables; $\chi 2$-trend tests for ordered categorical variables; and $\chi 2$ tests for binomial and unordered categorical variables. Statistical analysis was performed using Stata® 14 software.

Results

Population

During the 6-year study period, 75 CTD-ILD patients were followed-up at this unit with a mean follow-up of 49 ± 31 months amounting to 646.2 patients-years. The mean age at the time of ILD diagnosis was 56 ± 15.5 years-old, there was a clear female predominance (77.3%) and the mean duration of CTD was 8.9 ± 7.5 years. CTD was diagnosed before ILD in 57% of patients, with a median interval of 49.1 [23.7–127.15] months separating the two diagnosis. ILD was diagnosed first in 8% of patients (n = 6) with CTD being diagnosed shortly after (mean interval of 5.1 months). Diagnosis was simultaneous in 35% of patients.

The CTD were, by order of prevalence, SSc (34.7%; n = 26), RA (20%; n = 15), overlap syndrome (13.3%; n = 10), mixed CTD (9.3%; n = 7), autoimmune myopathy (6.7%; n = 5), ANCA-positive vasculitis (5.3%; n = 4), undifferentiated CTD (5.3%; n = 4) and Sjögren syndrome (2.7%; n = 2).

Imaging and biopsy

Nonspecific interstitial pneumonia (NSIP) was the most common HRCT pattern, present in 60% of patients, followed by usual interstitial pneumonia (UIP) in 36% of patients and a pattern of lymphocytic interstitial pneumonia (LIP) in the remaining 3 patients. One patient with anti-synthetase syndrome had a predominance of NSIP pattern overlapped with organizing pneumonia (OP) features. Out of the patients with NSIP pattern, 42.2% had a diagnosis of SSc and 24.4% had overlap syndrome or mixed CTD with a predominance of scleroderma findings. Among patients with SSc, 58% had extensive disease (>20% involvement[19]) on HRCT. A LIP pattern was found in 2 patients with Sjögren syndrome and 1 with polymyositis. Other common findings were pleural thickening (n = 16), lung nodules (n = 14) and pleural effusion (n = 5).

While not mandatory for the diagnosis, lung biopsy was performed in 11 patients who had conflicting HRCT findings or a broader differential diagnosis, 3 being compatible with

NSIP and 3 with UIP. The remaining 5 biopsies had nonspecific findings.

Pulmonary function tests

PFT were carried out in all patients at the time of ILD diagnosis. A restrictive pattern was found in 46% whilst only 6% had an obstructive pattern. Isolated diminished DLCO was present in 35% of patients and 13% had all results within the normal range. ANCA-positive vasculitis, autoimmune myopathies and mixed CTD, were the subgroup of patients who presented with more severe lung involvement at diagnosis (Table 1).

At time of diagnosis only 2 patients had arterial pressure of oxygen below 60 mmHg on room air and only 3 patients had minor hypercapnia.

Pulmonary hypertension

Nine patients (12%) had signs of pH on transthoracic echocardiography (pulmonary artery systolic pressure $\geq$40 mmHg), with a mean pressure of 60.8 $\pm$ 23.8 mmHg. Five patients had SSc and the other 4 had mixed CTD or overlap syndrome with a predominance of scleroderma findings. Echocardiographic data was missing in 13 patients.

Five patients underwent right heart catheterization (RHC). Two of them did not have a confirmation of PH, the others had a mean pulmonary artery pressure of 40 $\pm$ 2.1 mmHg and a mean pulmonary vascular resistance of 10.4 $\pm$ 6 Wood Units. Of these 3, all with SSc, 1 was classified as having group I PH, the others were group III. In the remainder 4 patients with echocardiographic signs of PH, RHC was not conducted as the procedure was considered too risky or of no added benefit to the management of these particular patients.

Autoantibodies

Anti-nuclear antibodies were positive in 79% of patients (titre $\geq$1:320 in 80%).

Amongst SSc patients, 54% were anti-Scl70 positive, 15.4% were anti-centromere positive and 7.7% were anti-PM-Scl positive.

Amongst RA patients, 73.3% were simultaneously rheumatoid factor (mean value of 338 $\pm$ 266 UI/mL) and anti-citrullinated protein (anti-CCP) positive (mean value of 170.1 $\pm$ 160.4 UI/mL)

In overlap syndromes, the most frequently found serologic markers were anti-SSA (present in 40% of patients) followed by anti-SSB, anti-Scl70, anti-PM-Scl, rheumatoid factor and anti-CCP (all present in 20% of these patients). All patients classified as having mixed CTD were anti-RNP positive. Four out of the five patients with autoimmune myopathy were diagnosed with anti-synthetase syndrome (3 were anti-Jo1 positive and the other was anti-PL12 positive). The patient with polymyositis was anti-Ku positive (anti-MDA5 was not tested).

Treatment

Systemic corticosteroids were by far the most used drug, being used at some point during the course of disease in 86.7% of the patients. Mycophenolate mofetil was used in 36% of patients, cyclophosphamide in 33% and azathioprine in 29.3%. Methotrexate (MTX) was used prior to ILD diagnosis in 32% of patients (n = 23), but was then switched to another immunossupressor drug (mainly mycophenolate) in all but 2 patients. Out of the patients who were treated with MTX, 3 (13%) had lung fibrosis considered to be caused by the drug.

Biologic drugs were used in 39% of the patients, with tocilizumab and rituximab being the most used as first-line therapy (13 patients each), followed by etanercept (3 patients). Sixty percent of the patients with RA were on biologic treatment, as were 23.1% of SSc. Tocilizumab was the most used biologic in RA but this decision was driven by joint disease in all but one patient. All patients with ANCA-positive vasculitis and anti-synthetase syndrome were on rituximab (Table 1). Five patients required a biologic switch due to failure of first-line choice (3 patients were switched from tocilizumab to rituximab, 2 patients were switched from etanercept to tocilizumab). In 3 of these patients the switch was decided based on ILD progression, in the other 2 patients the decision was made due to ongoing activity of the joint involvement (both patients had overlap syndrome). Throughout the follow-up period there were no exacerbations of the ILD caused by the starting of biologic treatment.

Two patients with SSc were recently treated with nintedanib (one with UIP pattern, the other NSIP).

Six patients of the nine diagnosed with pH were prescribed specific treatment targeted at PH: 3 bonsentan, 1 alprostadil, 1 iloprost and 1 sildenafil. The last two patients were later switched to bonsentan.

Mortality

This cohort had a mortality rate of 20% (15/75 patients) during the analyzed period, with a mean survival of 67.8 $\pm$ 57.3 months since CTD diagnosis and 37.8 $\pm$ 20.9 months since ILD diagnosis. Mortality rate was higher in RA and overlap syndrome (Table 1).

Comparing deceased patients with the survivors, the first group was older at the time of CTD diagnosis (58.6 $\pm$ 4.9 vs 51.5 $\pm$ 2.7 years-old, p = 0.23), older at the time of last follow-up (66.4 $\pm$ 11.1 vs 60.4 $\pm$ 15.2 years-old, p = 0.03) and more frequently male (33 vs 20%, p = 0.31). UIP pattern on HRCT was related with higher mortality but the difference was not significant. There were no significant differences regarding other imaging patterns, diagnosis of SSc, corticotherapy and ANA positivity. The presence of pH was clearly associated with higher mortality (OR 14.41, p = 0.006) and so was the use of biologics (OR 5.56, p 0.025).

Discussion

This population of 75 CTD-ILD patients constitutes a relevant sized population with a long mean follow-up time of 49 $\pm$ 31 months over the span of 6 years. ILD was diagnosed prior to CTD in only 8% of patients but this is probably

Table 1 Description of main characteristics analyzed by disease subgroups and the global cohort.

	SSc (n = 26)	RA (n = 15)	Overlap S. (n = 10)	Mixed CTD (n = 7)	AI Myopathy (n = 5)	ANCA + vasculitis (n = 4)	Total (n = 75)[b]
Demographic characteristics							
Female sex, n (%)	21 (81)	11 (73)	7 (70)	6 (86)	3 (60)	2 (50)	58 (77)
Age at CTD diagnosis, y	54 ± 16	54 ± 18	52 ± 10	51 ± 10	39 ± 25	61 ± 8	52 ± 16
Age at ILD diagnosis, y	58 ± 18	61 ± 14	59 ± 10	55 ± 13	42 ± 23	62 ± 7	56 ± 16
HRCT at time of ILD diagnosis							
NSIP, n (%)	19 (73)	6 (40)	8 (80)	5 (71)	3 (60)[a]	2 (50)	45 (60)
UIP, n (%)	7 (27)	8 (53)	1 (10)	2 (29)	2 (40)	2 (50)	27 (36)
LIP, n (%)	0	0	1 (10)	0	0	0	3 (4)
PFT at time of ILD diagnosis							
Spirometry pattern, n (%)							
Normal	12 (46.2)	5 (33)	5 (50)	2 (29)	2 (40)	2 (50)	35 (46)
Restrictive	13 (50)	8 (53)	4 (40)	5 (71)	3 (60)	2 (50)	35 (46)
Obstructive	1 (3.8)	2 (13)	1 (10)	0	0	0	5 (6)
Mean FVC, % predicted	86.1 ± 31.8	85.3 ± 21.3	107.6 ± 29	71.7 ± 31.9	76.4 ± 20	75.5 ± 12	85 ± 27.3
Mean DLCO, % predicted	50.4 ± 23.7	62.4 ± 36.1	68.7 ± 18.9	49.8 ± 11.8	62.1 ± 14.2	33.7 ± 22.2	52.7 ± 23.3
Treatment							
Corticosteroids, n (%)	22 (85)	15 (100)	8 (10)	5 (71)	5 (100)	4 (100)	65 (87)
MTX, n (%)	6 (23)	8 (53)	4 (40)	4 (57)	0	0	23 (32)
RTX, n (%)	2 (7.7)	1 (6.7)	1 (10)	1 (14)	4 (80)	4 (100)	13 (17.3)
TCZ, n (%)	4 (15.4)	7 (46.7)	1 (10)	0	0	0	13 (17.3)
Mortality rate, n (%)	5 (19.2)	5 (33.3)	3 (30)	0	0	1 (25)	15 (20)

SSc - Systemic sclerosis; RA - Rheumatoid Arthritis; Overlap S. - Overlap syndrome; CTD - connective tissue disorder; AI myopathy - Autoimmune myopathy; ILD - Interstitial lung disease; HRCT - High-resolution computerized tomography; NSIP - Nonspecific interstitial pneumonia; UIP - Usual interstitial pneumoniae; LIP- Limphocytic interstitial pneumonia; PFT - Pulmonary function test; FVC - Forced vital capacity; DLCO - Diffusing capacity for carbon monoxide; MTX - Methotrexate; RTX - Rituximab; TCZ – Tocilizumab.

[a] One patient with anti-synthetase syndrome presented with overlap NSIP/OP.

[b] Total includes subgroups shown plus undifferentiated CTD (n = 4) and Sjögren syndrome (n = 2).

biased since this unit is primarily focused on CTD with a background in internal medicine. More importantly, diagnoses were simultaneous in 35% of patients, emphasizing the relevance of lung involvement in these conditions. It is important to note that all patients had a definite diagnosis of a CTD, hence no patient fell within the recently suggested definition of ''interstitial pneumonia with autoimmune features''.[20]

Most patients presented with a NSIP pattern on HRCT but more common findings such as pleural thickenings and effusions can point towards a possible underlying CTD in an ILD patient. The majority of SSc patients had extensive lung disease on HRCT at the time of ILD diagnosis, again reinforcing the relevance of this condition, particularly in light of the fact that it can be clinically silent during a significant amount of time.[3] Lung biopsy was seldom used and rarely provided additional information.

Regarding PFT, an isolated diminished DLCO (35% of patients) may be the only abnormality. ANCA-positive vasculitis and mixed CTD were the subgroups with the most impactful disease at diagnosis. In ANCA-positive vasculitis the severity of the lung disease was mainly on account of a very low DLCO, which was probably caused by vasculitic disease rather than ILD *per se*.

Regarding treatment, corticosteroids remain the first-line but the use of other immunosuppressants such as mycophenolate mofetil is increasing.

Methotrexate was stopped in most patients upon ILD diagnosis, even if only 3 patients presented with fibrosis admitted being related to it. Over the years MTX-associated lung disease has been a controversial topic, with earlier studies pointing towards a slightly increased risk of lung fibrosis.[21] MTX was stopped for most patients to prevent it from being a confounding factor in the follow-up and because safer and equally effective drugs were available. In retrospect, and in light of a recent multivariate analysis showing that there was no association between development of RA-ILD and MTX use and that the drug could in fact have a protective role, the drug could have been safely continued.[22]

Biologic drugs are being increasingly used in CTD-ILD. The most used ones were tocilizumab and rituximab and their use was mainly dictated by the extra-pulmonary manifestations of the underlying CTD—tocilizumab was predominantly used in RA and rituximab for vasculitis and autoimmune myopathies. In this population, biologics were deemed safe to start in patients with ILD as there were no exacerbations upon the start of biologics, contrary to some prior reports.[23] The use of biologics was associated with worse survival but this is probably related to disease severity rather than drug-related complications.

The antifibrotic nintedanib was used in 2 SSc patients with extensive lung fibrosis, after positive safety results in idiopathic pulmonary fibrosis,[24] and might be a promis-

ing option for slowing ILD progression in these patients, as shown by the SENSCIS Trial.[17] However, criteria for nintedanib use in SSc-ILD is up for debate,[25] and both our patients remained on background immunossuppressive treatment. Evidence is emerging for the use of antifibrotics in other CTDs. The recently published INBUILD Trial showed that nintedanib leads to a lower annual rate of decline in FVC in patients with progressive fibrosing interstitial lung diseases, including patients with autoimmune diseases, the majority of them with RA-ILD and also including patients with mixed CTD.[26]

With 20% mortality rate and a mean survival of 37.8 ± 20.9 months, ILD constitutes an important burden on CTD patients and significantly impacts their prognosis. In this cohort, pH was the single most important mortality predictor (OR 14.41, $p = 0.006$).

Even though this article provides an overview of the general population encountered at an autoimmune diseases unit, some particular subsets of patients are not as strongly represented in the cohort (e.g. autoimmune myopathies) and this could lead to an underrepresentation of more specific and less common findings, as is the case of organizing pneumonia. At the other end, it could lead to an overrepresentation of rare findings, such as the LIP pattern in a patient with polymyositis. Heterogeneity regarding the underlying CTDs, disease duration, treatment and follow-up and the retrospective nature of the study may limit the interpretation of some of the results. The data presented reflects the clinical expertise of a single institution that has its main focus on CTD and may not be fully representative of practices elsewhere.

Conclusion

To the best of our knowledge this is the largest cohort of CTD-ILD presented by a Portuguese centre.

ILD is a potential complication of virtually every CTD, constitutes an important burden on these patients and significantly impacts their prognosis. A systemic and multidisciplinary overview is essential for adequate management, in order to fill in the remaining gaps regarding early diagnosis, follow-up and treatment of these patients.

Author contributions

RPO conceived the idea for the manuscript, collected the data, wrote the first draft and co-wrote the paper. RR collected the data and co-wrote the paper. LM collected the data, was responsible for statistical analysis and co-wrote the paper. BG, SO and JDA conceived the idea for the manuscript. All authors reviewed and approved the final version of this manuscript.

Conflicts of interests

The authors have no conflicts of interests to declare.

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REVIEW

Virtual reality for COPD rehabilitation: a technological perspective

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KEYWORDS
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Abstract Virtual Reality (VR) is a promising technology for implementing personalized, motivating and controlled rehabilitation scenarios. Although its clear potential benefits, VR has been poorly investigated in pulmonary rehabilitation. This review analyses the state of the art, by searching the scientific and grey literature, regarding the use of VR for the rehabilitation of patients with chronic obstructive pulmonary disease, providing a technological perspective. First, the main characteristics of the included systems are presented in terms of visualization devices, way of interaction and type of feedback they provide. Then, results of the selected studies are reported considering feasibility, safety, usability and user experience as outcomes. Finally, the main findings are discussed and future directions for research are outlined.

Introduction

Chronic obstructive pulmonary disease (COPD) is a widespread chronic disease considered a leading cause of mortality and morbidity worldwide.[1] It represents a substantial health and economic burden for both developed and low-income countries, with financial impact on national health care systems.[2] Due to an impaired respiratory function, COPD leads to an umbrella of comorbidities: physical impairment, cognitive decline, social isolation and lower quality of life. Pulmonary Rehabilitation (PR) is an evidence-based non-pharmacological treatment, consisting of a comprehensive intervention performed by a multidisciplinary team[3]; it includes physical training, learning breathing techniques, psychological support and nutritional advice. Since the advent of new technologies, researchers have been working on different solutions to improve the rehabilitation process both from the clinical and the eco-

Abbreviations: AVGs, Active Video Games; COPD, chronic obstructive pulmonary disease; FOV, Field of View; HMD, Head Mounted Display; PR, Pulmonary Rehabilitation; SUS, System Usability Scale; VR, Virtual Reality; VE, Virtual Environment.

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Figure 1 An example of a Virtual Reality-based system for physical endurance training.

nomic point of view.[4] These include, for example, mobile applications for the self-management of COPD,[5] telemonitoring systems exploiting multiple sensors[6] and digital environments for exercise training. Within these solutions, Virtual Reality (VR) represents a powerful tool for improving exercise training allowing personalized treatments, performance monitoring and quantitative measurement—also integrating sensors and external devices.[7,8] Virtual Reality, by creating engaging scenarios may enable the ''attentional shift'', distracting the patient from negative sensations (e.g. fatigue, breathlessness) during physical activity[9]; VR can be also effective in increasing motivation, by turning repetitive exercises—typical of the sometimes-boring conventional protocols—in engaging and enjoyable tasks.[10] Moreover, VR helps to simulate realistic scenarios that would be otherwise challenging or impossible to reproduce in the real world, in a safe and controlled way. The possibility of providing contextualized tasks which stimulate the cognitive functions of the patients, fosters the transfer of skills acquired during the rehabilitation sessions to activities of daily living.[11] In the context of COPD, VR is especially suitable for physical and breathing training. Physical training mainly includes endurance training, aimed to condition the muscles of ambulation and improve cardiorespiratory fitness, and strength training, in which local muscle groups are trained by repetitive movements performed with relatively heavy loads[3]; breathing training consists of different techniques (e.g. diaphragmatic breathing, pursed-lip breathing, inspiratory sighs) aimed at altering respiratory muscles recruitment and improving their performance thus decreasing breathlessness.[12] Hereafter we will consider these components of the intervention when referring to PR. Although it has been extensively used successfully in the treatment of different groups of patients e.g. post-stroke,[13] patients with Mild Cognitive Impairment,[14] frail elderly,[15] children with neuromotor deficits,[16] the application of VR to rehabilitation of COPD is still not fully explored. An example of a VR system for physical training is shown in Fig. 1. The aim of this work is to analyse the current state of the art in this topic, focusing on technical aspects and on the user's perception of technology.

With respect to the analysis of the technical aspects, we need to clarify the term ''Virtual Reality'', which researchers often use when referring to any computer-based device that provides visual and audio stimuli, e.g. videogames, on a monitor.[17] However, in VR, the user, surrounded by a 3D computer-generated representation, is ''transported'' into the virtual environment (VE), should be able to move in it and to interact with the virtual objects in a natural way as he/she is part of the scene.[18] In fact, two key factors that characterize a VR system are *immersion* and *interaction*. These elements, as described in Table 1, influence the *sense of presence*, which in turn affects the effectiveness of the VR experience, e.g. the training.[19]

All these technical aspects contribute to the realism of the experience, the satisfaction of the user and, consequently, to the effectiveness of the rehabilitation intervention. In addition, when considering a system for rehabilitation two essential requirements are feasibility and safety, which should be evaluated in the context of use. A third factor that should be considered is usability, which should always be high for any kind of technology. Moreover, the overall user experience should be positive and engaging and, therefore, investigating different aspects such as enjoyment, interest, and acceptability is crucial for creating solutions that are well perceived by the patients. Digital solutions, including VR, should induce a positive user experience in patients because ''if the users feel like the technology does not match their needs and preferences, or cannot be embedded in their routines, it will not be used''.[26] For all these reasons, it is important to consider these aspects both when designing and when evaluating a VR system for rehabilitation.

To the best of our knowledge, this work represents the first analysis providing a technological perspective on VR for PR. However, the increasing interest in understanding whether and how such technology could be effectively applied in this field is demonstrated by four reviews published between February 2019 and May 2020.[27–30] All the four reviews focus mainly on the clinical effectiveness of videogames for patients with respiratory diseases. Three of them analyse exergames (i.e. exercise + videogame) for physical training, while Sanchez and colleagues include also studies providing educational intervention.[29] We will include in our analysis only the systems for physical and breathing training since these are the elements of PR that may benefit the most from an interactive multi-stimuli training environment, like the one provided by VR. Simmich and colleagues examine the effectiveness of game-based interventions vs. traditional protocols on physiological outcome measures, adherence and enjoyment in subjects with chronic respiratory diseases.[28] All respiratory conditions are admitted including asthma, thus widening the target population to children. Since age is a key factor in the perception and adoption of technology, our review will focus only on elderly patients. Similarly, Wang and colleagues published a systematic review including controlled trials but limiting the analysis to COPD patients.[30] Based on the seven papers they have analysed, the authors conclude that exergames, in particular active video games (AVGs), are useful and enjoyable as an adjunct to PR. The review by Butler et al. presents controlled studies involving different chronic diseases and considers exercise capacity as the primary outcome; secondary outcomes are dyspnoea, fatigue, energy expenditure as well as enjoyment and user preference.[27] The analysis by

Table 1 Definitions.

Virtual Reality	a three-dimension computer-generated representation of a reality that can be similar or completely different from the real world where the participant is able to move in a natural way while receiving multisensory stimulation
Immersion	a quality of the system's technology, an objective measure of the extent to which the system presents a virtual environment capable of delivering an inclusive (i.e. shutting out physical reality), extensive (i.e. depending on the sensory modalities accommodated), surrounding (i.e. the extent to which the virtual environment is panoramic rather than limited to a narrow field of view) and vivid (indicating the resolution, the fidelity of the virtual representation) illusion of reality.[20] Depending on the level of immersion it provides a VR system can be: semi-immersive (e.g. a large projected screen) or immersive (e.g. a head mounted display).
Interaction	the combination of hand gestures, natural echo on the screen and manipulation of virtual objects that allow the user to navigate within the scene, to identify objects and to modify them.[21]
Sense of presence	a subjective measure of a state of consciousness, the psychological sense of being in the virtual environment.[20,22]
Feasibility	a feasibility study is an iterative, formative and adaptive study that focuses on conducting research to examine whether the study can be done.[23]
Usability	the extent to which a specific user achieves a definite goal by effectively, efficiently and satisfactorily using a system within a specified context.[24]
User experience	encompasses user perceptions and responses resulting from the use or the anticipated use of a product, system, or service ISO.[25]

Sanchez et al. also covers not only COPD but also chronic bronchitis, emphysema, asbestosis, asthma, cystic fibrosis and bronchiectasis.[29] Like the other reviews, the analysis is focused on clinical outcomes (e.g. respiratory function, exercise capacity, symptoms, quality of life); knowledge of the disease is also considered with respect to educational interventions.

All the reviews mentioned share a clinical perspective, focusing on the comparison of physiological response and clinical outcomes with a control group. Instead, the present work provides a technological point of view through the analysis of the characteristics of the proposed systems in terms of technology and user experience. The aim of our work is thus to analyse the state-of-the-art-technology and to identify gaps in the existing literature regarding the application of VR to respiratory rehabilitation—and in particular training exercise (physical and breathing).

Methods

Since our analysis focuses on the technological aspects rather than on clinical effectiveness, a scoping review has been preferred. Such a methodology allows inclusion of not only the scientific but also the grey literature, which in this case may present preliminary works not yet eligible for full publication process. We observed the recommendations on scoping studies by Arskey & O'Malley[31] to guarantee the application of a rigorous protocol.

Literature search and study selection

A literature search was carried out between September 2019 and November 2019; an update was carried out on October 31st 2020 in the following scientific databases: MEDLINE, IEEExplore, Scopus (EMBASE). Grey literature was analysed through Google Scholar. The search was restricted to year 2000 in the past because VR technology—in terms of both hardware and software—has significantly improved starting from 1999.[32]

The authors searched the databases and selected the systems that met the following inclusion criteria.

- The system is designed for pre-elderly (between 50–65 y. old) or elderly (>over 65 y. old); main target users are COPD patients;
- It provides physical or breathing training;
- It is a digital solution, VR application or exergame/active videogame providing a virtual scenario and (at least) visual and/or audio stimuli, active interaction and feedback.

Mobile apps for self-management and apps for rehabilitation—e.g. based on written or video instructions—not providing an interactive virtual scenario were excluded as considered out of the scope of our analysis.

Data extraction and analysis

The following information was retrieved for each of the articles,: year and type of publication, type of training, technology used, interaction device, visualization device, the presence and the type of physiological sensors integrated in the system.

Results

The study selection process and keywords are reported in Fig. 2. As a result, 21 articles, published between 2011 and 2020, were included in the analysis. As a scoping review, all types of publications have been admitted: 10 journal papers,

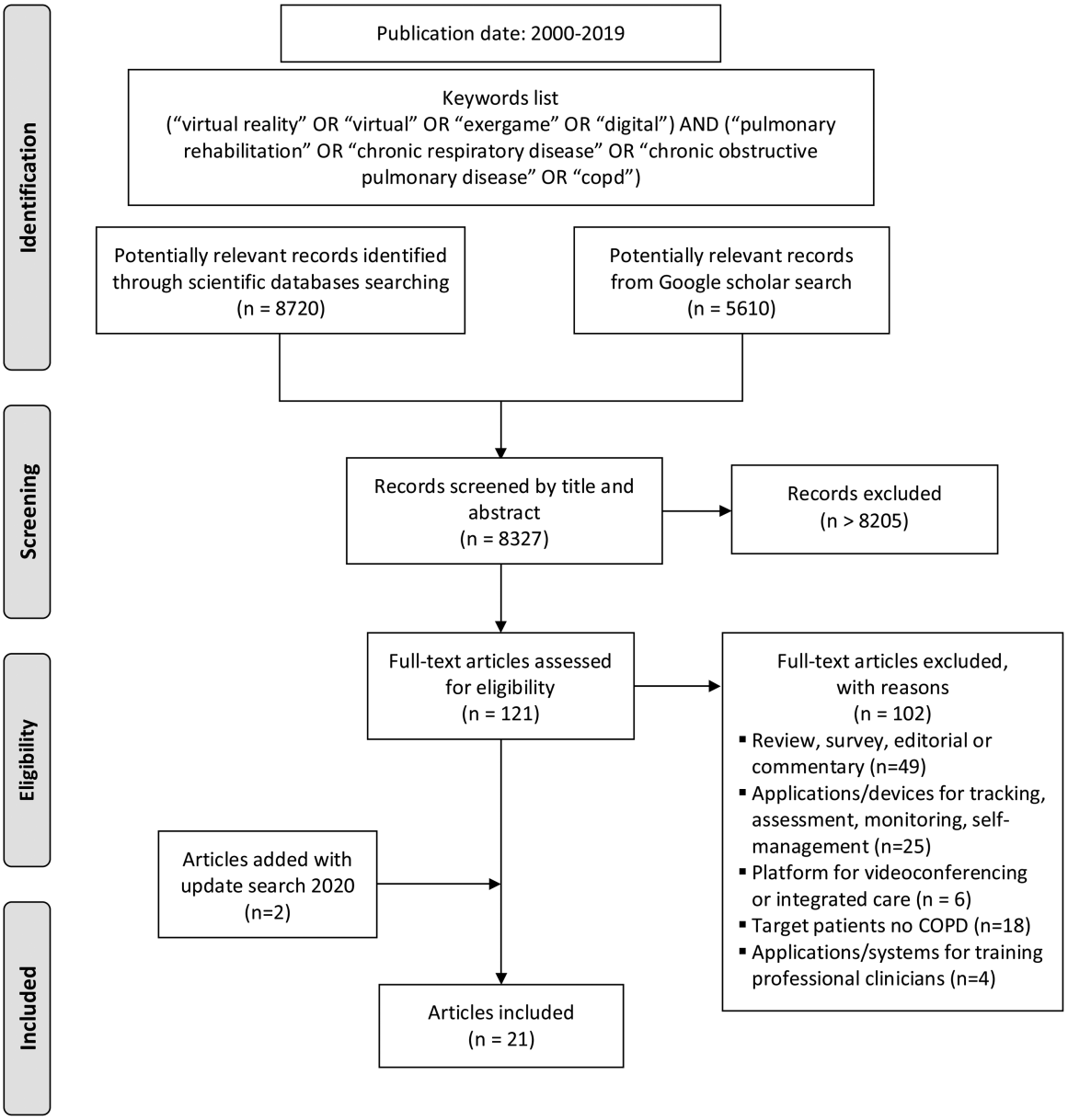

Figure 2 Flow diagram of study selection.

5 conference proceedings papers, 5 abstracts and a book chapter.

Training systems characteristics

The literature search focused on systems designed for physical and/or breathing training. Most of the systems (73%) are designed for physical exercise; around 16% provides breathing exercises only and 21% allows for both training modalities.

Most of the studies (68%) use active video games (AVGs) as a training tool for both physical and breathing exercises. Active video games, usually experienced through a PC/TV monitor or a *mobile* device screen, fall into the *exergames* category. Exergames, coupling physical activity and videogames, show some of the features of VR, e.g. *gamification*, even if they are characterized by lower naturalistic sensory-motor interaction, limited ecological validity and lower degree of immersion. Regarding the reviewed studies, AVGs are based on consumer devices and, in particular, on Microsoft Kinect for XBOX, Nintendo Wii fit—either with or without the Balance Board. Six systems out of 21 are considered VR systems (see Introduction). Two studies provide training feedback and guidance through *mobile* applications. The main characteristics of the identified systems are summarised in Table 2.

Visualization

Different types of devices were used (see Fig. 3—Panel a) to display virtual contents to the user, each characterized by specific field of view (FOV), dimension and providing a given level of immersion. Most of the systems identified used a

Table 2 Main characteristics of the training systems (AVG = Active Video Game, VR = Virtual Reality, Y = yes, N = no, Semi = semi-immersive, Full = immersive, N* = not specified but likely not).

Authors	Article	Training	Type	Virtual scenario	Interaction	Immersion
Albores et al. 2011 [33]	Abstract	Physical (aerobic + upper body + lower body + balance)	AVG	3D mini-games cartoon-like: run in outdoor scenario, flapping arms to fly, free step on a stage, obstacle course (Wii fit plus)	Y	N
Albores et al. 2013 [34]	Journal	Physical (aerobic + upper body + lower body) + Breathing	AVG	3D mini-games cartoon-like: run in outdoor scenario, flapping arms to fly, free step on a stage, obstacle course (Wii fit plus)	Y	N
Colombo et al. 2019 [35]	Conference paper	Physical (aerobic + lower body)	VR	3D VE: bicycle ride in a park	Y	Semi
Dikken et al. 2015 [36]	Conference paper	Physical (aerobic + lower body)	VR	3D VE: bicycle ride on a roadway in a forest	Y	N
Jung et al. 2020 [37]	Journal	Physical	VR	3D virtual coach avatar showing how to perform exercises	N	Full
LeGear et al. 2014 [38]	Journal	Physical (aerobic + upper arm + lower body)	AVG	3D mini-game sports realistic scenarios: marching, dancing, air punching (EA SportsActive)	Y	N*
Makhabah et al. 2015 [39]	Abstract	Physical (upper body + lower body + aerobic) + Breathing	AVG	3D realistic scenario virtual coach on a mat: yoga, strength training, aerobic (Wii fit)	Y	N*
Marqueste et al. 2011 [40]	Abstract	Physical (lower body)	AVG	3D scenario with 2D representation of the board to guide the user on the next step (Wii fit)	Y	N*
Mazzoleni et al. 2014 [41]	Journal	Physical (upper body + lower body + aerobic) + Breathing	AVG	3D game realistic scenario avatar on a mat either controlled by the patient or as virtual coach (Wii fit plus)	Y	N
Moorhouse et al. 2019 [42]	Book chapter	Physical (also educational contents)	VR	3D virtual coach avatar showing how to perform exercises	N	Full
Parent et al. 2017 [43]	Conference paper	Physical (upper body + lower body)	AVG	3D mini-games realistic avatar in a gaming scenario: squat movements; punch targets appearing; twist the core to navigate avoid bombs stopping (Shape Up XBOX fitness)	Y	N

Table 2 (*Continued*)

Authors	Article	Training	Type	Virtual scenario	Interaction	Immersion
Parent et al. 2018 [44]	Journal	Physical (aerobic + upper body + lower body)	AVG	3D mini-game realistic avatar in a gaming scenario: running on a railway with obstacles; punch targets appearing; twist the core to navigate avoid bombs stopping; (Shape Up XBOX fitness)	Y	N
Qin et al. 2014 [45]	Abstract	Breathing	VR	2D mini-games: filling a balloon inhaling to lift a backet from a well to hydrate flowers; feeding the character rhytmically; inhale to strech a slingshot exhale to get the best launch angle and cough to shoot the penguin	Y	N
Rutkowski et al. 2019 [46]	Journal	Physical (balance + aerobic + upper body + lower body)	AVG	3D mini-games in realistic scenarios: underwater scenario; cross-country running on a railway avoiding obstacles; rafting; hitting balls in a sports hall (Kinect Adventures)	Y	Semi
Rutkowski et al. 2020 [47]	Journal	Physical (balance + aerobic + upper body + lower body)	AVG	3D mini-games in realistic scenarios: underwater scenario; cross-country running on a railway avoiding obstacles; rafting; hitting balls in a sports hall (Kinect Adventures)	Y	Semi
Stafford et al. 2016 [48]	Conference paper	Breathing	*mobile*	2D mini-game: avoiding obstacles with a ball moved according to breathing (inhaling - go up; exhaling; go down)	Y	N
Sutanto et al. 2019 [49]	Journal	Physical (aerobic + upper body + lower body) + Breathing	AVG	3D mini-games free run in realistic scenarios + yoga deep breathing/half-moon; torso twist with a virtual coach on a mat (Wii fit plus)	Y	N
Tabak et al. 2012 [50]	Journal	Physical (lower body)	AVG	2D mini-games: catching balls with a submarine	Y	N
Tekerlek et al. 2017 [51]	Abstract	Physical (aerobic + lower body)	VR	Not specified	(Not enough information)	Full
Wardini et al. 2013 [52]	Journal	Physical (aerobic + upper body + lower body)	AVG	3D mini-games cartoon-like: run/cycling in outdoor scenario, free step on a stage, obstacle course, stepping in a rhythm parade, boxing, canoeing (Wii fit plus + Wii sports + Wii resorts)	Y	N
Xu et al. 2013 [53]	Conference paper	Breathing	*mobile*	2D game: moving a ball through a pathway with obstacles	Y	N

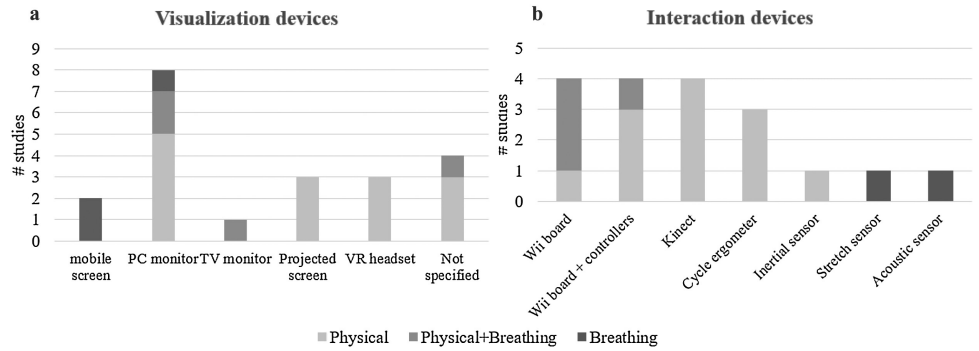

Figure 3 The visualization (a) and interaction (b) devices grouped according to the type of training (In panel a: Not specified are likely to be either PC monitor or TV monitor).

flat screen of small to medium dimensions and limited FOV providing no immersion: a PC monitor (n = 8), a TV (n = 1), a tablet/smartphone display (n = 2). In 4 cases, the authors did not explicitly specify the type of visualization device, however, based on the described systems, it is very likely that a PC/TV monitor was used.[38–40,52] Wider screens with a greater FOV were used in 3 studies in the form of a large projected screen.[35,46,47] In this case, the VE covers a large part of the FOV thus allowing the viewer to be partly immersed in the virtual scenario (semi-immersive). Only 3 studies used a head mounted display (HMD), characterized by higher FOV providing a fully immersive experience.[37,42,51]

Interaction and exercise feedback

To allow the user interact with the virtual contents, the analysed systems use different devices as shown in Fig. 3—Panel b. Most systems (n = 8) are based on the Nintendo Wii fit consisting of the Balance Board—a board embedded with weight sensors placed at the four corners detecting the weight displacement over it—and one or two controllers—usually held in the hands and measuring the hands' displacement through an accelerometer. The user interacts with the VE either moving on the Balance Board (e.g. stepping or swinging) or through the movements of the arms detected by controllers. Four of the included studies used the Microsoft XBOX Kinect, which features an RGB camera, a depth sensor and a microphone array.[43,44,46,47] It can track the whole body and compute position and orientation of each joint of the skeleton. The user's body movement is usually mapped to the human-like body skeleton of a virtual avatar. Those systems providing cycling training (n = 3) used a cycle-ergometer with sensors for measuring the cycling speed, which controls the navigation in the VE.[35,36,51] The solution presented by Tabak et al. consists of an accelerometer attached to the patient's hip detecting the vertical displacement during the squat movement.[50] The systems for breathing training employed either acoustic sensors[48,53] (i.e. a microphone placed at the mouth of the user) or a stretch sensor[45,48] (i.e. a chest elastic band) to measure the respiratory signal, through which the user controls specific virtual objects.

In most cases (n = 10), feedback on the performance is provided to the patient through a human-like virtual avatar, controlled by the user's movement, in third-person perspective. In two of the cycling systems, the user navigates the environment in first-person perspective, as if he/she is riding a virtual bicycle.[35,36] In all systems for physical training, the patient receives visual and audio feedback on correct movements and remaining time/time passing. In the studies using commercial AVGs, correct movements are often represented by the increase of the total score. When an aerobic task is foreseen—e.g. cycling or jogging in place—also real-time physical parameters, such as cycling speed or distance travelled, are shown to the patient. Few systems include physiological parameters as feedback during the exercise: three of them show heart rate and oxygen saturation level to either the patient or the physiotherapist only[35,42,50]; one of the AVGs reports energy expenditure.[38]

Study results

Seventeen papers—the characteristics of which are summarised in Table 3—present a clinical study involving COPD patients. Among these, 5 randomized controlled trials compared the outcomes of a group of patients training in VR with those assessed in patients undergoing traditional rehabilitation. Assessments were performed before and after the rehabilitation period, which lasted from 2 to 8 weeks, corresponding to the typical duration of PR. Five pilot studies and one longitudinal descriptive study present results of a VR-based physical training program on COPD patients. Three qualitative studies focused on the user experience investigating patients' attitude towards the use of technology for rehabilitation. Participants of all studies are adults, most of them are elderly: average age is over 65 for 10 out of 17 studies; two studies do not provide details on participants' age.[39,40]

The study results are presented hereinafter focusing on the aspects of interest of our analysis: feasibility, safety, usability and user experience.

Feasibility and safety

The included studies demonstrate that using VR solutions for training is feasible for patients with COPD. Albores and colleagues designed an intervention based on 6 Nintendo Wii exergames involving upper and lower limbs.[33] Results in a small group of patients demonstrated the feasibility of such intervention, which elicits a level of exercise intensity similar to that recommended by standard protocols. The Nintendo Wii system has also been proven safe and feasible as an additional tool to traditional protocols with

Table 3 Characteristics of the included studies (M = male, F = female, CG = control group, EG = experimental group, HR = heart rate,VO2 max = maximum rate of oxygen consumption, SpO2 = oxygen saturation, RPE = rate of perceived exertion, FETCO2 = end-tidal fractional concentrations of CO2, HRQL = health-related quality of life, SUS = system usability scale).

Authors	Study type	Duration	Sample size	Target users	Outcomes
Albores et al.[33]	Pilot study	Single session	5	COPD (n = 5); age 68 ± 6; 1 M/4 F	1) exercise capacity 2) HR 3) max VO2 4) minute ventilation 5) inspiratory capacity
Albores et al.[34]	Longitudinal descriptive	18 weeks (6 of usual care + 12 home exercise training)	20	COPD (n = 20); age 68 ± 10; 6 M/14 F	1) exercise capacity 2) health status 3) dyspnea 4) sit-to-stand in 30 test 5) arm lift repetitions
Colombo et al.[35]	Qualitative study	Single session	9	COPD, bronchial asthma (n = 9); age 69 ± 8; 4 M/5 F	1) SUS 2) Acceptability (Technology Acceptance Model)
Jung et al.[37]	Pilot study	8 weeks	10	COPD (n = 10); age: 68.9 ± 5; 6 M/ 4 F	1) focus groups and interviews (also see Moorhouse); 2) dyspnea 3) fatigue 4) emotional function 5) mastery 6) depression, anxiety 7) patient activation 8) strength, mobility, flexibility (self-reported)
LeGear et al.[38]	Cross-over	Single session (2 conditions)	10	COPD (n = 10); age: 65; 5 M/5 F	1) energy expenditure 2) SpO2, HR 3) RPE 4) Dyspnea (Borg scale) 5) Blood pressure 6) Enjoyment 7) Perceived safety
Makhabah et al.[39]	Randomized controlled trial	6 weeks	20	COPD (n = 20); age/gender: not specified;	1) exercise capacity

Table 3 (*Continued*)

Authors	Study type	Duration	Sample size	Target users	Outcomes
					2) dyspnea 3) baseline and transitional dyspnea 4) quality of life
Marqueste et al.[40]	Cross-over	Single session (2 conditions)	16	COPD (n = 16); age: 68.9 ± 11 (EG)/73.5 ± 9.2 (CG); gender: not specified;	1) ventilatory th 2) HR 3) max oxygen uptake 4) respiratory exchange ratio and timing
Mazzoleni et al.[41]	Randomized controlled trial	3 weeks	40	COPD, ILD, Asthma, Bronchiectasis, RCD (n = 40); age: 68.9 ± 11 (EG)/ 73.5 ± 9.2 (CG); gender	1) lung and respiratory muscle function 2) arterial blood gases 3) exercise capacity 4) dyspnea 5) health status 6) HRQL 7) Emotional response
Moorhouse et al.[42]	Qualitative study	8 weeks	10	COPD (n = 10); age: 68.9 ± 5; 6 M/ 4 F	focus groups and interviews area of improvements, satisfactions, perceptions, immersive learning, usability, intention to use
Parent et al.[43]	Pilot study	Single session	14	COPD (n = 14); age: 69.6 ± 5 (M); 74 ± 6 (F); 8 M/6 F	1) HR 2) ventilation and breathing rate 3) oxygen uptake 4) % quadricep saturation
Parent et al.[44]	Pilot study	Single session	14	COPD (n = 14); age: 69.6 ± 5 (M); 74 ± 6 (F); 8 M/6 F	physiological response 1) oxygen uptake 2) minute ventilation 3) tidal volume 4) FETCO2 at peak exercise

Table 3 (*Continued*)

Authors	Study type	Duration	Sample size	Target users	Outcomes
					5) effort perception 6) dyspnea 7) number of repetitions subjective responses 8) enjoyment 9) satisfaction
Rutkowski et al.[46]	Randomized controlled trial	2 weeks	68	COPD (n = 68); age: 60.5 ± 4.3 (EG)/ 62.1 ± 2.9 (CG); 35 M/33 F	1) physical fitness
Rutkowski et al.[47]	Randomized controlled trial	2 weeks	106	COPD (n = 106); age: 60.5 ± 4.3 (EG)/ 62.1 ± 2.9 (CG); 47 M/63 F	1) strength upper lower body 2) flexibility upper and lower body 3) agility and dynamic balance 4) exercise capacity
Sutanto et al.[49]	Randomized controlled trial	6 weeks	20	COPD (n = 20); age: 65.1 ± 7.5 (EG)/ 65.6 ± 4.7 (CG); 19 M/1 F	1) exercise capacity/tolerance 2) dyspnea 3) quality of life
Tabak et al.[50]	Qualitative study	Single session	19	COPD (n = 19(; age: 47—72; gender not specified	1) SUS 2) SpO2, HR
Tekerlek et al.[51]	Cross-over	3 single sessions	7	Chronic respiratory diseases (n = 7); age 53 ± 17; 2 M/5 F	1) exercise capacity 2) HR 3) SpO2 4) dyspnea 5) affective responses 6) satisfaction
Wardini et al.[52]	Pilot study	3—4 weeks	32	COPD (n = 32); age: 66 ± 9; gender not specified	1) adherence 2) attendance rate 3) dyspnea 4) Spo2 5) HR 6) enjoyment

a group of 32 elderly training for 3–4 weeks.[52] In a more recent study by Albores and colleagues, the same intervention proved safe and feasible in an unsupervised scenario with patients training independently at home for 12 weeks with no adverse effects.[34] The same system was also used by LeGear and colleagues in a cross-over trial with 10 patients performing a single session of training including marching, dancing and two air punching exercises.[38] An education session with therapists explaining and demonstrating the exergames was performed prior to the training. All participants found the intervention enjoyable and safe; they all felt comfortable with the possibility of performing the exercises at home without supervision. Relatives and colleagues evaluated the feasibility of a training program based on high intensity AVGs by Microsoft Kinect XBOX.[44] In this study, the original descriptions of some tasks, provided by the manufacturer, have been adapted to match the patients' requirements better, e.g. ''Squat as much as you can'' has been modified to ''Sit and stand on chair''. Although most participants enjoyed the intervention and expressed their willingness to have the system at home, not all of them felt sufficiently confident about using it by themselves. More clear instructions and reminders (e.g. using pictures) should be added to ease the interaction especially for those patients who have little experience with technology. Moreover, monitoring the physiological response is considered crucial for both clinicians and patients to ensure safety in home-based setting. In most of the cases, safety was assured by the presence of a therapist, monitoring the vital signs and symptoms (e.g. heart rate, SpO2, fatigue) during the whole exercise session using external devices, as used in the standard practice. These include pulse oximeters,[38,41] respiratory monitor,[41] heart rate sensors,[47] activity monitor to measure energy expenditure[38] and a portable metabolic analyzer.[44] In a few cases, these measurements were integrated in the application receiving data from a heart rate band and a pulse-oximeter,[36] a finger clip[50] and a wrist worn pulse-oximeter.[35,37]

Usability and user experience

Three studies evaluated the usability, either through a standard tool (i.e. the System Usability Scale – SUS) or through one-to-one interviews. For both the cases in which the SUS was used, the usability was excellent.[35,50] In both cases, however, the interaction between the user and the virtual contents was quite simple, representing a limitation to the positive results. In the system by Colombo et al. the user navigates the VE by simply cycling on the real ergometer[35]; in Tabak et al., the user controls the exercise—i.e. moving a submarine to collect bubbles—through his/her movements acquired by an accelerometer attached to the hip.[50] When a higher level of interaction was required, i.e. using a VR headset for performing exercises, the patients found the system fairly easy to use even if some technical aspects could be improved (e.g. ''adding the possibility to pause the system easily'') to make the interaction easier.[37,42]

Two studies explicitly include the evaluation of acceptability, assessed through ad-hoc questionnaires and spontaneous comments by the users. Colombo et al. focused attention on four variables: intention to use, perceived ease of use, perceived usefulness and subjective norm, which represents the perceived social pressure to engage or not to engage in a specific behaviour (here adhering to the treatment).[35] Mazzoleni et al. evaluate the acceptability of a Nintendo Wii program in a group of patients undergoing 3-week rehabilitation addressing the following items: ''comfort'', ''absence of pain'', ''fatigue'', ''enjoyment'', ''advantages'', ''desire to continue'' and ''suggest to anyone''. In both studies, the acceptability was high.[41] Even if a direct comparison cannot be made due to different methodology, both results suggest that patients show positive attitudes towards the use of technology for performing physical exercise. It is worth mentioning that both protocols foresaw the presence of a physiotherapist supervising the situation.

Tekerlek compared cycling on a stationary bike in three conditions: no feedback, music and VR. Patients reported low satisfaction—assessed through a 10-cm Visual Analog Scale—when in the VR condition mainly due to characteristics of the headset (weight, induced over sweating); they found the virtual content (video) repetitive and boring.[51] A little discomfort with the use of an HMD has been reported in the study presented by Moorhouse et al. and Jung et al.[37,42] Even if patients found the interaction quite easy to use, some of them complained about the weight of the device. The authors also performed focus groups and one-to-one interviews with participants to investigate all aspects of the VR training, which was divided into modules of increasing difficulty. A few patients found some modules too easy; a more personalized solution would make the VR experience more challenging and attractive. Nevertheless, all participants were satisfied with the training program; they reported a sense of satisfaction and increased motivation when successfully achieving a new training goal, e.g. completing a level of difficulty. Moreover, knowing that their usage and data were being tracked by health practitioners represented a strong motivator to adhere to the treatment. These qualitative results were supported by quantitative self-reported data presented in Jung et al. demonstrating improvements also in anxiety disorders, self-confidence and perceived physical strength and mobility.[37]

In general, all studies reported that patients enjoy training with technology finding the virtual contents fun and motivating either at home or as part of the rehabilitation program in the hospital.[35,44,50,52]

Discussion

Although the application of VR to PR is still developing, our review supports its feasibility, and its potential effectiveness to improve patients' motivation and engagement thus maintaining the benefits of rehabilitation over a longer period of time.

The papers included in our analysis are mainly focused on physical training; some are about teaching breathing techniques while few others combine breathing and physical exercise. This is in line with the standard practice for PR, which foresees physical training as cornerstone. The effects of breathing exercises on dyspnoea and overall patient's health condition is, instead, variable so that their role in the comprehensive management of COPD is not as widespread as physical activity.[12] Even if physical activity seems to also

improv cognitive functions and the use of VR itself is able to stimulate cognitive functions even without specific tasks, more research should focus on investigating the effect of integrating specific cognitive training in PR programs.[14,54] In fact, no studies providing cognitive training have been identified even if the literature suggests that, also due to the typical age of COPD patients, cognitive decline impacts on their quality of life.[55]

Most of the available studies employed AVGs, based on consumer devices, adapting the level of difficulty to the patients' needs. As a result, most of the proposed solutions did not follow a user-centred design approach; AVGs have a wider and more heterogenous audience. Patients with COPD have specific needs and are in a vulnerable condition so that additional safety concerns should be considered (e.g. assuring that the intensity of the exercise is adequate through real-time monitoring). However, commercial exergames, which undergo product testing based on standards for quality, guarantee functional safety and reliability. Moreover, they provide attractive graphics and audio feedback. On the other hand, for prototypes, only basic functional testing is performed while no functional safety standards are applicable because the development efforts would exceed the scope of a prototype build-up. Among the included studies, 7 prototypes have been specifically designed for elderly patients.

Strengths of these systems are that they are based on standard PR protocols following the guidelines provided by the American Thoracic Society and the European Respiratory Society: cycling on a stationary bike for those referring to physical training; ''pursed-lip breathing'' and ''holding breath and coughing'' for those pertaining breathing training.

The most common visualization modality is the flat screen (either PC or TV monitors), which is cheap and simple to use both for clinicians and for patients. This is in line with most of the rehabilitation systems for the elderly, even if, in recent years, more complex and immersive systems are successfully spreading in other fields, e.g. in neuro-motor rehabilitation.[13]

As explained in §1, the level of *immersion*, which is defined by the number and range of motor and sensory channels involved, influences the *sense of presence* and, as a consequence, may positively alter the effectiveness of the VR-based training. The importance of presence makes VR different to exergaming, which uses video feedback or distraction techniques (e.g., watching a video) where presence is not required. Our analysis demonstrates the first attempts to introduce more immersive solutions in PR too. Projected screens represent a valuable solution for providing a wider FOV, which should make the user feel more present in the VE, even if they require a proper set up and a dedicated room. This may be the reason why only three studies have preferred such a solution. Head Mounted Displays provide a higher level of immersion—and consequently sense of presence—and are more portable, while there are still concerns about using such devices for this group of patients. Regarding technical aspects of HMDs and their acceptability, the few available studies show different results. In one situation, most participants tolerated wearing the helmet well, but even though they found the experience acceptable, some of them would hav appreciated a lighter weight device. In the second case, most patients complained about the weight of the device and the over sweating induced. The differing results are likely to be related to the different headsets used.

The other factor influencing presence is the *interaction*, which depends on the device through which the interaction is made possible and the feedback provided to the user (see Table 1). The more realistic the interaction—i.e. the user reacts as if he/she were actually there—the higher the level of ecological validity, which represents an important advantage of VR.[56] Interaction with the virtual contents was simple and natural in most of the analysed systems thanks to specific embedded sensors (e.g. accelerometers, encoders, acoustic sensors) able to measure the physical performance, e.g. in terms of hand's position and rotation, cycling speed and breathing rate. In most studies, physiological parameters were assessed using external devices both to assure safety and to assess primary outcomes (e.g. heart rate, energy expenditure). Embedding monitoring functionality in the applications may represent a step towards more efficient and more complete solutions, able both to provide a comprehensive overview to the clinicians and to be used by the patients at home with low supervision.

Given these characteristics, studies showed that VR-based training (aerobic, strength and breathing exercises) is feasible and safe for patients. A technological solution for health should be feasible—from technical, organisational and economic points of view—and safe, especially when dealing with vulnerable people, e.g. elderly, children, patients.[26] Regarding the studies analysed, the feasibility has been proven both as an alternative solution to standard protocols and as integrative one. Although few studies demonstrated that home-based training is feasible, most of them preferred a supervised scenario with an expert clinician constantly monitoring and guiding the patient. Further research should focus on evaluating feasibility in unsupervised situations. Continuity of care at home is indeed one of the main challenges in improving PR and the treatment of chronic conditions in general. Furthermore, promoting effective home-based rehabilitation is becoming more and more crucial, also given the recent COVID-19 pandemic, which has highlighted the need for more effective interventions that do not require patients, who are at higher risk of a more severe infection, to physically go to hospitals or clinical care facilities. Regardless of the level of supervision, we found that a familiarization session and step-by-step instructions are needed in order to make the patients—even the less confident—feel comfortable with technology.

As most of the studies are based on commercial exergames—which undergo product testing before being launched into market—only few studies evaluated the usability. Despite the scarcity of information, our analysis suggests that further research is needed to understand if more complex systems—such as HMDs—with a high level of interaction and immersion can be effectively used with COPD patients. In particular, the most advanced HMDs should be evaluated in order to guarantee the most comfortable experience thus avoiding weight and over sweating issues. Usability is a crucial requirement, especially for those users, such as the elderly, who may be less confident with technology; however, there are other factors influencing the

individual adoption of a technological solution which are worth investigating.

Only two studies presented results on acceptability; both showed that VR-based systems are considered useful and are well accepted by patients, who would like to have them at home. All patients were satisfied with this innovative way of training and enjoyed the virtual contents. They all found the proposed intervention highly motivating both because it distracts them from negative sensations (e.g. fatigue and breathlessness) and because it generates a report that the therapist can access thus inducing a sense of responsibility. Despite some evidence, the impact of these ''human'' factors on the motivation, engagement and, therefore, on the clinical outcomes is still under investigated.

Conclusions

In this paper, we investigate the use of Virtual Reality as a promising solution to improve both at home and in-hospital PR, providing a technological perspective and focusing on subjective experience of patients. Despite an increasing number of studies showing encouraging results demonstrating feasibility, acceptability and safety of VR for physical and breathing training of COPD, further research is needed. In particular, most of the systems identified are commercial exergames and are characterized by low levels of immersion and interaction. Further research should investigate whether higher immersion (e.g. using head mounted displays) and a more natural interaction (e.g. integrating physiological and motion sensors) enhances the rehabilitation outcomes, e.g., by inducing attentional shift from negative sensations.

Given the variety of factors affecting the successful implementation of technological solutions for health, cooperation between developers and clinicians is fundamental in order to maximize the benefits of VR for COPD rehabilitation. Only in this way can ad-hoc VR systems be built which exploit the most advanced technologies and which, at the same time, follow rigorous clinical protocols, with a real impact on patients' quality of life.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Molecular diagnosis of pulmonary tuberculosis using different respiratory specimens: The spotlight of induced sputum

Despite all the benefits already published of GeneXpert® MTB/RIF (Xpert) for tuberculosis (TB) diagnosis, which is one of the top ten causes of death, according to the World Health Organization,[1] there are a few studies comparing different pulmonary specimens - spontaneous sputum (SS), induced sputum (IS) and bronchoalveolar lavage (BAL). This study aims to analyse the Xpert accuracy in these samples for TB diagnosis and for rifampicin resistance identification in a tertiary TB reference centre in Brazil.

This retrospective study involved 1772 samples of patients who underwent bronchoscopy, SS collection or IS procedures. Each positive sample was simultaneously tested with Xpert, Acid-Fast Bacillus (AFB) smear using the Ziehl-Neelsen method and mycobacterial culture with drug susceptibility test (DST) processed by BACTEC Mycobacterial Growth in Tube® 960 or Lowenstein Jensen medium. Mycobacterial culture and DST were considered gold-standard methods.

The results were registered in a database at the Mycobacterial Laboratory of the Thorax Disease Institute, Federal University of Rio de Janeiro, a tertiary hospital in Brazil, between January 2017 and November 2019.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and likelihood ratios (LR) were calculated. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 21.0® software.

Of the 1772 pulmonary samples screened, 1717 (97%) were enrolled, and 55 were excluded from analysis (1 indeterminate Xpert and 54 contaminated cultures). Table 1 summarizes the demographics and clinical characteristics of the patients.

Among the 704 BAL samples, 103 were culture positive, and 91 of them tested Xpert positive. Of the 601 culture negative samples, 24 were Xpert positive. These discrepant samples included 3 patients who had recently been treated for TB, suggesting nonviable fragments of MTB detected.

The sensitivity, specificity, NPV, PPV, accuracy and LR ratios for BAL are described in Table 2.

302/1717 of the specimens were of the IS (17.5%), and the Xpert performed on these samples registered a sensitivity of 92% and a specificity of 97%.

There were 10 (3.3%) discordant results when Xpert and cultures in IS were compared. Of these, 7 were Xpert positive and culture negative, among which 6 patients were treated for TB, and 5 completed treatment (Table 1).

Among HIV-infected patients (55/302 patients), sensitivity was 71%, and specificity was 97%. The performance of Xpert in IS is described in Table 2.

The sensitivity and specificity of Xpert in SS were 94% and 97%, respectively. Based on the higher prevalence of TB among patients submitted to SS collection, this sample had a higher PPV than BAL and IS (Table 2). There were 14 samples with negative culture and with Xpert positive results. Among these patients, 6 were treated for TB (Table 1).

The performance of Xpert was confirmed in several studies, but only a few compared it in three different specimens that can be used for pulmonary TB diagnosis. In our study, we included 1717 respiratory samples and confirmed its good performance in pulmonary samples, especially in IS.

These results are in line with Luo et al.,[2] who showed that IS had a similar sensitivity, specificity and overall accuracy compared to BAL samples for TB diagnosis.

Notably, the high number of IS samples showed in our study has never been published before, with a sensitivity of 94% and a specificity of 97%. When compared with AFB, the sensitivity increased from 50% to 94%, and the likelihood of making an early diagnosis and prompt treatment increased. Chew et al.,[3] conducted in Singapore in hospitalized patients (3) evaluated the diagnostic performance of pooling two IS specimens into one microbiological test with the addition of Xpert. The sensitivity and specificity of the molecular test in that study were 88.4% and 100%, respectively.

Fifty-five (18.2%) of the IS samples were from HIV-positive patients, with a sensitivity and specificity of 71% and 97%,

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Table 1 Demographic and clinical characteristics of patients.

	Total	BAL	IS	SS	P value
	n=1717	N=704	N= 302	N=711	
Age Median (years, median [IQR])	52 [35—63]	56 [40—66]	45 [30—58]	49 [32—60]	< 0.001
Sex					<0.001
Male	919 (53.5)	365(51.2)	163(54)	390 (54.9)	
Female	798(46.5)	339 (48.2)	139 (46)	320 (45.1)	
HIV Status					<0.001
Positive	185 (10.7)	40 (5.7)	55 (18.2)	90 (10.7)	
Negative	1532 989.2)	664 (94.3)	247 (81.8)	621 (87.3)	
AFB Smear					<0.001
Positive	264(15.4)	68 (9.7)	31 (10.3)	54 (76.8)	
Negative	1453 (84.6)	636 (90.3)	271 (89.7)	165 (23.2)	
Culture					<0.001
Positive	376 (21.9)	103 (14.6)	52 (17.2)	221 (31.1)	
Negative	1309 (76.9)	589 (83.7)	242 (80.1)	478 (67.2)	
NMT	32 (1.9)	12 (1.7)	8 (2.6)	12 (1.7)	
Xpert					<0.001
MTB detected	388 (22.6)	115 (16.3)	56 (18.5)	217 (30.5)	
MTB not detected	1329 (77.4)	589 (83.7)	246 (81.5)	494 (69.5)	
Phenotypic DST					
RMP Resistant	47 (18.4)	4 (5.8)	8 (21.1)	35 (23.6)	0.006
INH Resistant	62 (24.4)	6 (8.8)	11 (28.8)	45 (30.4)	0.002
STR Resistant	35 (13.3)	9 (13.2)	8 (21.6)	18 (12.2)	0.325
EMB Resistant	22 (8.7)	2 (2.9)	5 (13.5)	5 (10.1)	0.116
Genotypic DST					<0.001
Resistant	69 (17.8)	6 (5.2)	11 (19.2)	52 (24)	
Susceptible	317 (81.7)	107 (93)	45 (80.4)	165 (76)	
Indeterminate	2 (0.5)	2 (1.7)	0 (0.0)	0 (0.0)	
Discrepant results[1]	45 (2.6)	24 (3.4)	7 (2.3)	14 (2.0)	0.222
TB treatment	20	8	6	6	
Outcome cure[2]	11	3	5	3	

Data presented as n of patients (%).
RIF= rifampicin; INH= isoniazid; STR= streptomycin; EMB= ethambutol.
[1] Discrepant results — positive Xpert and negative culture.
[2] Treatment for TB and considered cured by the Health Information Systems.

Table 2 Performance value of Xpert MTB/RIF and AFB for respiratory samples compared to culture.

	BAL	Sputum	Induced sputum
Samples			
Xpert			
Sensitivity %	88 [82—94]	92 [88—95]	94 [87—1]
Specificity %	96 [94—97]	97 [95—98]	97 [95—99]
PPV %	79 [71—86]	93 [90—98]	87 [78—96]
NPV %	98 [96—99]	96 [94—98]	99 [97—1]
RV +	22 [14—32]	32 [19—53]	34 [16—70]
RV -	0.12 [0.07—0.20]	0.08 [0.05—0.13]	0.06 [0.01—0.17]
Accuracy	95 [93—96]	95 [94—97]	97 [94—98]
AFB			
Sensitivity %	58 [49—68]	73 [68—79]	50 [36—64]
Specificity %	99 [98—1]	99 [98—1]	98 [96—1]
PPV %	88 [81—96]	97 [95—1]	84 [71—97]
NPV %	93 [91—95]	89 [86—92]	90 [87—94]
RV +	43 [21—88]	89 [33 — 237]	25 [10—62]
RV -	0.4 [0.33—0.53]	0.27 [0.22—0.33]	51 [39—67]
Accuracy	92 [90—94]	91 [87—93]	90 [85—93]

respectively. Lower accuracy in seropositive sputum samples has already been shown in other studies.[4]

Xpert sensitivity on BAL was 88%, which was much higher than AFB sensitivity (58%) obtained in the same samples. Our results are consistent with a previous study, in which the sensitivity varied from 80% to 84.5%.[5,6]

The PPV of the BAL Xpert was moderate (79%), like Theron et al.[7] showed, implying that false positives were common in patients who screened positive. In our study, this might be because some patients had various indications for undergoing bronchoscopy, and in Brazil, we have a high prevalence of TB.

The limitations in our study were mostly attributed to its retrospective design and to the lack of access to clinical and radiological information. We did not have access to all HIV serologies but only to positive HIV patients who were notified by the monitoring system for people with HIV. Furthermore, bronchoscopy was performed for various indications, not only for suspected TB, which may have reduced the PPV. At the time of our study, the new version of Xpert Ultra was not available, and as with other diagnostic tests, the high sensitivity was offset by a lower specificity.

In our study, the analysis of Xpert in IS showed a high accuracy, proving to be a useful test for TB diagnosis in patients with no spontaneous sputum and an alternative to bronchoscopy, because it is safe, inexpensive, less invasive and leads to minimal risks of complications than the latter.

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Ethics approval

The study was approved by the Institutional Ethics Committee under Protocol # 01561018.3.0000.5257.

Informed consent

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Validity and reliability of the one-minute sit-to-stand test for the measurement of cardio-respiratory responses in children with cystic fibrosis

To the editor

Maintaining exercise tolerance in individuals with cystic fibrosis (CF) is essential to limit the impact of the disease and increase survival.[1] The cardio-respiratory responses to exercise provide an indication of exercise tolerance, which can be used to prevent unwanted effects during exercise.[2] The 6-minute walk test (6MWT) is the gold standard field test for the evaluation of exercise capacity, however this test requires space and cannot always be performed.[3] The one-minute sit-to-stand test (STST1') can be performed in any setting and has recently been proposed as a reliable alternative for the measurement of exercise capacity in patients with CF.[4,5] The measurement of the heart rate (HR) response during the STST1' is valid and reliable in healthy children, but has not yet been validated in children with CF.[6] The aim of this study was to assess the validity and reliability of the measurement of cardiorespiratory responses (HR, respiratory rate (RR) and pulsed oxygen saturation (SpO2)) during the STST1' in children with CF.

This study is a secondary analysis of a previously published multicentre randomised cross-over trial (NCT03069625) and was approved by the Comité de Protection des Personnes Nord-Ouest III.[4] Children with CF, aged from 6 to 18 years who had been clinically stable for 4 weeks were recruited from 3 French CF centres.

Participants performed two rounds of the STST1' and 6MWT on the same day, with a 30 min minimum delay between each test, in a randomised order (computerised 1:1 block randomisation).[4] The HR response (initial and final HR, and percentage ΔHR: $((HR_f\text{-}HR_i)/HR_i)$ x100), RR response and SpO2 response (using the same indicators) were calculated for both the STST1' and 6MWT; data from the best performance of each test were used. Concurrent validity of the HR, RR and SpO2 responses was evaluated by correlation analysis with the same responses during the 6MWT: 0—0.19 = very weak, 0.20—0.39 = weak, 0.40—0.59 = moderate, 0.60—0.79 = strong and 0.80—1.0 = very strong. Intra-rater reliability was evaluated using intra-class correlation coefficients (ICC): <0.5 = poor, 0.5—0.75 = moderate, 0.75—0.90 = good, >0.90 = very good. Test-retest reliability was evaluated by calculation of the mean bias using the Bland-Altman method (pre-post comparisons [learning effect verification]). Statistical analyses were performed with Graph Pad Prism 8®, and the significance level was set at $p < 0.05$.

Thirty-six children participated. Mean age was 12.0 ± 3.5 years, and mean FEV1 was 95.8 ± 25.0%. The complete characteristics of the study sample have previously been described.[4] Performances during both tests were moderately correlated ($r = 0.480$; $p < 0.01$). HR, RR and SpO2 measured before both tests were moderately to strongly correlated ($r = 0.566$—0.790). Correlations between responses during the STST1' and 6MWT were moderate to strong and are detailed in the Table 1. The 6MWT elicited a higher cardio-respiratory response (HR and RR) than the STST1' in 26 out of 36 (72%) of the children.

The intra-rater reliability of the STST1' for the measurement of cardio-respiratory responses during exercise was moderate to very good (ICC>0.5). Evaluation of test-retest reliability showed there was no learning effect (Table 2). Mean bias was 0.6% and the limits of agreement were -36.6% to 37.8% (lower and upper bound) for the HR response; 3.8% (mean bias) and -70.4% to 78.0% (lower and upper bound) for the RR response; and -0.1% (mean bias) and -2.9% to 2.8 (lower and upper bound) for the SpO2 response.

The results of this study demonstrated the concurrent validity and reliability of cardio-respiratory responses measured during the STST1' in children with CF, despite large variability. Concurrent validity during exercise testing was moderate to strong, and intra-rater reliability was moderate to very good. Evaluation of test-retest reliability showed there was no learning effect. The values of the correlation coefficients suggest that the STST1' should be used with caution as a surrogate to the 6MWT but could be relevant when the latter cannot be performed. This is supported by the results of Reychler et al. who found a similar level of concurrent validity for the HR response during the STST1' ($r = 0.522$) in healthy children.[6]

However, in contrast with the results of Reychler et al.,[6] in the present study peak HR and RR were higher during the 6MWT than the STST1'. However, peak HRs at the end of the tests in that study were much higher than in the present study (∼140 beats min versus 126 and 116 beats min for the 6MWT and STST1' respectively). A possible explanation for

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Table 1 Concurrent validity of cardio-respiratory responses measured during the STST1' and 6MWT in children with CF.

Outcome	Best STST1'	Best 6MWT	Mean difference (95% CI)	*p*-value	Correlation coefficient	*p*-value
HR_i, bpm	95.8 ± 14.4	96.4 ± 17.8	-0.7 (-4.4 to 3.0)	0.706	0.790	<0.001
HR_f, bpm	116.3 ± 19.9	126.4 ± 23.9	-10.1 (-17.0 to -3.2)	0.005	0.585	<0.001
ΔHR_{i-f}, %	22.8 ± 22.1	32.6 ± 22.9	-9.8 (-17.2 to -2.5)	0.010	0.532	<0.001
RR_i, cpm	20.6 ± 4.9	20.1 ± 4.5	0.4 (-1.0 to 1.9)	0.546	0.566	<0.001
RR_f, cpm	26.6 ± 5.1	30.3 ± 9.7	-3.7 (-6.7 to -0.7)	0.018	0.410	0.013
ΔRR_{i-f}, %	35.4 ± 37.6	54.4 ± 45.3	-18.1 (-31.8 to -6.4)	0.004	0.603	<0.001
$SpO2_i$, %	96.8 ± 2.0	97.1 ± 2.0	-0.2 (-0.6 to 0.1)	0.199	0.752	<0.001
$SpO2_f$, %	96.6 ± 1.9	96.4 ± 2.8	0.3 (-0.4 to 0.9)	0.402	0.681	<0.001
ΔSpO2	-0.2 ± 1.4	-0.7 ± 2.4	0.5 (-0.2 to 1.2)	0.147	0.462	0.005

Data are shown as mean ± SD. Bpm: beats per minute; CI: confidence interval; Cpm: cycles per minute; HR_i: initial heart rate; HR_f: final heart rate; ΔHR_{i-f}: delta heart rate; RR_i: initial respiratory rate; RR_f: final respiratory rate; ΔRR_{i-f}: delta respiratory rate; $SpO2_i$: initial pulsed oxygen saturation; $SpO2_f$: final pulsed oxygen saturation; ΔSpO2: delta pulsed oxygen saturation; STST1': sit-to-stand test; 6MWT: 6-minute walking test

Table 2 Test-retest and intra-rater reliability of cardio-respiratory responses measured during the STST1' in children with CF.

			Test-Retest reliability		Intra-Rater Reliability		
Outcome	$STST1'_1$	$STST1'_2$	Mean difference (95% CI)	*p*-value	ICC	95%CI	*p*-value
HR_i, bpm	96.3 ± 18.7	97.0 ± 17.3	-0.7 (-4.9 to 3.5)	0.740	0.865	0.735-0.931	<0.001
HR_f, bpm	115.1 ± 20.6	115.4 ± 18.9	-0.4 (-5.0 to 4.3)	0.875	0.863	0.731-0.930	<0.001
ΔHR, %	21.5 ± 22.1	21.0 ± 21.7	0.6 (-5.9 to 7.0)	0.856	0.708	0.426-0.851	<0.001
RR_i, cpm	20.1 ± 3.3	20.7 ± 4.9	-0.6 (-2.3 to 1.1)	0.462	0.448	0.080-0.719	0.042
RR_f, cpm	25.6 ± 4.8	26.5 ± 5.3	-0.9 (-2.7 to 0.8)	0.283	0.644	0.301-0.818	0.002
ΔRR, %	30.2 ± 31.7	34.0 ± 38.0	-3.8 (-16.6 to 9.0)	0.550	0.574	0.164-0.783	0.007
$SpO2_i$, %	96.6 ± 2.0	96.9 ± 2.0	-0.2 (-0.5 to 0.1)	0.160	0.944	0.891-0.972	<0.001
$SpO2_f$, %	96.4 ± 1.9	96.7 ± 1.9	-0.3 (-0.7 to 0.2)	0.216	0.865	0.736-0.931	<0.001
ΔSpO2	-0.2 ± 1.5	-0.1 ± 1.4	-0.1 (-0.6 to 0.4)	0.822	0.649	0.311-0.821	0.001

Data are shown as mean ± SD. Bpm: beats per minute; CI: confidence interval; Cpm: cycles per minute; HR_i: initial heart rate; HR_f: final heart rate; ΔHR: delta heart rate; RR_i: initial respiratory rate; RR_f: final respiratory rate; ΔRR: delta respiratory rate; $SpO2_i$: initial pulsed oxygen saturation; $SpO2_f$: final pulsed oxygen saturation; ΔSpO2: delta pulsed oxygen saturation; STST1': sit-to-stand test

this difference is that healthy children have a different intrinsic motivation or perception of exercise testing procedures than children with CF.

To conclude, the measurement of cardio-respiratory responses during the STST1' is reliable and presents a moderate concurrent validity in children and adolescents with CF. The STST1' could therefore be relevant when the 6MWT cannot be performed.

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Declaration of Competing Interest

Dr. Combret, Dr. Prieur and Dr. Medrinal report performing consultations for Air Liquide Medical Systems, outside of the submitted work. Dr. Bonnevie reports grants from Fisher & Paykel, outside of the submitted work. The other authors have no conflicts of interest to disclose.

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LETTER TO THE EDITOR

Effect of a viral filter on cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is an important tool to identify and to evaluate the severity of cardiopulmonary diseases. Due to the outbreak of the COVID-19 pandemic, many pulmonary function laboratories suspended CPET.

Resting expiratory flow rates and minute ventilation are increased 10-fold during exercise.[1] This is an important issue during a respiratory virus pandemic, since it raises some concerns about the higher risk of aerosol production and virus transmission during CPET. Studies are emerging to work around this situation by assessing the potential of surgical or N95 masks and bacterial filters to mitigate this hazard.[2,3] However, there is some opposition to the use of increased ventilator resistance and water vapour saturation, which might compromise CPET's results.[4]

We conducted a study to evaluate the impact of a virus filter on CPET. A PFT filter (MicroGard II Vyaire Medical GmbH) was used, which provides 99.99% protection against virus and bacteria. Ten healthy volunteers with a mean age of 39 years-old ($\pm$6.1) and a body mass index of 23.6 Kg/m^2 ($\pm$3.6) performed two incremental cycling CPETs, based on Wasserman's protocol,[5] starting with 3 min at rest, then 3 minutes cycling without load, followed by cycling with incremental load up to volitional exhaustion that was defines as a drop in cadence of $\geq$ 10 rpm for 5 consecutive seconds despite verbal encouragement. Each subject performed the CPETs approximately 2 h apart, with and without the filter. They were familiar with the test since they were pulmonology residents, specialists or technicians that worked at the respiratory functional laboratory. Five of them were randomly selected to perform the first CPET with the filter and the other half started without the filter. The filter was placed in-line, downstream of the gas analyzer sample line (Fig. 1). The CPET's results for the same subject were compared using the same incremental load.

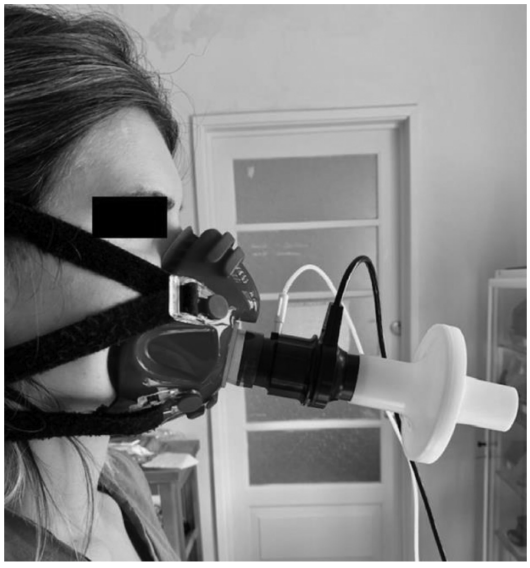

Fig. 1 Filter placed In-line and downstream of the gas analyzer sample.

At rest, we did not find any significant difference between tests. We found a significant increase in oxygen consumption (VO_2) in CPETs performed with the filter, both at anaerobic threshold (46.8% vs 52.5%, *p-value 0.032*) and at the peak exercise (82.0% vs 90.5%, *p-value 0.006)* — Table 1. We also found a significant increase in the partial pressure of end tidal oxygen ($P_{ET}O_2$, *p-value 0.009*) and carbon dioxide ($P_{ET}CO_2$, *p*-value $<$*0.001*) in CPETs performed with the filter. However, no difference was found in minute ventilation (VE) or the minute ventilation/carbon dioxide production slope (VE/VCO_2) measurements. Likewise, no difference was found between CPET's maximum load. We did not observe other statistically significant findings between CPETs (Table 1).

The increase VO_2 in CPETs performed with a filter found in our study is a surprising result, since oxygen consumption increases linearly with load (about 10 ml of oxygen consumed per watt of work and per kilogram)[5] and no difference was found on this variable. Therefore, the use of the filter did not impair the volitional tolerance and did not have an impact on effort, as we found no significant difference in dyspnea and leg fatigue measured by Borg's scale.[6]

In summary, in this small number of heathy subjects we observed significant differences in VO_{2AT}, VO_{2max}, $P_{ET}O_2$ and $P_{ET}CO_2$ that may be related to the resistance imposed by the filter requiring more effort from ventilatory muscles, which did not impact dyspnea in healthy individuals. These differences may have clinical impact on CPETs performed in some

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Table 1 Differences between CPETs with and without the filter.

	CPET without filter	CPET with filter	*p-value* (paired)
P_{AT} (W)	78 [70;80]	78 [70;80]	*0.786*
P_{max} (W)	171.4 ± 38.96	171 ± 39.64	*0.866*
HR (bpm)	170.1 ± 10.68	172.5 ± 9.32	*0.144*
BF (brpm)	34.1 ± 5.67	34.1 ± 4.38	*1*
RER_{max}	1.244 ± 0.06	1.232 ± 0.07	*0.615*
VE (l/min)	68.8 ± 15.47	72.3 ± 15.76	*0.288*
VO_{2AT} (% of predicted)	46.8 ± 8.89	52.5 ± 13.05	*0.032*
VO_{2max}(% of predicted)	82.0 ± 10.6	90.5 ± 12.48	*0.006*
VE/VCO_{2AT}	29.38 ± 3.24	29.29 ± 2.8	*0.804*
VE/VCO_{2max}	29.87 ± 3.27	28.95 ± 3.04	*0.135*
VE/VO_{2max}	36.85 ± 4.09	35.66 ± 5.25	*0.359*
$P_{ET}CO_{2AT}$ (mmHg)	36.611 ± 3.5	37.75 ± 2.71	*0.077*
$P_{ET}CO_{2max}$ (mmHg)	34.96 ± 3.34	38.247 ± 3.24	*<0.001*
$P_{ET}O_{2AT}$ (mmHg)	106.551 ± 3.25	106.13 ± 2.97	*0.692*
$P_{ET}O_{2max}$ (mmHg)	116.616 ± 2.8	113.909 ± 3.61	*0.009*
VE/VCO_2 slope	32.994 ± 3.09	32.465 ± 2.71	*0.275*
$Borg_{max}$ - dyspnea	3 ± 1.33	3.1 ± 0.99	*0.678*
$Borg_{max}$ − leg fatigue	3.6 ± 0.84	3.9 ± 1.1	*0.279*
SBP_{max} (mmHg)	166 ± 18.38	156 ± 17.13	*0.063*
DBP_{max} (mmHg)	75 ± 13.54	77 ± 11.6	*0.678*

Data are presented as mean ± SD or median [range]; *$p < 0.05$.
P_{AT} − anaerobic threshold power; P_{max} − maximum power; HR - heart rate; BF - breathing frequency; RER − respiratory exchange ratio; VE − minute ventilation; VO_{2AT} − anaerobic threshold oxygen consumption; VO_{2max} − maximum oxygen consumption; VE/VCO_{2AT} − anaerobic threshold ventilatory equivalent for carbon dioxide; VE/VCO_{2AT} − maximum ventilatory equivalent for carbon dioxide; VE/VO_{2max} − maximum ventilatory equivalent for oxygen; $P_{ET}CO_{2AT}$ − anaerobic threshold partial pressure of end tidal carbon dioxide; $P_{ET}CO_{2AT}$ − maximum partial pressure of end tidal carbon dioxide; $P_{ET}O_{2AT}$ - anaerobic threshold partial pressure of end tidal oxygen; $P_{ET}O_{2max}$ − maximum partial pressure of end tidal oxygen; SBP − systolic blood pressure; DBP - dyastolic blood pressure;

patients with respiratory diseases, but also for people with muscle weakness. This study provides us preliminary information concerning the use of filter in CPET, which might impair its interpretation. A perspective for future studies should include larger population samples and the assessment of patients with respiratory diseases and muscle weakness.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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LETTER TO THE EDITOR

Relapsed malignant pleural mesothelioma: An impressive response to Nivolumab monotherapy

Dear Editor,

Malignant pleural mesothelioma (MPM) is a locally aggressive and invasive tumour with a median survival of 12 months.[1] For the past few decades, it has also been considered a highly lethal condition because of its recurrence despite standard approaches. Currently, there is no recommended therapy for relapsed MPM after chemotherapy or front-line treatment and disease control has been less than 30% in all previous studies of second-line drugs.[2] Advances in immunotherapy have been shifting the paradigm in the treatment of several advanced cancers and, more recently, its value in MPM has been investigated as a possible future therapeutic option.[2,3]

A sixty-two-year-old male, active smoker, with type-2 diabetes *mellitus*, arterial hypertension, and a history of prolonged occupational exposure to asbestos in the past had an incidental finding of unilateral complex and exudative pleural effusion associated with massive thickening of the costodiaphragmatic pleura. Uniportal video-assisted thoracic surgery with pleural decortication was performed to manage complex pleural effusion and to collect samples that secured the pathological diagnosis. Post-surgery study was complemented by positron emission tomography scanning (Fig. 1), clarifying the diagnosis of an unresectable epithelioid MPM, with appearance of chest wall invasion. The patient was initially submitted to pemetrexed (500 mg/m^2) and carboplatin (area under the concentration-time curve: 5), a less nephrotoxic regimen considering his comorbidities, which was suspended after six treatment cycles due to disease progression, deterioration in Eastern Cooperative Oncology Group (ECOG) performance status to 2 and development of left posterolateral thoracic mass, painful on palpation, needing antalgic radiotherapy (total dose of 30 Gy in 10 fractions over 2 weeks). Chest computed tomography (CT) scan also reported dimensional lesion increase and clear invasion of the chest wall (Fig. 2A). In this context, anti-programmed cell death-1 (PD-1) monoclonal antibody immunotherapy was administered with single agent intravenous nivolumab 3 mg/Kg, every two weeks. Initial outpatient reassessments were performed on a 14-day schedule. It was possible to witness a progressive improvement in symptoms and weight recovery; after seven weeks the chest-CT showed near complete remission of the neoplastic lesion (Fig. 2B). The thoracic painful mass became non-palpable at the end of the fourth nivolumab cycle. Adverse events monitoring was performed before each treatment infusion. He presented moderate arthralgia as a possible immune-related side-effect, which was controlled with daily 5 mg prednisolone, without interrupting therapy. At the time this report was written, the patient has been maintained on 3 mg/Kg nivolumab infusions every two weeks, with an excellent sustained therapeutic response (Fig. 2C) and significant improvement in quality of life (current ECOG 1), without unacceptable pharmacological toxicity, maintaining benefits that came from immunotherapy throughout subsequent evaluations and well more than 24 months after diagnosis.

In fact, epithelioid tumours account for 60% of mesothelioma subtypes and have the best prognosis with more favourable response to chemotherapy than the other forms.[1,4]

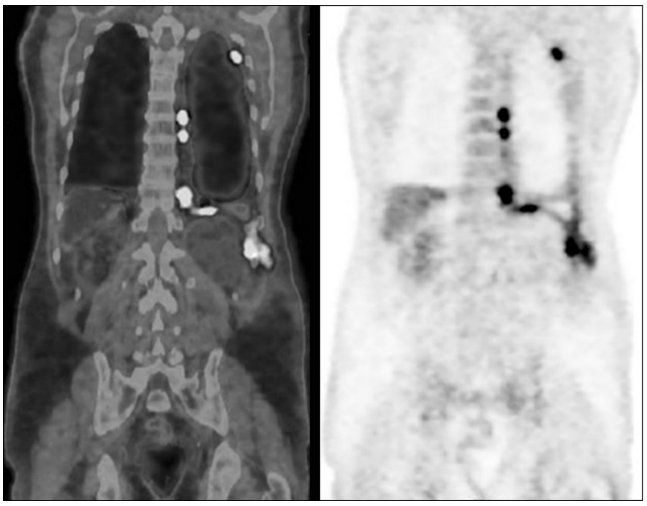

Fig. 1 Positron emission tomography scan prior chemotherapy, demonstrating a dispersed hypermetabolic thickening through the left pleura, especially the costodiaphragmatic region, invading the chest wall, and an homolateral pleural effusion with heterogeneous uptake of F-18 fluorodeoxyglucose (SUVmax 10.6).

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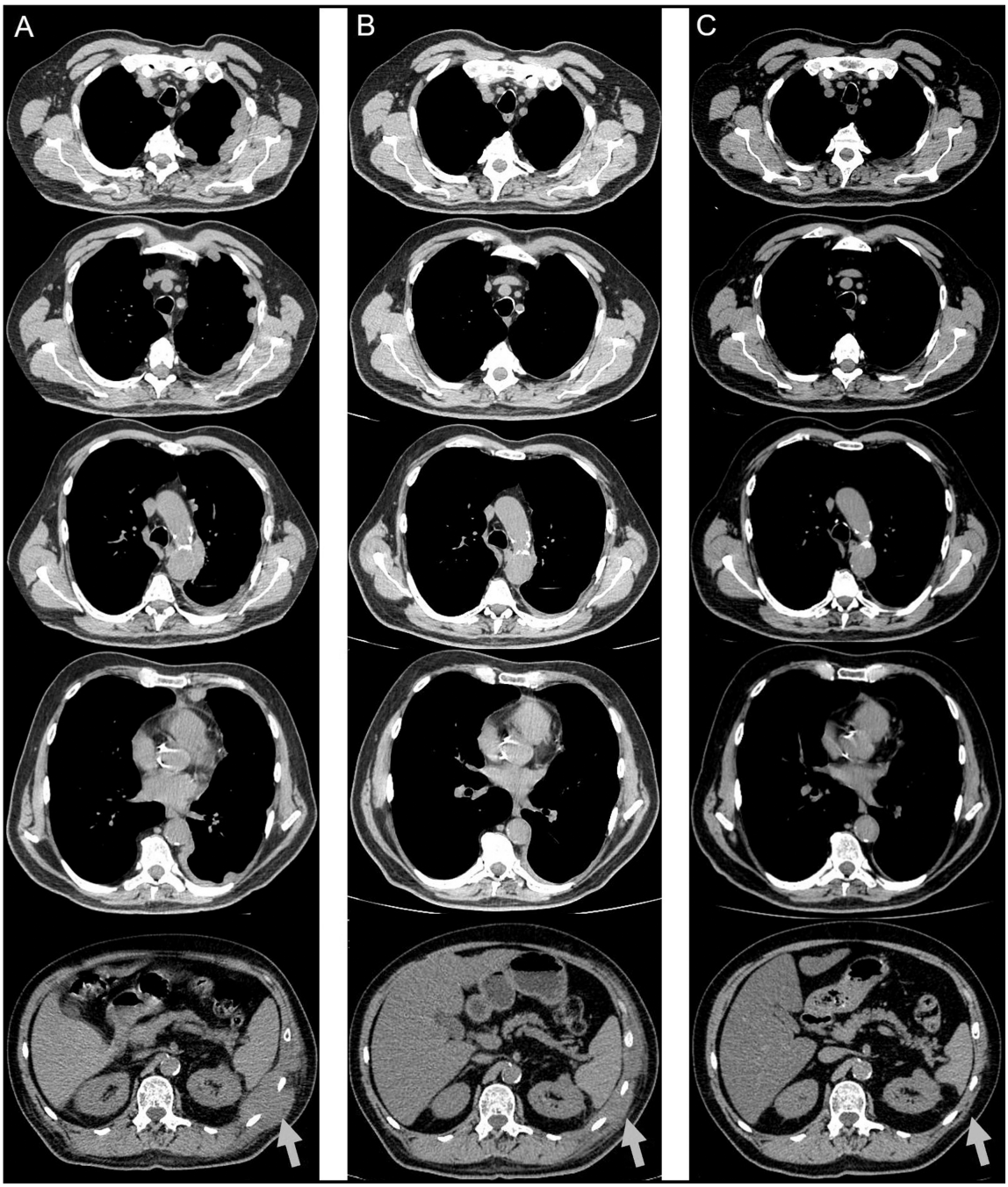

Fig. 2 Serial reassessments by computed tomography scan documenting the lesions' extension and evolution. (A) After 6 treatment cycles of carboplatin-pemetrexed chemotherapy, reflecting recurrence of disease in the left hemithorax. (B) After 4 treatment cycles of nivolumab, demonstrating parcial but impressive response. (C) After 37 treatment cycles of nivolumab with no evidence of recurrence and maintaining remarkable tumour response.

However, this report demonstrates the progressive character of malignant mesothelioma despite standard chemotherapy and less aggressive histologic type. Patient's declining status, low response to second-line therapies and chemotherapy-related complications contributed towards the use of immunotherapy as an off-label rescue strategy. This decision was also based on preliminary results from recent clinical trials that have suggested a potential role of anti-PD-1 monoclonal antibody in relapsed MPM, namely nivolumab as a single drug, with an acceptable safety profile, which was important to improve our patient compliance and tolerance.[2,3,5] Positive outcomes were rapidly achieved and confirmed from the first control-CT, maintaining a near-complete and sustained response ever since, largely exceeding expected survival time for this malignancy, with significant improvement in quality of life. PD-ligand1 (PD-L1)

expression has been reported in 40% of mesothelioma overall, with a higher rate in sarcomatoid histotype.[6] Nevertheless, this case is representative of epithelioid subtype and, although PD-L1 tumour proportion score has not been investigated, the impressive obtained response with nivolumab might support a dependency of mesothelioma on this immunological checkpoint.[7] As described in the literature, tumour immune microenvironment plays a key role in MPM pathogenesis, but to date, efficacy of PD-L1 expression status as a predictive biomarker for the response to nivolumab may be limited;[7] this is a critical area for more extensive studies. Lastly, immune checkpoint inhibitors are not without side-effects but, in this case, the potential benefit with nivolumab monotherapy outweighed the reported manageable adverse events.

We here present a case of epithelioid MPM which experienced a rapid disease progression after initial therapy but then had an exceptional and sustained response to single agent nivolumab. It is an impressive shift in prognosis by a novel rescue strategy, exceeding expected survival time and quality of life for this malignancy. Therefore, it highlights a promising role for this anti-PD-1 monoclonal antibody in future therapeutic options in those patients who have progressed after pemetrexed—platinum doublet chemotherapy. This example should strongly encourage research for biomarkers to select optimal candidates for immunotherapy in terms of efficacy and tolerance.

Patient consent

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

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Conflicts of Interests

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Clinical characteristics and outcome of SARS —CoV-2 infection in patients with cystic fibrosis managed at home

Lung disease in Cystic Fibrosis (CF) is characterised by bronchiectasis with persistent airways-based infection and inflammation and remains the main cause of morbidity and mortality.[1]

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), associated with the ongoing coronavirus disease 2019 (COVID-19) pandemic, has had a huge impact on world population. The presence of co-morbidities, such as CF, has been identified as a risk factor for severe disease.[2,3] The incidence is higher in people with CF versus the age-matched general population and significantly higher rates of admission to hospital and higher rates of intensive care have been recently reported, especially in patients receiving an organ transplant.[3] Mild illness was reported in CF children who did not have pre-existing severe lung disease.[4] Furthermore, the COVID-19 pandemic has created great interest in the use of telemedicine in CF patients since it can be a valid tool to assess their clinical condition.[5]

In this paper we evaluated clinical presentation, management and outcomes of CF patients with SARS-CoV-2, managed at home thanks to telemedicine.

We retrospectively reviewed clinical charts of all CF patients diagnosed with SARS-CoV-2 infection via a positive nasal/throat polymerase chain reaction (PCR) test and followed-up at CF centre of Florence, Italy, where we take care of both paediatric and adult patients.[6] Cases were recorded up to 30 June 2021. We enrolled only CF patients managed at home, thanks to telemedicine consultations. Diagnostic tests were performed where there were symptoms or in asymptomatic cases if the patients were at risk for positive familial or at work contact. We also compared, pre and post infection, the trend of body mass index (BMI, expressed as centile in patients younger than 20 years), or of the weight/length centile for infants and percentage predicted forced expiratory volume in one second (FEV_1) for patients aged 6 years and older. Data collected also included CFTR genotype, pancreatic and microbiological status, age at SARS-CoV-2 infection, pre-existing CF related diabetes (CFRD).

The study was approved by the Ethics committee (Florence, Ethics Clearance number 217/2021, on 7 September 2021) and we obtained from all patients (or from their legal guardian) their informed consent to allow the use of anonymous clinical data for research purposes.

Telemedicine consultation took place immediately following COVID-19 diagnosis and during the course of the infection [phone call, monitoring of oxygen saturation (SpO2) and screening for pulmonary symptoms suggestive of COVID-19]. In absence of criteria for hospitalisation, we advised the isolation of the patient and his family, the use of a home pulse oximeter and in the case of a reading of less than 92% or respiratory distress signs, the need for hospitalisation.

Eighteen (5.1%) out of 352 CF patients followed at our Regional centre suffered from SARS-CoV-2 infection. Thirteen (72.2%, 10 males, mean age at SARS-CoV-2 infection: 27 years, range 3 months-59 years) out of 18 were managed at home. We excluded 5 patients, 2 adults who needed hospitalisation due to lung transplant in 2 and 3 more cases with persistent fever with SpO2$<$ 92% .

Key characteristics and outcomes of enrolled CF patients diagnosed with SARS-CoV-2 infection are reported in Table 1. Nine (69%) out of 13 had pancreatic insufficiency. No patients had CFRD.

We compared the FEV_1 values and BMI or BMI centile obtained at a mean period of 33 days (range 17-50 days) before infection and at the first visit after recovery (negative PCR test), performed after a mean period of 50 days (range 7-116 days). No significant worsening was reported (Table 1).

Unlike the children described by Bain R et al,[4] only one child aged 4 years needed antibiotic and corticosteroid medication for increased cough and wheezing in the first 24 hours. Similarly, two adult patients were given antibiotic therapy because of increased coughing. All enrolled patients had normal values of SpO2 (96-98%).

Male gender, CFRD and being over 50 years of age have been shown to be associated with more severe SARS-CoV-2 infection in the general population.[2,7,8] In this small cohort we report a mild course of SARS-CoV-2 infection, despite 3 patients in our cohort being older than 50 years and 10 (77%) out of 13 patients being males. In addition, we report 7 more cases of CF patients with asymptomatic SARS-CoV-2 infection,[4] among them an adolescent and an adult patient, both with severe lung disease (case 2 and 3 of Table 1).

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Table 1 key characteristics and outcomes of enrolled CF patients diagnosed with SARS-CoV-2 infection.

Patient	First CFTR variant	Second CFTRvariant	Age atSARS-CoV-2 infection(years)	Symptoms	Microbiological status	Pre infection FEV_1 (%)	Post infection FEV_1 (%)	Pre infection BMI [a]	Post infection BMI [a]
1	2789+5G>A	1602delCT	54	Fever	*Burkholderia gladioli*	33	36	27.67	27.67
2	F508Del	CFTR Dele 2	14	None	MSSA	40	37	36.88	80.5
3	F508Del	N1303K	26	None	MSSA	53	53	25.51	25.21
4	E585X	Dele 22-24	10.5	Cough	MSSA	86	95	52.33	60.42
5	R347H	G542X	59	Myalgia, fever	MSSA	51	63	21.89	21.74
6	F508Del	A1006E	4.5	Cough, wheezing	MSSA	na[b]	na[b]	61.68	50.75
7	F508Del	(TG)12T5	10	None	MSSA	126	98	84.14	76.53
8	F508Del	G542X	30	None	*Stenotrophomonas maltophilia.*	72	76	19.72	20.26
9	G178R	L1065P	40	Cough, fever myalgia	MSSA	87	92	26.96	26.6
10	F508Del	G542X	3 months	None	Normal flora	na[b]	na[b]	0.65[c]	1.24[c]
11	F508Del	D192G	57.5	Cough	*Pseudomonas aeruginosa*	44	42	19.14	19.53
12	F508Del	F508Del	31	None	MSSA	61	65	20.27	20.13
13	F508Del	L1065P	13.8	None	MSSA	72	77	65.09	52.79

Abbreviations: SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; MSSA: Methicillin-susceptible *Staphylococcus aureus*; $FEV_{1:}$ predicted forced expiratory volume in one second; BMI: body mass index; CFTR: cystic fibrosis transmembrane conductance regulator; na: not available

[a] we report BMI data in patients younger than 20 years as BMI centile

[b] children aged < 6 years

[c] we refer to weight/length centile given the age of the child

Finally, we highlight a higher prevalence of SARS-CoV-2 infection, constantly increasing, in CF patients compared to previous studies.[2,3] However, no cases of infection occurred in the early period of the pandemic, probably due to the greater restrictive measures adopted in Italy in that period.

Management at home reduced the risk of hospital cross-infection and avoided hospital overcrowding.

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Conflict of Interest Disclosures

The authors declare no conflicts of interest relevant to this article to disclose.

A data availability statement

All reported data are available.

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LETTER TO THE EDITOR

Lung function and ventilatory response to exercise in asymptomatic elite soccer players positive for COVID-19

Dear Editor

Individuals recovering from SARS-CoV-2 (COVID-19) infection[1] show impaired lung function, particularly diffusion capacity (DLCO).[2] In addition, high prevalence of muscle weakness and impairment in physical performance have been reported in individuals without any prior motor limitations.[3,4] While data report cardiac injury among professionals athletes,[5-7] less is known about the potential damage to lung function and ventilatory response to exercise in asymptomatic elite athletes. Soccer is a highly physiologically demanding sport, with additional stress resulting from frequent matches and high load training sessions, ventilatory parameters playing a role in performance.[8,9]

In asymptomatic professional soccer players, we retrospectively report data of lung function and cardiopulmonary exercise tests after return to negativity to nasal/throat swabs for COVID-19 by polymerase chain reaction. We compare the findings with data of evaluations before the start of the sport season for license to professional activity.

The study was approved by the Ethical Committee of ICS Maugeri (2515 CE, February 9th, 2021) and participants signed the informed consent for the scientific use of their data.

Players underwent daily swabs to assess return to Covid negative. Before the sport season (T_0) and the day immediately after return to Covid negative (T_1: 14.3±5.4 days from testing positive), participants underwent flow-volume curve and cardiopulmonary incremental exercise test on treadmill according to standards [8,9] to be permitted to resume activity. Researchers performing analysis of data but not those performing assessments were blind to players' identity.

Data are shown as mean ± standard deviation (SD). A Student's t-test was carried out for differences between T_1 and T_0. In case of failure of normality test, a Mann-Whitney Rank Sum test was performed. Linear regressions between days of Covid positive and velocity at peak exercise (VEL_{peak}) and velocity at anaerobic threshold (VEL_{AT}) respectively, were also computed. A p value <0.05 was considered as statistically significant.

Sixteen players (22.9 ± 4.5 years; Body-Mass Index: 23.4 ± 1.9 Kg/m^2) from three teams were evaluated: as expected, none reported smoking habit or any relevant disease, with negative chest physical examination. After comprehensive evaluation, including cardiological tests, all players could return to sport professional activity.

As compared to T_0, at T_1 there was no significant reduction in dynamic lung volumes (Table 1). However, players showed a significant mean reduction in VEL_{peak} and VEL_{AT}, with a significant increase in oxygen consumption at anaerobic threshold to peak oxygen consumption ratio (Table 2). There was no significant correlation between days when Covid positive and T_1-T_0 changes in VEL_{peak} or VEL_{AT}.

We have no data for immediately before infection, therefore we had to compare data after return to Covid negative with pre sport season evaluation. It has been reported that a competitive season improves ventilatory profile response to exercise in elite athletes.[9] Therefore, we may argue that after the prolonged period of training and competitions performed before pandemic, the physical performance of our players would have been higher than at T_0, and as a consequence the differences with post return to Covid negative even greater.

What could be the cause of reduced physical performance in these individuals? It may be argued that rest and lack of training due to imposed quarantine (at least while Covid positive) may have influenced results. However, there was no significant correlation between days when Covid positive (and rest) and reduction in exercise velocity. In addition, due to the lack of assessment of DLCO we cannot exclude any lung involvement beyond dynamic lung volumes.

We were unable to report any data of cardiac function. However, we know that all these players were allowed to return to their activity after cardiological evaluation. A large screening has reported a 3.8% prevalence of

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Table 1 Individual and mean data of lung function.

	Player.	FEV_1, L	FVC, L	FEV_1/FVC, %	MEF_{25}, L/sec	MEF_{50}, L/sec	MEF_{75}, L/sec
T0	1	5.20	5.68	91.5	2.48	6.02	8.00
T1		5.12	6.04	84.8	2.46	6.26	10.01
T0	2	4.31	5.51	78.2	1.71	4.23	6.77
T1		4.44	5.87	75.6	1.58	4.32	6.35
T0	3	4.59	5.34	86.0	2.54	4.71	8.19
T1		4.41	5.03	87.7	2.49	3.94	7.72
T0	4	4.28	5.07	84.4	2.15	4.38	7.14
T1		4.55	5.35	85.0	2.54	4.87	8.29
T0	5	4.26	5.57	76.5	1.51	4.18	7.76
T1		4.17	5.33	78.2	1.53	4.05	8.35
T0	6	5.15	6.11	84.3	2.50	6.27	8.75
T1		5.11	6.24	81.9	2.49	5.47	10.13
T0	7	5.08	6.68	76.0	2.51	4.48	7.42
T1		5.32	7.23	73.6	2.25	4.65	7.84
T0	8	4.70	4.88	96.3	5.33	7.59	10.27
T1		4.90	5.40	90.7	3.49	7.57	10.26
T0	9	4.78	4.89	97.7	5.82	6.76	9.97
T1		5.53	5.94	93.1	5.66	6.89	7.77
T0	10	4.53	5.28	85.8	2.21	5.91	9.03
T1		5.00	5.31	94.2	2.30	5.74	9.52
T0	11	5.31	5.97	88.9	3.35	7.72	13.31
T1		5.31	5.94	89.4	3.77	8.44	14.31
T0	12	5.56	6.38	87.1	3.35	7.02	10.72
T1		5.76	7.20	80.0	2.57	5.91	10.87
T0	13	5.13	5.13	100.0	3.11	7.05	6.69
T1		5.27	6.08	86.7	2.94	6.97	8.34
T0	14	5.14	6.42	80.1	2.30	5.31	9.71
T1		4.95	6.30	78.6	2.01	5.20	9.11
T0	15	3.84	3.86	99.5	2.11	5.25	8.05
T1		3.78	3.80	99.5	3.75	6.58	7.30
T0	16	5.10	5.89	86.6	2.09	7.33	10.67
T1		5.21	6.15	84.7	2.62	7.53	9.92
(ì T0	mean±SD	4.8 ± 0.5	5.5 ± 0.7	86.5 ± 1.6	2.8 ± 1.2	5.9 ± 1.3	8.9 ± 1.8
(T1	mean±SD	4.9 ± 0.5	5.8 ± 0.8	86.5 ± 0.5	2.8 ± 1.0	5.9 ± 1.4	9.1 ± 1.9
P Value		0.077	0.316	0.986	0.692	0.981	0.735

Abbreviations. FEV1, Forced Expiratory Volume at 1 second; FVC, Forced Vital Capacity; MEF_{75}, maximal expiratory flow at 75% of FVC; MEF_{50}, Maximal Expiratory Flow at 50% of FVC; MEF_{25}, Maximal Expiratory Flow at 25% of FVC.

abnormalities in cardiologic screening of professional athletes 19±17 days after a positive test.[6] In another study 2.3% of athletes with recent infection were diagnosed with clinical and subclinical myocarditis.[7] Our study seems to suggest the importance of assessing lung function in the comprehensive evaluation of elite athletes.

Our study has the limitations of the small sample size and the flaws of a retrospective design like the lack of assessment of DLCO (or a chest CT scan), respiratory or peripheral muscle function and the lack of cardiological data.

In conclusion, with the above limitations, this study suggests that reduction in exercise performance in professional soccer players after return to negativity for COVID-19 is not associated with a reduction in dynamic lung volumes. Despite the relatively small sample size and the possible lack of external validity of these results, our findings may be useful for guiding sport medical supervisors of these players. Our study indicates also the need to assess lung function for a full evaluation of these individuals. However, to exclude any potential lung involvement, assessment also of DLCO should be mandatory.

Declaration of competing interest

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

Table 2 Individual and mean data of exercise test.

	Player.	VEL $_{AT}$, km/h	HR $_{AT}$, bpm	VEL $_{peak}$, km/h	HR $_{peak}$, bpm	$VO_{2\ AT}$, ml/kg/min	$VO_{2\ peak}$, ml/kg/min	$VO_{2\ AT}$/ $VO_{2\ Peak}$,%	VE $_{AT}$, L/min	VE $_{peak}$, L/min
T0	1	17.9	172	21.8	170	55.5	63.3	87.7	154	205
T1		15.9	178	20.2	193	51.9	51.6	100.6	142	179
T0	2	17.1	183	18.5	188	48.8	54.6	89.4	83	136
T1		15.7	171	17.5	181	55.9	60.0	93.2	106	135
T0	3	16.2	174	21.7	194	45.0	62.0	72.6	95	159
T1		15.0	173	20.2	199	46.2	64.2	72.0	78	173
T0	4	15.2	172	18.8	176	46.2	53.6	86.2	101	153
T1		13.9	169	18.4	192	43.4	49.8	87.1	102	147
T0	5	15.1	172	18.9	193	49.8	50.9	97.8	114	149
T1		15.7	168	19.8	190	54.3	53.9	100.7	117	158
T0	6	16.2	178	21.0	198	47.5	53.7	88.5	98	175
T1		13.2	178	15.1	186	46.5	44.7	104.0	90	78
T0	7	16.2	177	20.9	191	59.4	67.4	88.1	113	197
T1		15.7	174	17.8	182	64.0	58.7	109.0	129	155
T0	8	14.9	188	18.9	199	47.3	52.5	90.1	119	170
T1		15.9	182	18.9	194	50.5	48.9	103.3	124	154
T0	9	15.8	169	20.2	178	56.9	60.1	94.7	127	178
T1		16.0	172	20.0	181	55.1	62.8	87.7	123	176
T0	10	14.2	148	19.0	179	43.3	50.5	85.7	93	170
T1		15.2	152	17.1	166	51.4	54.3	94.7	140	137
T0	11	14.4	163	18.9	190	49.2	53.6	91.8	105	182
T1		13.4	179	18.5	209	50.2	46.3	108.4	115	181
T0	12	15.0	169	19.2	190	41.8	52.2	80.1	115	185
T1		13.8	168	18.9	189	43.0	53.7	80.1	110	183
T0	13	14.8	167	20.3	183	43.5	60.0	72.5	99	187
T1		15.1	158	18.8	174	51.1	59.0	86.6	120	168
T0	14	18.5	185	20.8	195	52.0	49.3	105.5	129	140
T1		14.7	169	18.9	185	48.9	50.7	96.4	126	144
T0	15	15.9	178	20.7	202	50.1	44.0	113.9	97	117
T1		15.3	183	17.1	189	39.7	52.1	76.2	75	123
T0	16	16.1	180	19.7	197	52.3	55.6	94.1	139	192
T1		13.9	164	19.0	188	50.9	52.5	97.0	116	174
T0	mean±SD	15.7 ± 1.3	172.0 ± 11.0	19.9 ± 1.1	188.2 ± 9.5	49.3 ± 5.0	55.3 ± 5.8	68.4 ± 10.9	115.5 ± 18.2	169.5 ± 23.8
T1	mean±SD	14.9 ± 0.9	169.0 ± 9.7	18.5 ± 1.3	186.0 ± 10.8	50.2 ±5.8	53.5 ± 5.8	76.8 ± 10.6	113.4 ± 18.8	153.4 ± 26.6
P Value		0.032	0.570	0.002	0.570	0.474	0.441	0.029	0.762	0.074

Abbreviations. VEL_{AT}, exercise velocity at anaerobic threshold; HR_{AT}, heart rate at anaerobic threshold; VEL $_{peak}$: velocity at peak exercise; HR_{peak}, heart rate at peak exercise; $VO_{2\ AT}$, oxygen consumption at anaerobic threshold; VO_{2peak}, oxygen consumption at peak exercise; VE_{AT}, Minute Ventilation at anaerobic threshold; VE_{peak}, minute ventilation at peak exercise.

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LETTER TO THE EDITOR

Feasibility of tele-rehabilitation in survivors of COVID-19 pneumonia

KEYWORDS
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Exercise;
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Physiotherapist;
Telerehabilitation;
Telemedicine

Dear Editor,

Survivors of COVID-19-associated pneumonia may experience a long-term reduction in functional capacity, exercise tolerance, and muscle strength, regardless of their previous health status or disabilities.[1–3] Telerehabilitation (TR) programs have proven effective in several conditions,[4–6] and have been also suggested for patients after COVID-19.[7] To date, however, no study has investigated whether early telerehabilitation after hospitalization for COVID-19-associated pneumonia is effective. We report a pilot study investigating the safety, feasibility, and efficacy of a 1-month TR program in individuals discharged after recovery from COVID-19 pneumonia [Ethical Committee approval 2440CE].

The study was conducted from April 1 to June 30, 2020 at the ICS Maugeri Institute of Lumezzane, Italy, a referral centre for pulmonary rehabilitation with a dedicated COVID-19 Unit. Inclusion criteria were: clinical stability; resting hypoxaemia or exercise-induced desaturation (EID) [$\geq$4% decrease in SpO_2 at the 6-min Walking Test (6MWT)[8]], or exercise limitation (6MWT: <70% of predicted), availability of home internet and ability to use technologies. Patients with cognitive deficits, severe comorbidities or physical impairment preventing exercise without medical supervision were excluded.

On admission to the program, patients received a pulse oximeter, a brochure illustrating exercises, a diary to record daily activities, and instructions for home exercises. The one-month program consisted of one hour daily of aerobic reconditioning and muscle strengthening and healthy lifestyle education. Twice a week, a physiotherapist (PT) contacted the patient—by video-call via a dedicated platform—to monitor progress. Exercise intensity was based on the Short Physical Performance Battery (SPPB)[9] test and EID and was divided into 4 arbitrary levels (1 = lowest intensity, 4 = highest intensity). Patients with SPPB < 10 or EID were included in the levels 1–2 and performed low-intensity aerobics (walking, free-body exercise, sit-to-stand) and balance exercises. Patients with SPPB $\geq$ 10 and no EID were included in the levels 3–4 and performed walking session with pedometer, aerobics with cycle ergometer or leg/arm crank, and strengthening exercises with a lightweight band. The intensity of the exercise session was progressively increased according to symptoms and cardio-respiratory parameters evaluation. Programs could be changed only under strict PT control. Chest physiotherapy exercises (lung expansion, strengthening of the respiratory muscles) could be added, if necessary. In addition to physiotherapy monitoring, for the first two weeks nurses tele-monitored patients daily to check their clinical needs; subsequently, patients received one weekly telephone/video call. If any symptoms/problems emerged, patients could always contact nurses (7/7 days) or physicians for a second-opinion consultation.

On admission to TR, anthropometrics, clinical status and lung function were collected (Table 1). On admission and discharge, 6MWT,[8] 1 min Sit-to-Stand (1MSTS),[10] and Barthel Dyspnoea Index[11] were assessed. Program adherence (i.e. number of performed/scheduled video-calls) was assessed. ''Pre'' to ''post'' program differences were analyzed by paired t- or Pearson Chi-square test. The percentage of patients reaching the minimal clinically important difference (MCID) for the measures was evaluated. Pearson correlation analysis assessed the change in outcome measures (observed in video calls) from baseline.

Out of 25 consecutive patients, 24 completed the program. Patients attended 7.2 ± 1.7 out of 8 video-calls scheduled and nurses made 13.4 ± 2.1 phone calls. Patients reported fatigue (70.8%), muscle pain (50.0%), exercise induced dyspnoea (50.0%), and sleep disorders (41.7%). No need for hospitalization or emergency room visits occurred. TR allowed patients to change their exercise capacity passing from an initial intensity level of 1.2 ± 2.1 to a final level of 3.1 ± 1.3. No adverse effect was reported. Fig. 1 shows the changes in outcome measures. Exercise capacity and Barthel dyspnoea significantly improved. The percentage of patients with EID at 6MWT was 62.5% at admission and 66.7%

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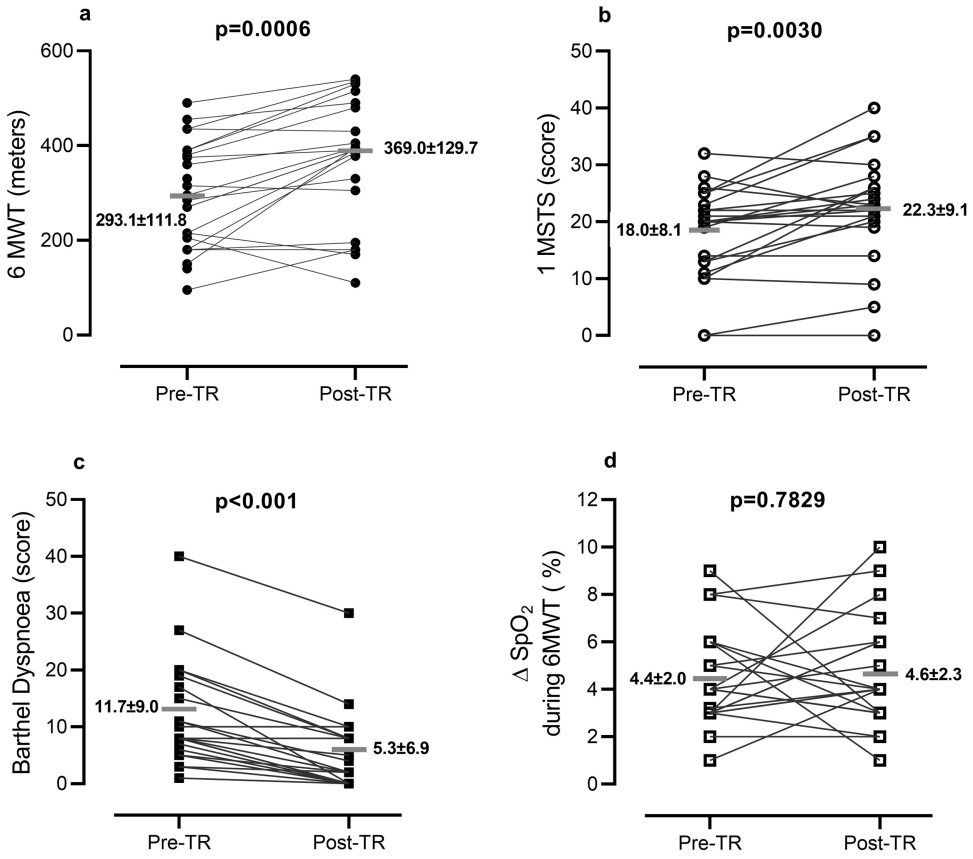

Figure 1 Individual changes in outcome measures between admission (pre-TR) and discharge from (post-TR) the program. Red bar represents the mean data.
Legend: 6MWT = 6 min Walking Distance; 1MSTS = 1 min Sit-to-Stand.

at discharge (P = 0.6624), while at 1MSTS it was 50.0% at admission and 41.6% at discharge (P = 0.6735).

At the end of the program, distance walked in 6MWT increased in 75.0% of patients, remained stable in 4.2%, and decreased in 20.8% of patients; 17 patients (70.8%) improved 6MWT above the MCID (30 m).[8]

The number of sit-to-stands increased in 62.5%, remained stable in 16.6%, and decreased in 20.8% of patients; 12 patients (50.0%) improved 1MSTS above the MCID (3 rises).[10] Barthel dyspnoea improved in 83.3%, remaining unchanged in 16.7% of patients; in 50% of patients, the dyspnoea decrease was 6.5 points above the MCID.[11]

This preliminary report, although limited by the small sample size and absence of a control group, confirms the feasibility and safety of a dedicated TR program for survivors of COVID-19 pneumonia. After one month of TR, patients improved exercise tolerance and dyspnoea. However, approximately 20% of patients were non-responders. No adverse events were found. As with chronic cardiopulmonary diseases, telerehabilitation may help to avoid a gap in service delivery following hospital discharge of COVID-19 patients and should be integrated into their follow-up. Further randomized control trials are needed.

Table 1 Demographic, anthropometric, physiological and clinical characteristics of patients at the start of the TR program. Data as mean ± SD or number (%).

Characteristics	Measure
Male, n (%)	11 (45.8)
Age, years	66.0 ± 8.7
BMI, kg/m^2	25.1 ± 5.6
SpO_2, %	95.4 ± 2.3
FiO_2, %	23.5 ± 4.3
Oxygen therapy at rest, n (%)	6 (20.8)
CIRS1, score	2.0 ± 0.5
SPPB, score	7.1 ± 4.3
FEV_1, % pred.	84.6 ± 19.0
FVC, % pred.	77.9 ± 18.3
FEV_1/FVC, %	89.9 ± 13.1
MIP, cmH_2O	76.1 ± 28.8
MIP, % pred.	82.2 ± 22.9
MEP, cmH_2O	86.7 ± 31.7
MEP, % pred.	49.2 ± 13.7
Clinical History, n (%)	
Invasive Mechanical Ventilation	12 (50.0)
CPAP	17 (70.8)
Tracheostomy	7 (29.2)
Oxygen Therapy	24 (100.0)
6MWT, meters	298.4 ± 111.7
6MWT, % predicted	55.1 ± 21.6
1MSTS, number of sit-to-stand rises	18.0 ± 8.1
1MSTS, % predicted	52.6 ± 26.4
Barthel dyspnoea, score	11.7 ± 9.0

CIRS1 = Cumulative Illness Rating Scale 1, BMI = Body-Mass Index, SPPB = Short Physical Performance Battery, SpO_2 = pulse oxymetry, FiO_2 = Inspired Oxygen Fraction, FEV_1 = Forced Expiratory Volume at first second, FVC = Forced Vital Capacity, MIP = Maximal Inspiratory Pressure, MEP = Maximal Expiratory Pressure, CPAP = Continuous Positive Airways Pressure, 6MWT = 6-Min Walk Test, 1MSTS = 1 min Sit-to-Stand.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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