Heart & Lung 60 (2023) 95–101

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

A temporal examination of inspiratory muscle strength and endurance in hospitalized COVID-19 patients

Filip Dosbaba[a,*], Martin Hartman[a,b], Ladislav Batalik[a,c], Vojtech Senkyr[a], Ivana Radkovcova[a], Svatopluk Richter[d], Kristian Brat[e], Lawrence P. Cahalin[f], Magno F. Formiga[g,*]

[a] Department of Rehabilitation, University Hospital Brno, Brno 62500, Czech Republic
[b] Department of Rehabilitation and Sports Medicine, 2nd Faculty of Medicine, Charles University, University Hospital Motol, Prague, Czech Republic
[c] Department of Public Health, Faculty of Medicine, Masaryk University Brno, Brno 62500, Czech Republic
[d] Department of Radiology and Nuclear Medicine, University Hospital Brno, Brno 62500, Czech Republic
[e] Department of Respiratory Diseases, University Hospital Brno, Brno 62500, Czech Republic
[f] Department of Physical Therapy, University of Miami Miller School of Medicine, Coral Gables, FL, United States
[g] Master's Program in Physical Therapy and Functioning, Department of Physical Therapy, Federal University of Ceara, Fortaleza, CE, Brazil

A R T I C L E I N F O

Article History:
Received 1 July 2022
Revised 6 March 2023
Accepted 10 March 2023
Available online 13 March 2023

Keywords:
COVID-19
Inspiratory muscle performance
Inspiratory muscle endurance
Maximal inspiratory pressures
Test of Incremental Respiratory Endurance

A B S T R A C T

Background: The two most common symptoms associated with COVID-19 are dyspnea and fatigue. One possible cause of such symptoms may be inspiratory muscle weakness.
Objectives: The purpose of this study was to examine inspiratory muscle performance (IMP) from intensive care unit discharge (ICUD) to hospital discharge (HD) in patients with COVID-19 hypothesizing that IMP would be markedly depressed at both ICUD and HD.
Methods: IMP was examined at ICUD and HD via the PrO2 device (PrO2 Health, Smithfield, RI) which provided the maximal inspiratory pressure (MIP), sustained MIP (SMIP), inspiratory duration (ID), and fatigue index test (FIT). Patient symptoms were assessed at ICUD, HD, and 1-month post-HD.
Results: 30 patients (19 men, 11 women) with COVID-19 were included. The mean±SD age, BMI, and length of ICU and hospital stay was 71±11 yrs, 27.9 ± 6.3 kg/m, 9 ± 6 days, and 26±16 days, respectively. The mean±SD MIP, SMIP, ID, and FIT of the entire cohort at ICUD vs HD were 36±21 vs 40±20 cm H2O, 231± 157 vs 297±182 PTU, 8.8 ± 4.2 vs 9.5 ± 4.6 s, and 9.0 ± 9.4 vs 13.1 ± 12.3, respectively, with only SMIP and FIT significantly greater at HD (p=.006 and 0.03, respectively). SMIP at HD was significantly related to resting dyspnea at HD (r=-0.40; p=.02). The SMIP and FIT of men were found to increase significantly from ICUD to HD, but no measure of IMP in the women increased significantly from ICUD to HD. At least one COVID-19-related symptom was present 1 month after HD with the most persistent symptoms being fatigue, cough, and dyspnea in 47%, 40%, and 37% of the patients, respectively.
Conclusions: A significant reduction in IMP exists in patients with COVID-19 at both ICUD and HD and no measure of IMP in women was observed to increase significantly from ICUD to HD. Impaired inspiratory muscle endurance rather than strength was associated with greater dyspnea at HD.

Introduction

The two most common symptoms associated with acute and post-COVID-19 are dyspnea and fatigue,[1] with one possible cause of such symptoms being inspiratory muscle dysfunction. Pathological changes in the diaphragm of COVID-19 patient's post-mortum have been reported and include increased expression of genes involved in fibrosis and histological evidence of fibrosis which was not observed in controls without COVID-19 receiving a similar duration of mechanical ventilation and intensive care unit (ICU) length of stay.[2] Furthermore, 76% of survivors from severe COVID-19 were observed to have

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; FIT, fatigue index test; HADS, hospital anxiety and depression scale; HD, hospital discharge; ICU, intensive care unit; ICUD, intensive care unit discharge; ID, inspiratory duration; IMP, inspiratory muscle performance; IMT, inspiratory muscle training; MIP, maximal inspiratory pressure; RV, residual volume; SMIP, sustained maximal inspiratory pressure; SRHS, self-reported health status; TIRE, Test of Incremental Respiratory Endurance; TLC, total lung capacity; ICC, intraclass correlation coefficient

* Corresponding authors.
E-mail addresses: dosbaba.filip@fnbrno.cz (F. Dosbaba), magno@miami.edu (M.F. Formiga).

https://doi.org/10.1016/j.hrtlng.2023.03.007

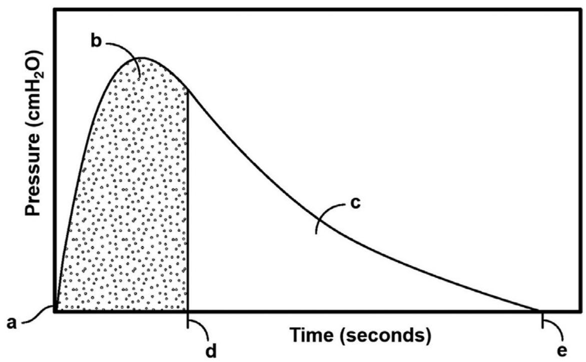

Fig. 1. The pressure-time curve generated using the TIRE protocol (a). The time (d) and area covered to inspire a mass of 500 ml of air (b) is compared to the total inspiratory duration (e) and total area covered (c) over the entire maneuver. The FIT score is therefore calculated as (total area × total time) / ($area_{500ml}$ × $time_{500ml}$), with higher FIT scores indicating less susceptibility to inspiratory muscle fatigue.

impaired diaphragm contractility and 20% demonstrated diaphragmatic atrophy.[3,4]

Several studies have reported on the effects of COVID-19 on the inspiratory muscles of which most have found decreased inspiratory muscle strength. In one study, 7 COVID-19 ICU survivors had a maximal inspiratory pressure (MIP) that was 42% of the predicted value while survivors of the general ward had MIP values that were 87% of the predicted values.[5] Two other studies examined MIP after hospital discharge for COVID-19 with both studies finding marked inspiratory muscle weakness (all subjects in one study had a MIP that was less than −25 cm H_2O and in the other study a MIP percent of predicted value of 65% was observed).[6,7] Thus, in view of the limited available literature that has examined MIP in patients with COVID-19, inspiratory muscle strength appears to be impaired.[3–8] However, none of the above studies have longitudinally examined MIP in the same patients prior to discharge from the ICU and after recovering in the general ward prior to discharge from the hospital. Also of note is that none of the above studies examined inspiratory muscle endurance which may also be impaired in patients with COVID-19.

The novel Test of Incremental Respiratory Endurance (TIRE) includes the measurement of MIP as well as several other measures that provides a comprehensive assessment of inspiratory muscle strength, endurance, work, and propensity to fatigue. Fig. 1 provides a graphic depiction of the measurements obtained during TIRE testing via the PrO2 device in which the MIP, sustained maximal inspiratory pressure (SMIP), inspiratory duration (ID), and the fatigue-index test (FIT) are highlighted and Table 1 provides a description of the above TIRE measurements. The above measures provide a more global assessment of IMP than MIP alone in apparently healthy individuals and in a variety of patient populations including chronic obstructive pulmonary disease (COPD), heart failure, and spinal cord injury.[9–14] In fact, in both COPD and heart failure the SMIP rather than MIP more accurately captures the pathophysiological manifestations of disease, and in heart failure the ID was more highly correlated to peak oxygen consumption than MIP (r = 0.65 versus 0.50).[9–12]

In view of the limited literature examining IMP in a longitudinal manner in patients with COVID-19, we sought to investigate the change in IMP from the ICU to hospital discharge using the TIRE method to better understand the natural progression of COVID-19 on IMP in hospitalized patients. We also report on the symptoms patients with COVID-19 experienced during hospitalization and 1-month after hospital discharge.

Methods

Study subjects

Subjects were consecutively recruited from the COVID-19 ICU at the University Hospital Brno and were included if they met the following criteria: (a) hospitalized in the ICU for at least two days with RT-PCR-confirmed COVID-19, (b) ability to perform the required inspiratory maneuvers and physical tests. Demographic and other patient characteristics were obtained from patient records and included age, height, weight, body mass index (BMI), smoking status, self-reported health status (SRHS) prior to COVID-19, Charlson Comorbidity Index (CCI), and COVID-19 severity. SRHS was coded as 1, 2, and 3 for good, moderate, and poor health, respectively, which is a commonly used method and has been found to be a good to very good surrogate measure of many health indices such as medical conditions, physical activity, and disability[15,16] as well as respiratory muscle performance[17] and mortality.[18,19] The CCI is a commonly used instrument to capture comorbidity impact and has been found to have good to very good reliability and validity.[20] COVID-19 severity was categorized as mild (patients with COVID-19 not requiring hospitalization), moderate (with or without signs of pneumonia with an oxygen saturation ≥ 90% on room air), severe (clinical signs of pneumonia with one or more of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or oxygen saturation < 90% on room air), and critical (presence of ARDS) using methods previously found to be valid and reliable.[21] Written informed consent was obtained from all subjects. The University Hospital Brno Ethics Committee approved all procedures (04−101,121/EK).

Table 1
Measurements obtained from the Test of Incremental Respiratory Endurance (TIRE) via the PrO2 device.

Measurements*	Measurement Properties	Clinical Significance
Maximal Inspiratory Pressure (MIP)	Maximal inspiratory pressure obtained from RV at 1−2 s of inspiration measured in cm H_2O with greater values associated with greater inspiratory muscle strength	Common measure of inspiratory muscle strength
Sustained Maximal Inspiratory Pressure (SMIP)	Inspiratory pressure throughout inspiration from RV to TLC measured in PTU with greater values associated with greater single-breath inspiratory work capacity	New measure of single-breath inspiratory work capacity (area under the curve) incorporating measures of strength and endurance
Inspiratory Duration (ID)	Duration of inspiration from RV to TLC measured in seconds with greater ID associated with greater inspiratory endurance	Surrogate measure of inspiratory endurance
Fatigue-Index Test (FIT)	Combined ratio measure of MIP, SMIP, and slope of SMIP without a unit of measure with higher values associated with less propensity to fatigue	Measures the propensity to fatigue similar to the tension-time index.

RV=residual volume, TLC=total lung capacity, PTU=pressure time units.
* Measurements are obtained through a 2 mm hole within the mouthpiece of the PrO2 device.

Measurements

IMP was examined at ICU discharge (ICUD) and hospital discharge (HD) using the TIRE method via the PrO2device (PrO2 Health, Inc., Smithfield, RI) which provided MIP, SMIP, ID, and FIT. IMP was measured using American Thoracic Society Guidelines for MIP and SMIP and both were obtained from residual volume (RV) with MIP measured at 1−2 s of inspiration and SMIP measured at total lung capacity (TLC). ID and FIT were measured from RV to TLC. All IMP measures were compared to PrO2 normative values to obtain% of predicted values.[22] The PrO2 device has an operating pressure of ± 400 cm H_2O, resolution of 1 cm H_2O, and accuracy of ± 1% with measurements obtained through a 2 mm hole within the mouthpiece to prevent use of the buccinator muscles. The PrO2 device has excellent reliability (ICC range of 0.975 to 0.994 for its outcome measures) as well as known-groups and convergent validity.[23]

CT scans of the lungs were performed to determine the percentage of lung involvement due to COVID-19 using the Philips IntelliSpace Portal. Data on medications, mechanical ventilation, length of mechanical ventilation, length of ICU stay, length of hospitalization, and mental health using the Hospital Anxiety and Depression Scale (HADS) were obtained. The HADS has very good to excellent reliability with Cronbach alpha values from 0.84 to 0.93 in patients similar to those in our study and good to very good validity when compared to other anxiety and depression measures with correlation coefficients ranging 0.49 to 0.83.[24,25] Examination of patient symptoms was performed at ICUD, HD, and 1-month post-HD. At ICUD and HD, the level of resting dyspnea was measured via the Borg Dyspnea Scale of 1−10 which is one of the most commonly used tools to examine dyspnea with good to very good reliability, responsiveness, and validity.[26] At HD and 1-month post-HD the following symptoms were examined and coded as 0 and 1 for no and yes, respectively: dyspnea, fatigue, chest tightness, peripheral muscle pain, cough, dysphagia, pain/burning in the lungs, racing heart rate, heart palpitations, headache, and dizziness. Dichotomous measurements of the above symptoms provide acceptable surrogate measures of symptoms obtained with more specific instruments.[24−26] General physical therapy was provided twice daily to patients in the ICU and general ward consisting of 30 min of combined breathing, strengthening, and functional exercises without inspiratory muscle training (IMT).

Statistical analyses

Statistical analyses included the assessment of normality of data via both Kolmogorov-Smirnov and Shapiro-Wilk analyses, the calculation of mean±SD and proportions of discrete non-continuous variables as well as paired t-tests, independent t-tests, correlation analyses using Spearman's and Pearson's analyses based on the distribution of the data, as well as linear and logistic regression.

Linear regression analyses examined the percent change in IMP from ICUD to HD (four separate models for MIP, SMIP, ID, and FIT) as the dependent variable using independent variables that are known to influence IMP which included gender (coded as 0 and 1 for men and women, respectively), BMI, mechanical ventilation (coded as 0 and 1 for no and yes, respectively), comorbid conditions using the CCI, SRHS (coded as 1, 2, and 3 for good, moderate, and poor health, respectively), and smoking status (coded as 1, 2, and 3 for current smoker, former smoker, and never smoked, respectively).

Logistic regression examined the effect of the same independent variables described above on a favorable change in IMP (increase in IMP) or unfavorable change in IMP (decrease in IMP) from ICUD to HD which also resulted in four separate models for change in MIP, SMIP, ID, and FIT. Finally, a Sankey diagram was generated via SankeyMATIC to visualize and analyze the symptoms associated with COVID-19 during hospitalization and 1-month post-HD with the width of each line being proportional to the flow rate. The level of statistical significance was set at $p<.05$.

A priori sample size estimation was performed using data from previous publications focusing on known-groups validity and convergent validity of SMIP and its ability to distinguish between known-groups and correlation to functional performance, respectively.[11] The correlation of SMIP to 6-minute walk test distance was previously observed to be 0.427 (p-value=0.00) which ensured that a sample size of 30, using a one tailed test with p=.05 and 0.80 power was sufficient for this study (G*Power 3.1.9.7).

Results

Patient characteristics are shown in Table 2. A large percentage of the participants never smoked and reported a moderate-to-good level of health prior to COVID-19 despite having a relatively high CCI. Furthermore, slightly more than $^3/_4$ of the subjects had severe COVID-19 and in the 19 subjects in whom CT scans of the lungs were obtained, only one subject had 76−100% lung involvement. In the ICU, few patients received neuromuscular blocking agents, but 90% received high dose glucocorticoids and slightly over $^1/_3$ of the subjects were administered statins. The HADS anxiety and depression scores decreased significantly from ICUD to HD for the entire cohort (p=.002 and 0.001, respectively), but was driven by a significant decrease in men (p=.005 and 0.002, respectively) that did decrease in women, but was not statistically significant (p=.21 and 0.14, respectively) (Table 2). The mean±SD level of resting dyspnea of the entire cohort decreased from ICUD to HD (1.5 ± 1.6 vs 1.1 ± 1.8), but was not significantly less (p=.11). Despite this, SMIP at HD was significantly related to resting dyspnea at HD (r=−0.40; p=.02) and MIP as well as FIT at HD were near significant correlates to resting dyspnea at HD (r=−0.32 and −0.33, respectively; p=.07 for both). Fig. 2 displays the stem and leaf plots of the resting dyspnea levels at ICUD and HD of both men and women showing the different perceptions of dyspnea between genders.

IMP at ICUD was significantly reduced compared to normative values and although the SMIP and FIT improved significantly in the general ward prior to HD, almost all measures remained significantly below normative values especially in women (Table 2). Only SMIP and FIT were significantly greater at HD (p=.006 and 0.03, respectively). The MIP, SMIP, and ID% of predicted values of the entire cohort at ICUD vs HD were 43±25 vs 46±22%, 56±35 vs 70±37%, and 98±49 vs 100±44%, respectively, and were significantly less (p=.001) than estimated values except ID. The SMIP at ICUD as well as MIP, SMIP, and FIT at HD of men were significantly greater than that of women. The SMIP and FIT of men increased significantly from ICUD to HD, but no measure of IMP in the women increased significantly from ICUD to HD. The MIP and SMIP% of predicted values for men at ICUD vs HD were 46±25 vs 51±23% and 65±38 vs 82±39%, respectively, while the same measures for women were much lower without significant change at 37±24 vs 37±20% and 41±23 vs 48±19%, respectively.

The symptom profiles of the patients from ICUD to HD and one month after HD are shown in Fig. 3. Although the frequency with which symptoms persist after COVID-19 has not yet been well established, our findings suggest that 90% of the subjects still experienced at least one COVID-19 related symptom 1 month after HD, with 20% presenting with a greater number of symptoms than earlier during hospitalization. The main persistent symptom was fatigue that affected nearly half of the subjects (46.6%) followed by cough and dyspnea (40% and 36.6%, respectively).

The results of correlation analyses are shown in Table 3. The% change in the FIT from ICUD to HD was unrelated to any of the independent variables and no measure of IMP was significantly related to HADS anxiety or depression scores at ICUD or HD. Few significant relationships between symptoms and IMP at HD were observed, but

Table 2
Characteristics of the study subjects.

Variable	Entire group	Males	Females
N (% of total)	30 (100)	19 (63.3)	11 (36.7)
Sample characteristics			
Age (years)	71.1 ± 11.3	70.6 ± 12.8	72.1 ± 9.0
Height (cm)	171.8 ± 8.5	176.9 ± 4.8	163.2 ± 6.0**
Weight (kg)	81.9 ± 15.9	82.8 ± 14.2	80.4 ± 19.2
BMI	27.8 ± 6.2	26.6 ± 5.5	30.2 ± 7.1
Smoking status			
Current smoker (% of total)	1 (3.3)	0	1 (3.3)
Former smoker (% of total)	2 (6.7)	1 (3.3)	1 (3.3)
Never smoker (% of total)	27 (90)	18 (60)	9 (30)
SRHS prior to COVID-19			
Good health (% of total)	12 (40)	7 (23.3)	5 (16.7)
Moderate health (% of total)	16 (53.3)	10 (33.3)	6 (20)
Poor health (% of total)	2 (6.7)	2 (6.7)	0
Charlson Comorbidity Index (0–33)	4.4 ± 1.9	4.5 ± 1.9	4.2 ± 2.1
COVID-19 severity			
Moderate (% of total)	5 (16.7)	4 (13.3)	1 (3.3)
Severe (% of total)	23 (76.7)	14 (46.7)	9 (30)
Critical (% of total)	2 (6.7)	1 (3.3)	1 (3.3)
CT scan lung involvement			
1–25%	5 (26.3)	3 (15.8)	2 (10.5)
26–50%	8 (40)	4 (21.1)	4 (21.1)
51–75%	5 (25)	3 (15.8)	2 (10.5)
76–100%	1 (5)	1 (5)	0
ICU stay			
Length of ICU stay (days)	9.2 ± 6.0	9.5 ± 7.2	8.7 ± 3.8
Mechanical Ventilation (% of total)	5.0 (16.7)	4 (13.3)	1 (3.3)
Length of MV (days)†	1.2 ± 3.3	1.4 ± 3.4	1.0 ± 3.3
NMBA			
Yes (% of total)	3 (10)	2 (6.7)	1 (3.3)
No (% of total)	27 (90)	17 (56.7)	10 (33.3)
High dose glucocorticoids			
Yes	27 (90)	16 (53.3)	11 (36.7)
No	3 (10)	3 (10)	0
Statins			
Yes	10 (33.3)	8 (26.7)	2 (6.7)
No	20 (66.7)	11 (36.7)	9 (30.0)
IMP at discharge			
MIP (cmH2O)	36.3 ± 21.3	41.1 ± 22.1	28.2 ± 18.2
SMIP (PTU)	231.5 ± 157.3	287.8 ± 164.3	134.3 ± 82.1**
ID (seconds)	8.8 ± 4.1	9.4 ± 3.2	7.9 ± 5.5
FIT	9.0 ± 9.4	10.9 ± 8.6	5.7 ± 10.2
Mental health at discharge			
HADS anxiety (0–21)	6.3 ± 4.6	6.7 ± 5.3	5.8 ± 3.5
HADS depression (0–21)	5.7 ± 3.5	6.0 ± 3.9	5.2 ± 2.7
Hospital stay			
Length of hospital stay (days)	25.7 ± 15.6	25.4 ± 18.6	26.3 ± 9.3
IMP at discharge			
MIP (cmH2O)	39.5 ± 20.0	46.0 ± 20.0	28.3 ± 14.8**
SMIP (PTU)	297.0 ± 181.7*	376.0 ± 179.3	160.6 ± 74.4**
ID (seconds)	9.4 ± 4.6	10.3 ± 4.2	8.1 ± 5.2
FIT	13.1 ± 12.3*	17.4 ± 13.1	5.9 ± 6.2**
Mental health at discharge			
HADS anxiety (0–21)	3.6 ± 4.0	3.2 ± 4.2	4.4 ± 3.9
HADS depression (0–21)	3.5 ± 3.1	3.6 ± 3.3	3.6 ± 3.1

N=sample size, BMI=body mass index, SRHS=self-reported health status, CT=computerized tomography, ICU=intensive care unit, NMBA=neuromuscular blocking agent, IMP=inspiratory muscle performance, MIP=maximal inspiratory pressure, SMIP=sustained maximal inspiratory pressure, ID=inspiratory duration, FIT=fatigue index test, HADS=hospital anxiety and depression scale.

* $p \leq .001$ for ICU discharge to hospital discharge comparisons of the entire cohort.

** $p \leq .01$ for men versus women comparisons.

† Length of mechanical ventilation for the 5 patients was 3, 4, 5, 11, and 14 days.

both headaches and racing heart rate at HD were significantly related to MIP at HD (r=−0.42 and −0.39, respectively; $p<.05$) and a trend in the relationship between dyspnea and MIP at HD was observed (r=−0.30; p=.10). Also, peripheral muscle pain at 1-month post-HD was significantly related to MIP (r=−0.38; p=.03) and a near significant relationship was observed between SMIP and peripheral muscle pain at 1-month post-HD (r=−0.33; p=.07) with a trend in the relationship between headache 1-month post-HD and SMIP (r=−0.30; p=.11). Fig. 4 shows the relationship between the SMIP at ICUD and% change in SMIP at HD as well as the relationship between SMIP at ICUD and gender.

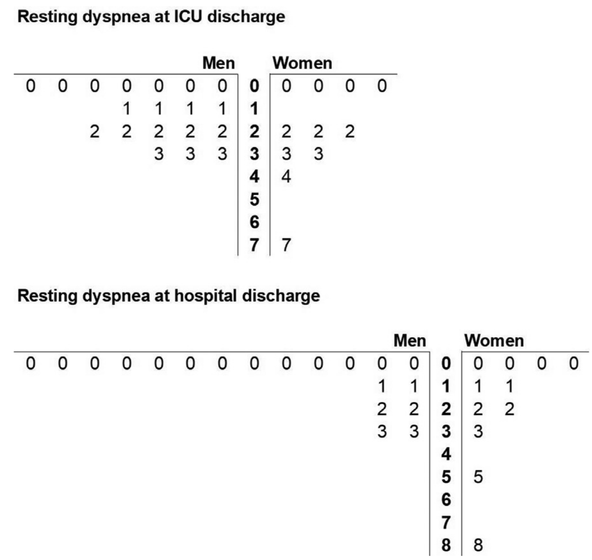

Fig. 2. Stem and leaf plots of resting dyspnea in men and women at ICUD and HD.

Gender-specific correlation analyses of IMP found only one significant relationship in women which was SMIP at ICUD being significantly related to the FIT at ICUD (r = 0.76; p=.006). More significant correlations existed in men including the relationship between MIP at ICUD and SMIP at ICUD (r = 0.63; p=.004) and% change in MIP at HD (r=−0.46; p=.04) as well as the relationship between SMIP at ICUD and FIT at ICUD (r = 0.90; p=.0001). A near significant relationship between SMIP at ICUD and ID at ICUD (r = 0.44; p=.05) as well as FIT at HD and resting dyspnea at HD (r=−0.39; p=.09) were also observed.

Linear regression analyses found that the significant predictors of the% change in ID were smoking status (unstandardized β coefficient of 0.473; p=.01) and SRHS (unstandardized β coefficient of −0.276; p=.03) with a model r-squared value of 0.42 and overall model p-value of 0.03. The CCI was a significant predictor of the% change in FIT (unstandardized β coefficient of −0.322; p=.03) with a model r-squared value of 0.33 and overall model p-value of 0.12. The results of logistic regression analyses found SRHS to be a significant (p=.04) predictor of a favorable change in ID (an increase) with a β coefficient of −1.800 and Exp (β) of 0.165 and 95% CI (0.030–0.926). Also, SRHS was the only variable that trended towards significance (p=.13) in predicting a favorable change in the FIT with a β coefficient of −1.230 and Exp (β) of 0.292 and 95% CI (0.058–1.468).

Discussion

The results of this study identified the significant reduction in IMP in patients with COVID-19 at ICUD. The MIP did not significantly improve prior to HD for the entire cohort, but the SMIP and FIT did improve significantly yet SMIP remained significantly below normative values. One of the key findings of this study is that no measure of IMP in women improved from ICUD to HD while men were observed to have significant improvements in both SMIP and FIT, but not MIP. These findings highlight the importance of examining additional measures of IMP besides MIP. Furthermore, women were observed to have no significant change in the HADS anxiety and depression scores from ICUD to HD while men were found to have significant improvements in both measures from ICUD to HD, but were unrelated to the

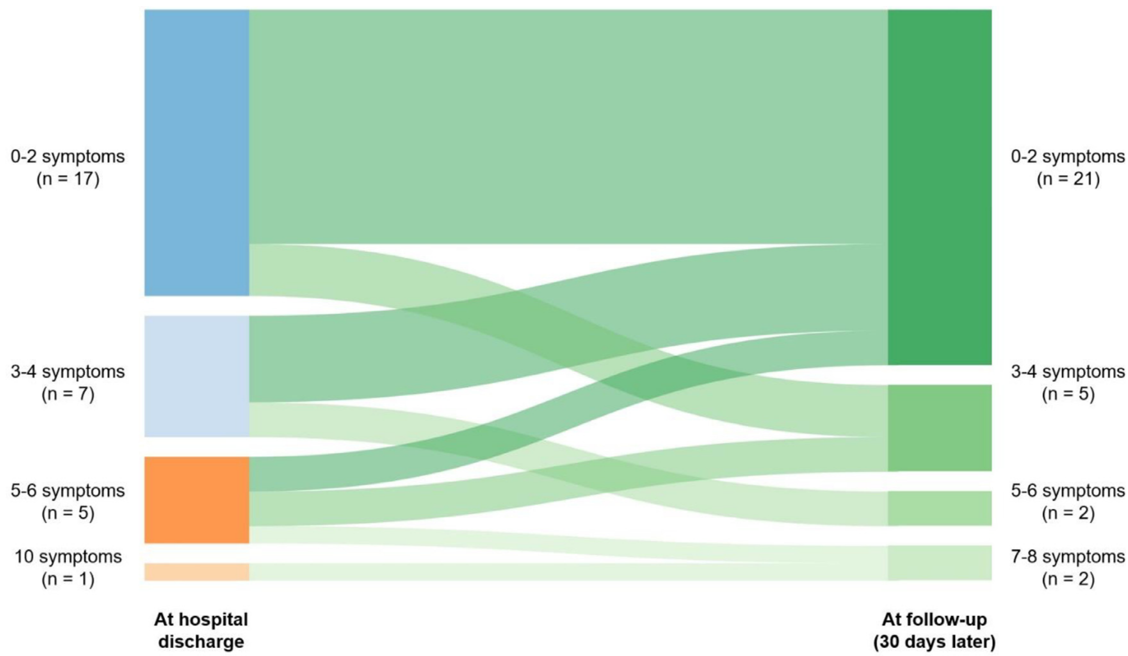

Fig. 3. Diagram depicting the change in the total number of COVID-19-related symptoms still present at hospital discharge and 1 month after infection. The width of each line is proportional to the flow rate.

improvements in IMP suggesting the need for further investigation of HADS and IMP in men and women with COVID-19. Our findings strongly suggest that targeted IMT may be an important adjunct in the rehabilitation of patient's post-COVID-19 and especially in women should the results of this study be confirmed.

A limited available cross-sectional literature has examined MIP in patients with COVID-19 with findings that inspiratory muscle strength appears to be impaired with COVID-19.[3–8] However, none of the existing studies have longitudinally examined MIP in the same patients prior to discharge from the ICU and after recovering in the general ward prior to HD and none have examined inspiratory muscle endurance. Our findings suggest that men significantly improved two measures of IMP related to endurance and the propensity to fatigue, but women were observed to have no significant improvement in any measure of IMP.

The TIRE measures most affected in our study included both the MIP and SMIP. In men, the% of predicted MIP at ICUD was only 46% of the predicted value and increased to only 51% of the predicted value at HD. In women, the% of predicted MIP at ICUD was significantly lower than that in men at 37% of the predicted value which remained at 37% of the predicted value at the time of HD. These findings suggest a need for interventions to improve the MIP values towards more normal predicted values in both men and women hospitalized with COVID-19. The SMIP% of predicted values in men were significantly greater than those of women at ICUD and at HD (65±38% vs 41±23% and 82±39% vs 48±19%, respectively), but in both men and women were below the expected SMIP values with women remaining below 50% of the predicted value throughout their hospitalization in a measure associated with strength, endurance, and work. However, the IMP findings in women should be interpreted cautiously because of the small sample size. Nonetheless, further investigation of the TIRE measures in patients with COVID-19 appears warranted.

The role that SRHS prior to COVID had on the results of our study are important to highlight. In both linear and logistic regression SRHS was found to be a significant predictor of the% change in ID and favorable change in ID from ICUD to HD, respectively. Also, SRHS was the only variable that trended towards significance in predicting a favorable change in the FIT from ICUD to HD. Thus, patients with better SRHS prior to COVID appear to have a better ability to improve IMP more than patients with poor SRHS. This is not surprising since better SRHS has been associated with better IMP.[17] These findings and the results of our study highlight the important role of maintaining a healthy lifestyle to combat infectious diseases like COVID-19.

Factors directly and indirectly related to the symptoms and poor IMP of the patients in our study as well as inability to improve IMP include the results of our linear regression analyses in which the CCI was a significant negative predictor of the% change in FIT and the finding that smoking status was a positive predictor of the% change in ID. Patients who never smoked were more likely to have a greater% change in ID than current and former smokers. Also, patients with a greater CCI were more likely to have less% change in the FIT. Thus, the pathophysiological effects of smoking and comorbid conditions

Table 3
Correlation matrix of inspiratory muscle performance at baseline, percent change at hospital discharge, and gender.

Variables	ICU MIP	ICU SMIP	ICU ID	ICU FIT	% change MIP	% change SMIP	% change ID	Gender
ICU MIP	1							
ICU SMIP	.63*	1						
ICU ID	−0.33	.39*	1					
ICU FIT	.16	.82*	.79*	1				
% change MIP	−0.49*	−0.17	.46*	.10	1			
% change SMIP	−0.39*	−0.36*	−0.02	−0.28	.60*	1		
% change ID	.12	−0.05	−0.28	−0.16	−0.20	.41*	1	
Gender	−0.30	−0.48*	−0.18	−0.27	−0.09	.02	−0.10	1

* $p < 0.05$.

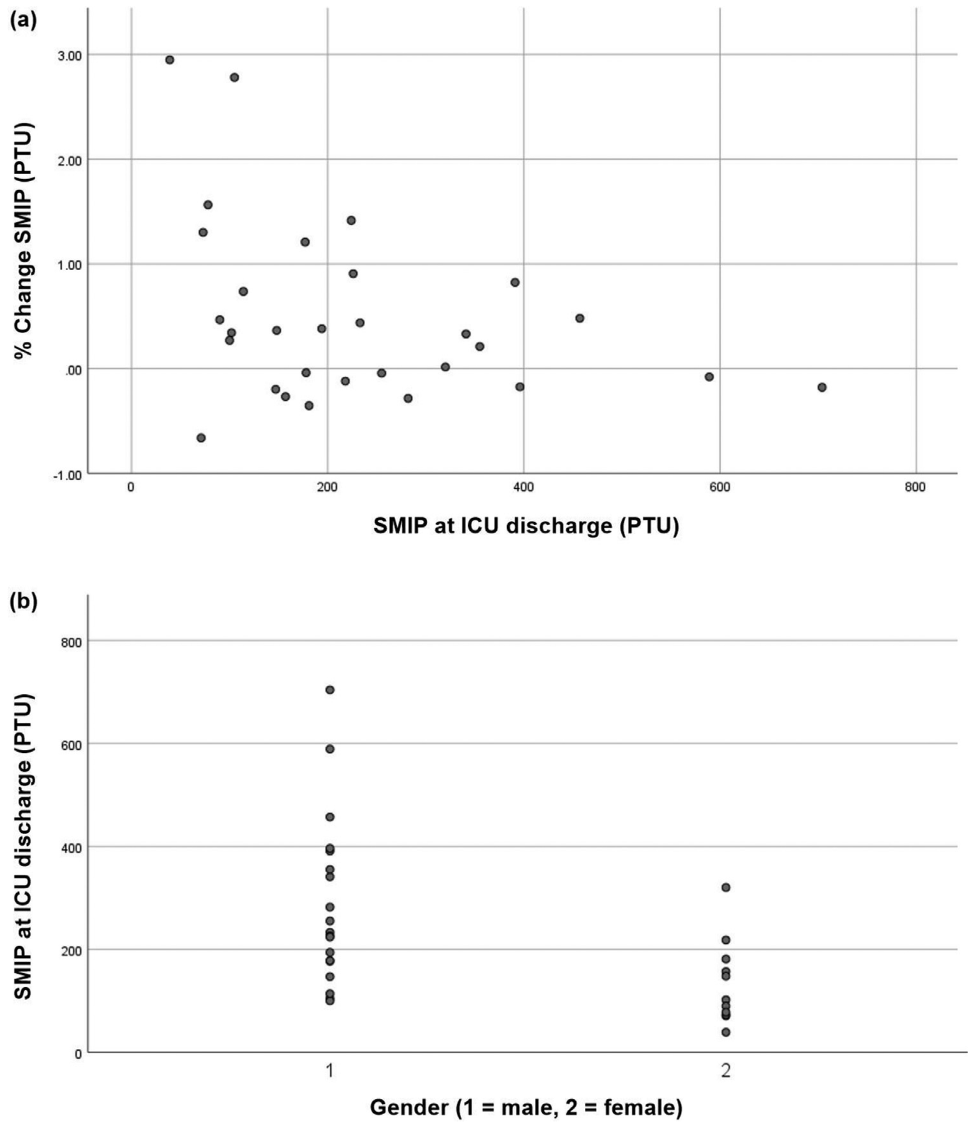

Fig. 4. Scatterplot of (a) SMIP at ICUD to% Change in SMIP at HD and (b) SMIP at ICUD by gender.

appear to contribute to less of an improvement in IMP during hospitalization for COVID-19 likely because of the inflammatory processes associated with smoking and comorbid conditions and the cytokine storm associated with COVID-19.[1–4] Additionally, the increase in fibrotic tissue from COVID-19 may be responsible for the development of pulmonary abnormalities and dysfunctional breathing observed in patients with long COVID.[27,28] Regardless, the profound impairment in IMP that we and others have observed in patients with COVID-19 suggests that the dyspnea, fatigue, and dysfunctional breathing associated with COVID-19 may in part be due to poor IMP which in patients with COVID-19 and a variety of other patient populations has been improved with IMT.[28–32]

The finding of IMP in patients with COVID-19 being below normative values at the time of discharge from the ICU and hospital is not surprising, but the profound impairment in IMP that persisted throughout hospitalization highlights the role that targeted IMT may have on this patient population both in the ICU, general ward, and after discharge from the hospital. Particular IMP measures may respond more favorably than others to IMT. One study of IMT in 16 patients with COVID-19 found that IMT at 50% of MIP improved MIP more than IMT at 30% of MIP (21% vs 11%) suggesting that higher intensity IMT may be more beneficial to improve inspiratory muscle strength of patients with COVID-19.[8] However, 7 patients performed IMT at 30% of MIP while the other 9 patients performed IMT at 50% of MIP highlighting the small sample size and need for subsequent study of different IMT intensities and methods in patients with COVID-19.[8]

The limitations of this study include a modest sample size and unequal number of men and women in the study. However, the sample size of our study is greater than the majority of studies that have examined MIP in a cross-sectional manner in patients with COVID-19.[5–8] Additionally, our study examined a variety of IMP measures in a longitudinal and comprehensive manner. However, we did not have access to measures of IMP prior to ICU admission for COVID-19 which is a limitation to the study, especially because of the high level of comorbidity in the patients which could have impacted IMP unfavorably. Although there were fewer women than men in our study, we have accounted for gender differences by performing a variety of gender-specific analyses that have provided important data and findings highlighting the manner that IMP of men and women may respond to COVID-19. Such limitations we believe may be strengths of our study and suggest the need for gender-specific investigation of the effects COVID-19 may have on IMP and subsequently on therapeutic efforts to address the marked impairment in IMP from COVID-19. Regardless, the findings that we have observed in women should be interpreted cautiously in view of the small sample size.

Conclusions

This study identified a significant reduction in IMP in patients with COVID-19 prior to ICUD which significantly improved in the general ward prior to HD, but remained significantly below normative values, especially in women. The symptoms of the study population reflected that which has been previously reported, but no previous study appears to have addressed the longitudinal symptomatology nor comprehensive examination of IMP in patients with COVID-19. The results of the above study strongly suggest that targeted IMT may be an important adjunct in the rehabilitation of patients post-COVID-19.

Funding

Supported by Ministry of Health of the Czech Republic (University Hospital Brno, 65,269,705), No. NU21J-09−00,004.

Declaration of Competing Interest

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

References

1. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603–605.
2. Shi Z, de Vries HJ, Vlaar APJ, van der Hoeven J, Boon RA, Heunks LMA, et al. Diaphragm pathology in critically Ill patients With COVID-19 and postmortem findings from 3 medical centers. *JAMA Intern Med*. 2021;181(1):122–124.
3. Farr E, Wolfe AR, Deshmukh S, Rydberg L, Soriano R, Walter JM, et al. Diaphragm dysfunction in severe COVID-19 as determined by neuromuscular ultrasound. *Ann Clin Transl Neurol*. 2021;8(8):1745–1749.
4. Helmy MA, Magdy Milad L, Osman SH, Ali MA, Hasanin A. Diaphragmatic excursion: a possible key player for predicting successful weaning in patients with severe COVID-19. *Anaesth Crit Care Pain Med*. 2021;40(3): 100875.
5. Debeaumont D, Boujibar F, Ferrand-Devouge E, Artaud-Macari E, Tamion F, Gravier FE, et al. Cardiopulmonary exercise testing to assess persistent symptoms at 6 months in people with COVID-19 who survived hospitalization: a pilot study. *Phys Ther*. 2021;101 (6).
6. Abodonya AM, Abdelbasset WK, Awad EA, Elalfy IE, Salem HA, Elsayed SH. Inspiratory muscle training for recovered COVID-19 patients after weaning from mechanical ventilation: a pilot control clinical study. *Medicine*. 2021;100(13):e25339.. (Baltimore).
7. Jalušić Glunčić T, Muršić D, Basara L, Vranić L, Moćan A, Janković Makek M, et al. Overview of symptoms of ongoing symptomatic and post-COVID-19 patients who were reffered to pulmonary rehabilitation - first single-centre experience in croatia. *Psychiatr Danub*. 2021;33(Suppl 4):565–571.
8. Li L, Yu P, Yang M, Xie W, Huang L, He C, et al. Physical therapist management of COVID-19 in the intensive care unit: the west china hospital experience. *Phys Ther*. 2021;101(1).
9. Formiga MF, Campos MA, Cahalin LP. Inspiratory muscle performance of former smokers and nonsmokers using the test of incremental respiratory endurance. *Respir Care*. 2018;63(1):86–91.
10. Formiga MF, Vital I, Urdaneta G, Campos MA, Cahalin LP. Beyond inspiratory muscle strength: clinical utility of single-breath work capacity assessment in veterans with COPD. *Respir Med*. 2019;147:13–18.
11. Formiga MF, Vital I, Urdaneta G, Balestrini K, Cahalin LP, Campos MA. The BODE index and inspiratory muscle performance in COPD: clinical findings and implications. *SAGE Open Med*. 2018;6: 2050312118819015.
12. Laoutaris ID, Adamopoulos S, Manginas A, Panagiotakos DB, Cokkinos DV, Dritsas A. Inspiratory work capacity is more severely depressed than inspiratory muscle strength in patients with heart failure: novel applications for inspiratory muscle training. *Int J Cardiol*. 2016;221:622–626.
13. Palermo AE, Janyszek E, Young A, Villane A, Kirk-Sanchez NJ, Cahalin LP, et al. Inspiratory muscle performance and anthropometric measures-novel assessments related to pulmonary function in people with spinal cord injury: a pilot study. *Arch Phys Med Rehabil*. 2021.
14. Palermo AE, Kirk-Sanchez NJ, Garcia KL, Nash MS, Cahalin LP. Inspiratory muscle performance is related to seated balance function in people with SCI: an observational study. *Arch Phys Med Rehabil*. 2021.
15. Lundberg O, Manderbacka K. Assessing reliability of a measure of self-rated health. *Scand J Soc Med*. 1996;24(3):218–224. https://doi.org/10.1177/140349489602400314. SepPMID: 8878376.
16. Stewart AL, Ware JE, Jr JEW. *Measuring Functioning and Well-Being: The Medical Outcomes Study Approach*. eds. Duke University Press; 1992.
17. Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular health study research group. *Am J Respir Crit Care Med*. 1994;149(2 Pt 1):430–438.
18. Wuorela M, Lavonius S, Salminen M, Vahlberg T, Viitanen M, Viikari L. Self-rated health and objective health status as predictors of all-cause mortality among older people: a prospective study with a 5-, 10-, and 27-year follow-up. *BMC Geriatr*. 2020;20(1):120.
19. Lorem G, Cook S, Leon DA, Emaus N, Schirmer H. Self-reported health as a predictor of mortality: a cohort study of its relation to other health measurements and observation time. *Sci Rep*. 2020;10(1):4886.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383.
21. Organization WH. Living guidance for clinical management of COVID-19. 2021; https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2. Accessed May 6, 2022.
22. Garcia C, Denis TS, Colas-Salgado S, Eisenhardt B, Formiga MF, Cohen M. Normative values for the Test of Incremental Respiratory Endurance (TIRE). *C108 Adv Lung Funct Assess*. 2022. A6363-A.
23. Formiga MF, Roach KE, Vital I, Urdaneta G, Balestrini K, Calderon-Candelario RA, et al. Reliability and validity of the test of incremental respiratory endurance measures of inspiratory muscle performance in COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1569–1576.
24. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res*. 2002;52 (2):69–77. https://doi.org/10.1016/s0022-3999(01)00296-3. FebPMID: 11832252.
25. Boxley L, Flaherty JM, Spencer RJ, Drag LL, Pangilinan PH, Bieliauskas LA. Reliability and factor structure of the Hospital Anxiety and Depression Scale in a polytrauma clinic. *J Rehabil Res Dev*. 2016;53(6):873–880. https://doi.org/10.1682/JRRD.2015.05.0088. PMID: 28273327.
26. Mahler DA, Horowitz MB. Perception of breathlessness during exercise in patients with respiratory disease. *Med Sci Sports Exerc*. 1994;26(9):1078–1081. SepPMID: 7808239.
27. van Voorthuizen EL, van Helvoort HAC, Peters JB. Persistent exertional dyspnea and perceived exercise intolerance after mild COVID-19: a critical role for breathing dysregulation? *Phys Ther*. 2022;102(10).
28. Mancini DM, Brunjes DL, Lala A, Trivieri MG, Contreras JP, Natelson BH. Use of cardiopulmonary stress testing for patients with unexplained dyspnea post-coronavirus disease. *JACC Heart failure*. 2021;9(12):927–937.
29. Beaumont M, Forget P, Couturaud F, Reychler G. Effects of inspiratory muscle training in COPD patients: a systematic review and meta-analysis. *Clin Respir J*. 2018;12 (7):2178–2188.
30. Lötters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *Eur Respir J*. 2002;20(3):570–576.
31. Wu J, Kuang L, Fu L. Effects of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. *Congenit Heart Dis*. 2018;13 (2):194–202.
32. Smart NA, Giallauria F, Dieberg G. Efficacy of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. *Int J Cardiol*. 2013;167(4):1502–1507.