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Association between muscle quality index and pulmonary function in post-COVID-19 subjects

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Abstract

Background The SARS-CoV2 pandemic impacted many critically ill patients, causing sequelae, affecting lung function, and involving the musculoskeletal system. We evaluated the association between lung function and muscle quality index in severely ill post-COVID-19 patients.

Methods A cross-sectional study was conducted on a post-COVID-19 cohort at a third-level center. The study included patients who had experienced severe-to-critical COVID-19. Anthropometric measurements, such as body mass index (BMI) and handgrip strength, were obtained to calculate the muscle quality index (MQI). Additionally, spirometry, measurements of expiratory and inspiratory pressure, and an assessment of DLCO in the lungs were performed. The MQI was categorized into two groups: low-MQI (below the 50th percentile) and high-MQI (above the 50th percentile), based on sex. Group differences were analyzed, and a multivariate linear regression analysis was performed to assess the association between respiratory function and MQI.

Results Among the 748 patients analyzed, 61.96% required mechanical ventilation, and the median hospital stay was 17 days. In patients with a low MQI, it was observed that both mechanical respiratory function and DLCO were lower. The multivariate analysis revealed significantly lower findings in mechanical respiratory function among patients with a low MQI.

Conclusion The Low-MQI is an independent predictor associated with pulmonary function parameters in subjects with Post-COVID-19 syndrome.

Keywords Pulmonary function, Muscle quality index, DLCO, Respiratory muscle strength

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Background

Post-COVID-19 syndrome is characterized by the development of signs and symptoms during or after an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), with symptoms persisting for more than 12 weeks and not attributable to alternative diagnoses [1]. A longitudinal cohort study revealed that 68% of subjects experienced symptoms at 6 months, and 49% experienced symptoms at the 1-year mark following the initial acute viral infection caused by SARS-CoV-2 [2].

Additionally, the severity of COVID-19 infections is associated with the presence or persistence of signs and symptoms in post-COVID-19 individuals [3]. The most common manifestations include pulmonary, musculoskeletal, hematologic, cardiovascular, endocrine, renal, and gastrointestinal symptoms [4]. Muscle weakness or fatigue, dyspnea, and sleep disturbance are among the most frequently reported symptoms [2].

Regarding musculoskeletal manifestations, in the acute phase of COVID-19 many subjects exhibit body composition changes, including a loss of muscle mass and strength. The muscular impairment can be attributed to various factors such as anorexia, malnutrition, and especially the severity of the illness. Hospitalized subjects have more significant pro-inflammatory states, oxidative stress, increased protein catabolism, and prolonged hospital stays, negatively impacting muscular mass. In addition, in subjects who require intensive care unit, invasive mechanical ventilation (IMV) and using neuromuscular blockers and corticosteroids negatively affect the peripheral muscles, the intercostal muscles, and the diaphragm, the primary muscle in charge of breathing [5–10].

Concerning the post-COVID phase, the pro-inflammatory state and endothelial dysfunction persist, as well as an increase in adipose tissue [11, 12]. Low muscle mass/strength and adipose tissue excess possess strongly interconnected physiopathologic mechanisms that exacerbate one another, resulting in a vicious cycle. This cycle leads to a reduction in protein synthesis, increased protein degradation, fat infiltration into skeletal muscle, promotion of lipotoxicity, exacerbation of inflammation [13], oxidative stress, and mitochondrial dysfunction [13–16]. Low muscle mass/strength loss and the accumulation of intramuscular fat contribute to muscle contractility impairment [17, 18].

The muscle strength can be easily assessed through handgrip strength (HGS). HGS has been demonstrated to be associated with whole-body muscle strength and skeletal muscle mass index (SMI), as well as pulmonary function, morbidity, and mortality in diverse populations [19–24].

The muscle quality index (MQI), obtained by dividing HGS by body mass index (BMI) (i.e., MQI = HGS/BMI), has emerged as a health and physical function indicator [25–28]. Existing evidence suggests that low MQI is linked to metabolic markers [28], metabolic syndrome [25], the prediction of cardiovascular disease risk factors [27], and physical function [28]. However, the association between the strength/BMI index and pulmonary function remains undefined. We aim to assess the association between MQI and pulmonary function in post-COVID-19 subjects.

Methods

A cross-sectional study was conducted at the Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas" in Mexico City.

The study focused on moderate to severe COVID-19 subjects with a confirmed diagnosis of COVID-19 by PCR testing. Moderate to severe COVID-19 was considered in those patients who, during the acute phase of the disease, required hospitalization with blood oxygen saturation $\leq 93\%$, PaO2/FiO2 ratio < 300 (arterial partial pressure of oxygen/fraction of inspired oxygen).

In the study, those patients during the acute phase were moderate to severe and were subsequently discharged were included. Data were collected from outpatient evaluations 3 months post-acute COVID-19 infection during routine clinical examinations of post-COVID-19 subjects between June 1, 2020, and May 30, 2023 (Fig. 1). Subjects who could not be contacted, declined to participate, or died before the follow-up visit were excluded.

Outcome measures

Anthropometric, clinical, and demographic variables were evaluated during the post-COVID-19 clinical management delivered to patients at our institute.

Anthropometry

Weight and height were measured according to the manual reference for anthropometric standardization [29]. All subjects wore light clothing and were barefoot.

Body mass index (BMI)

BMI was estimated by weight in kilograms divided by height in meters squared.

Handgrip strength (HGS)

Handgrip strength was measured using a mechanical Smedley Hand Dynamometer (Stoelting, Wood Dale, UK) according to the technique described in Rodriguez et al., which consists of subjects standing with their arms stretched parallel to the trunk, then picking up the dynamometer and applying the maximum force with the

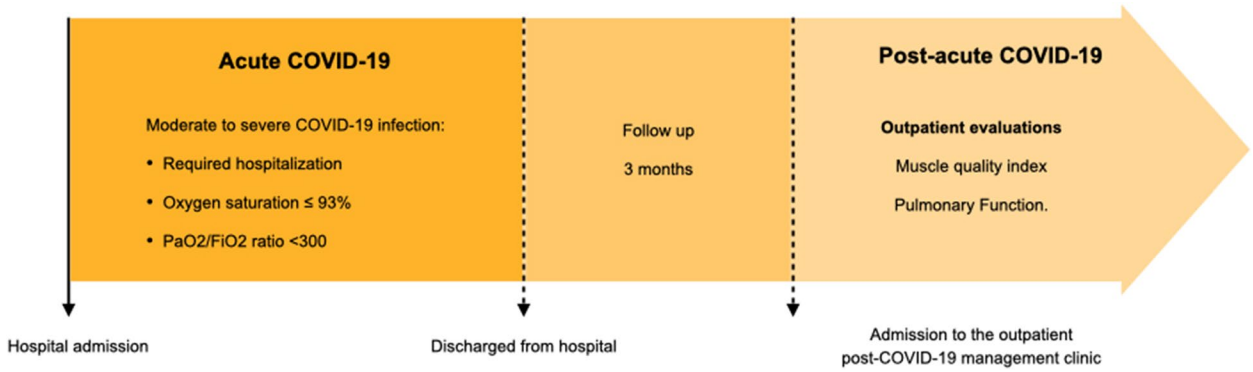

Fig. 1 Study flow diagram

dominant hand. The measurement was repeated three times, one minute apart, to avoid fatigue. The maximum value was recorded in kg [30].

Muscle quality index (MQI)

MQI was calculated by dividing HGS by BMI and subsequently categorised as follows: Low-MQI ≤ 50th percentile and High-MQI > 50th percentile, considering gender (50th percentile MQI: 0.54 for women and 0.99 for men).

Pulmonary function

Forced spirometry was performed using a portable spirometer (EasyOne Pro Lab, Ndd Medical Technologies Inc., Zürich, Switzerland) and carried out by an experienced respiratory medicine technician in accordance with American Thoracic Society/European Respiratory Society standards [31] The analyzed spirometric variables included forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) before and after administering a bronchodilator, peak expiratory flow rate (PEFR), and maximum expiratory flow between 25 and 75% of the FVC (MEF 25–75). Following a 15-minute rest, participants performed a maximal forced inspiration and a forceful expiration using a nose clip. Spirometry reference values were derived from Mexican-American individuals [32].

Respiratory muscle strength

Maximal inspiratory pressures (MIP) and maximal expiratory pressures (MEP) were measured in accordance with ATS/ERS 2002 guidelines using MicroRPM equipment (CareFusion, Micromedical, UK) [33].

Carbon monoxide diffusing capacity (DLCO)

A skilled respiratory technician conducted tests for DLCO using EasyOne pro® equipment from Ndd Medical Technologies Inc., Zürich, Switzerland. The assessment accounted for altitude and hemoglobin, employing predicted values for the Latino population [34].

Statistical analysis

Analyses were conducted using the commercially available software STATA version 14 (Stata Corp., College Station, TX, USA). Categorical variables were expressed as frequencies and percentages. The Shapiro-Wilk test assessed the normality of continuous variables; normal variables were expressed as mean and standard deviation, while non-normal variables were reported as median and percentiles 25–75. Comparisons between study groups (Low-MQI vs. High-MQI) were analyzed using the chi-square test for categorical variables and the t-test or Mann-Whitney U test for continuous variables. To evaluate the association between low-MQI and pulmonary function, linear regression models were performed using each variable of pulmonary function as a dependent variable and Low-MQI as an independent variable. The multivariate linear regression models were adjusted by bivariate analysis for variables with $p < 0.10$, such as age, diabetes, hypertension, ischaemic cardiopathy, and IMV, and multicollinearity was checked with the variance inflation factor. A p-value of 0.05 was considered statistically significant. A p-value of 0.05 was considered statistically significant.

Results

Seven hundred and forty-eight patients were assessed, with a mean age of 54.61 ± 0.44 years; 63.90% were male and BMI were 30.39 ± 6.21. The low-MQI group comprised older individuals with a higher prevalence of hypertension, obesity and fatigue compared to the high-MQI group. Respect to hospitalary parameters during COVID-19 acute phase, low-MQI group had higher IMV,

duration of IMV, and a longer hospital stay compared to the high-MQI group (Table 1).

In terms of pulmonary function, the Low-MQI group exhibited lower FEV1 in liters and percentage, FVC in liters and percentage, MEF 25–75, PEFR, FEV1/FVC ratio, DLCO, MIP, MEP than high-MQI group (Table 2).

Additionally, Table 3 showed that Low-MQI was lower FEV1 in liters and percentage, FVC in liters and percentage, MEF 25–75, PEF, MIP, and MEP in both bivariate and multivariate models adjusted for age, diabetes, hypertension, ischaemic cardiopathy, and IMV. However, no significant difference was found in DLCO in either the crude or adjusted models.

Discussion

The primary finding of our research demonstrated a negative association between low-MQI and mechanical pulmonary function, as well as respiratory muscle strength in subjects with post-COVID syndrome.

In relation to pulmonary function, this is influenced by various factors such as age, sex, gestational weeks, muscular strength, the immune system, and exposure to toxic agents such as tobacco, wood smoke, asbestos, and respiratory infections. In a post-COVID-19 infection, a meta-analysis conducted by Lee and Cols demonstrated that impaired diffusion capacity was the most prevalent abnormality on pulmonary function tests at 35%. Restrictive patterns were identified in 8%, while persistent ground-glass opacities and pulmonary fibrosis had a prevalence of 34% [35]. FEV1 reduction is a significant predictor of mortality in the general population [36, 37], and serves as a marker for cardiovascular mortality [38]. It was observed that low-MQI independently predicts lower FEV1, as subjects with low-MQI had 4.87% less FEV1 (β: -4.87, CI 95%; −7.58 to −2.17, $p < 0.001$) and 3.53% less FVC (β: -3.53, CI 95%; −6.45 to −0.62, $p < 0.018$) than those with high-MQI, adjusted for confounding variables. Various researchers have demonstrated a negative association between low muscle mass, impaired in muscular performance and low muscle strength, or sarcopenia, with FEV1 and FVC [39–41]. van Gassel et al. observed that 3 months after hospital

Table 1 Demographic and clinical characteristics in Post-COVID-19 patients

	All ***n*** **= 748**	**Low-MQI** ***n*** **= 375**	**High-MQI** ***n*** **= 373**	**p-value**
Age, years	54.61 ± 0.44	58.01 ± 0.60	51.26 ± 0.61	< 0.001
Male, n (%)	478 (63.90)	238 (63.47)	240 (64.34)	0.803
BMI, kg/m^2	30.39 ± 6.21	31.74 ± 7.25	29.04 ± 4.58	< 0.001
Comorbidities				
Diabetes, n(%)	260 (34.76)	142 (37.87)	118 (34.64)	0.074
Hypertension, n(%)	282 (37.70)	163 (43.47)	119 (31.90)	0.001
Obesity, n(%)	333 (44.52)	201 (53.60)	132 (35.39)	< 0.001
Ischemic cardiopathy, n(%)	54 (7.22)	33 (8.80)	21 (5.63)	0.094
Pulmonary disease, n(%)	119 (15.91)	65 (17.33)	54 (14.48)	0.286
Thyroid disease, n(%)	44 (5.88)	23 (6.13)	21 (5.63)	0.770
Hepatopathy, n(%)	19 (2.54)	12 (3.20)	7 (1.88)	0.250
HIV, n(%)	9 (1.20)	5 (1.33)	4 (1.07)	0.743
Asthma, n (%)	24 (3.21)	13 (3.49)	11 (2.93)	0.668
COPD, n (%)	13 (1.74)	9 (2.40)	4 (1.07)	0.165
Post-COVID symptoms				
Fatigue	40.11 (300)	44.53 (167)	35.66 (133)	0.013
Dyspnea	13.50 (101)	15.47 (58)	11.53 (43)	0.115
Anosmia	8.16 (61)	9.07 (34)	7.24 (27)	0.361
Muscular pain	37.30 (279)	38.67 (145)	35.9 (134)	0.438
Hospitalary parameters				
PaO2/FiO2	176.2 ± 91.2	170.20 ± 85.90	183.03 ± 96.69	0.180
Oxygen saturation, %	75.73 ± 16.09	73.87 ± 16.65	77.67 ± 15.29	0.012
VMI, n(%)	461 (61.96)	268 (71.66)	193 (52.16)	< 0.001
Duration VMI, d	16 [10–25]	18 [11–28]	15 [9–24]	0.043
Length of hospital stay, d	17 [10–29]	21 [12–35]	14 [9–23]	< 0.001

HIV Human immunodeficiency virus, *COPD* Chronic Obstructive Pulmonary Disease, *VMI* Ventilation Mechanical Invasive

Table 2 Pulmonary function according to muscle quality index

	All	Low MQI	High MQI	p-value
Spirometry				
Pre Bronchodilator				
FEV1, L	2.70 ± 0.02	2.50 ± 0.03	2.91 ± 0.03	< 0.001
FEV1, %	92.25 ± 0.66	90.15 ± 0.99	94.35 ± 0.86	< 0.001
FVC, L	3.34 ± 0.35	3.08 ± 0.04	3.60 ± 0.05	< 0.001
FVC, %	88.08 ± 18.14	85.94 ± 20.04	90.37 ± 15.76	< 0.001
MEF 25–75, %	3.18 ± 0.04	3.01 ± 0.06	3.36 ± 0.06	< 0.001
PEFR, L	8.74 ± 0.09	8.13 ± 0.13	9.35 ± 0.13	< 0.001
FEV1/FVC	2.75 ± 0.02	2.55 ± 0.03	2.96 ± 0.03	< 0.001
Post Bronchodilator				
FEV1, L	2.75 ± 0.02	2.55 ± 0.03	2.96 ± 0.03	< 0.001
FEV1, %	94.13 ± 18.02	92.12 ± 19.07	93.06 ± 16.6	< 0.001
FVC, L	3.33 ± 0.03	3.09 ± 0.04	3.58 ± 0.04	< 0.001
FVC, %	87.73 ± 0.68	85.80 ± 1.06	89.69 ± 0.84	0.004
MEF 25–75, %	3.49 ± 0.05	3.31 ± 0.07	3.68 ± 0.07	0.000
PEFR, L	8.93 ± 0.10	8.34 ± 0.14	9.52 ± 0.14	< 0.001
FEV1/FVC	0.83 ± 0.00	0.82 ± 0.00	0.83 ± 0.00	0.867
Other pulmonary test				
DLCO, %	72.20 ± 22.97	68.49 ± 23.46	75.98 ± 21.85	< 0.001
MIP, CmH_2O	94.95 ± 1.03	89.75 ± 1.44	99.71 ± 1.41	< 0.001
MEP, CmH_2O	117.85 ± 1.38	111.27 ± 1.84	124.44 ± 20.13	< 0.001

*FEV*1 Forced Expiratory Volume in One second, *FVC* Forced Vital Capacity, *MEF* Maximum Expiratory Flow between 25 and 75%, *PEFR* Peak Expiratory Flow Rate, *DLCO* Carbon monoxide diffusing capacity, *MIP* Maximal Inspiratory Pressures, *MEP* Maximal Expiratory Pressure

discharge in post-COVID-19 subjects requiring IVM, those subjects with decreased physical function had lower FEV1 and DLCO [42].

In the general population, both the BMI and central obesity have exhibited an inverse relationship with FEV1% and FVC% [43, 44].

Research indicates an inverse association between BMI and both FEV1 and FVC [6, 8, 45]. This is attributed to the detrimental impact of excess adiposity, particularly centralized fat, on pulmonary function. Studies by Kwack and Cols demonstrated significant associations between subcutaneous thoracic fat, intra-thoracic fat, subcutaneous abdominal fat, and lower FEV1 and FVC [46]. The presence of excessive adipose tissue, particularly around the chest and abdomen, has been linked to worse lung function, likely due to difficulties in respiratory mechanics. The latter results from restrictions on lung expansion and increased resistance to diaphragmatic contraction during respiration, consequently causing reduced lung volume [45, 46].

Nonetheless, Koo et al. demonstrated that COPD patients with sarcopenic obesity exhibited poorer lung function compared to individuals without sarcopenia or obesity [47]. Moreover, those with sarcopenic obesity presented elevated levels of C-reactive protein, IL-6, and reduced exercise tolerance [48]. Additionally, sarcopenic obesity is linked to an increased risk of restrictive lung disease among the elderly [49].

As previously stated, a series of interconnected mechanisms between low muscle mass and strength and excess adipose tissue lead to alterations in the catabolism and anabolism of proteins and glycogen, as well as energy utilization [13, 50]. Additionally, mitochondrial dysfunction, diminishing muscle fiber number, decreased capillary density, increased oxidative stress, and inflammation occur along with adipose tissue infiltration. Such events promote myofibril atrophy and loss of muscle function both in peripheral muscles and those responsible for respiration, such as the diaphragm and intercostal muscles [13–16, 51].

Low muscle mass/strength and an excess of adipose tissue independently impair lung function [24, 40, 44]. Moreover, they possess synergistic mechanisms that result in a vicious cycle [47, 48].

The MQI is an emerging indicator of health and physical function [28] that represents a valuable tool for clinical practice, as it is a low-cost and easy tool to assess skeletal muscle quality, taking into account the important relationship between muscle strength and adipose tissue, which and predicting lung function, respiratory muscle

Table 3 Association between low muscle quality index and pulmonary function

	Crude Model			Adjusted Model		
	β	CI (95%)	p-value	β	CI (95%)	p-value
Pre Bronchodilator						
FEV1, L	−0.40	−0.51 to −0.30	< 0.001	−0.25	−0.34 to −0.16	< 0.001
FEV1, %	−4.20	−6.80 to −1.60	0.002	−4.87	−7.58 to −2.17	< 0.001
FVC, L	−0.52	−0.65 to −0.38	< 0.001	−0.31	−0.44 to −0.19	< 0.001
FVC, %	−4.42	−7.19 to −1.65	0.002	−3.53	−6.45 to −0.62	0.018
MEF 25–75, %	−0.35	−0.52 to −0.17	< 0.001	−0.25	−0.42 to −0.08	0.003
PEFR, L	−1.22	−1.59 to −0.85	< 0.001	−0.79	−1.15 to −0.43	< 0.001
FEV1/FVC	0.00	−0.00 to 0.01	0.900	−0.00	−0.01 to 0.00	0.585
Post Bronchodilator						
FEV, L	−0.40	−0.51 to −0.29	< 0.001	−0.24	−0.34 to −0.15	< 0.001
FEV1, %	−3.93	−6.59 to −1.27	0.004	−4.45	−7.21 to −1.68	0.002
FVC, L	−0.49	−0.62 to −0.36	< 0.001	−0.29	−0.42 to −0.17	< 0.001
FVC, %	−3.89	−6.56 to −1.22	0.004	−2.89	−5.68 to −0.11	0.041
MEF 25–75, %	−0.37	−0.57 to −0.17	< 0.001	−0.28	−0.47 to −0.09	0.003
PEFR, L	−1.17	−1.57 to −0.78	< 0.001	−0.74	−1.13 to −0.35	< 0.001
FEV1/FVC	−0.00	−0.00 to 0.00	0.868	−0.00	−0.01 to 0.00	0.561
Other pulmonary test						
DLCO, %	26.64	−41.18 to 94.47	0.441	51.05	−20.21 to 122.32	0.160
MIP, CmH_2O	−9.95	−13.94 to −5.97	< 0.001	−5.84	−9.83 to −1.84	0.004
MEP, CmH_2O	−13.17	−18.53 to −7.80	< 0.001	−8.14	−13.57 to −2.71	0.003

*FEV*1 Forced Expiratory Volume in One second, *FVC* Forced Vital Capacity, *MEF* Maximum Expiratory Flow between 25 and 75%, *PEFR* Peak Expiratory Flow Rate, *DLCO* Maximum Diffusing Capacity of the Lung, *MIP* Maximal Inspiratory Pressures, *MEP* maximal Expiratory Pressure. Adjusted model by age, sex, diabetes, hypertension, ischaemic cardiopathy, and invasive mechanical ventilation

strength in post-COVID-19 subjects. The assessment of MQI allows the identification of subjects at risk for opportune therapeutic management.

In terms of respiratory muscle functionality, in post-COVID-19 subjects who were hospitalized for severe COVID-19 infection, after resolution of the active infection, there was a lower thickening ratio between diaphragm thickness at end-inspiration/end-expiration compared with non-COVID subjects [52]. Inspiratory muscle functions can be assessed by MIP, while expiratory muscle strength is evaluated through MEP or PEFR.

Our study demonstrated a negative association between low-MQI and respiratory muscle strength, as evaluated by PEF, MIP, and MEP. Participants with low-MQI exhibited a 0.74 L lower PEFR than those with High-MQI (β: -0.79, CI 95%; −1.15 to −0.43, $p < 0.001$). PEFR is associated with respiratory muscle strength, low skeletal muscle mass, and sarcopenia [21, 53, 54] Kera and Cols. employed PEFR to define respiratory sarcopenia [54]. The PEFR was found to be associated with the 5-year mortality rate in an older population [55]. Additionally, we observed that individuals with low-MQI exhibited 8.14 cmH2O lower MEP (β: - 8.14, CI 95%; −13.57 to −2.71, $p = 0.003$) and 5.84 cmH2O less MIP (β: - 5.84, CI 95%; −9.83 to −1.84, $p = 0.004$) than those with High-MQI. MEP evaluates the strength of abdominal and intercostal muscles, while MIP measures the diaphragm's strength—the most crucial muscle for respiration [56] Various studies have demonstrated a positive association between HGS and respiratory muscle strength; Shin and Cols showed that in adults over 60 years of age, for each kilogram of HGS, MIP increased by 1.96 cmH2O and MEP by 1.10 cmH2O [56]. Moreover, it has been noted that protein synthesis deterioration and mitochondrial degradation are more prominent in sarcopenic obesity than in sarcopenia or obesity alone [51].

Strengths and limitations

This study possesses inherent limitations due to its cross-sectional design, such as not being able to determine causality between variables. In addition, we do not know the subjects' lung function and muscle quality before COVID-19 infection. Another significant limitation is that as this is the first study to evaluate the association between MQI and lung function in the post-COVID syndrome population, it is impossible to contrast our results in other post-COVID syndrome populations. Nonetheless, the study's strengths include

a large sample size to provide sufficient statistical power for conducting multiple linear regression analyses and adjusting for confounding variables.

Conclusions

The low-MQI serves as an independent predictor linked to pulmonary function parameters among individuals experiencing post-COVID-19 syndrome. The MQI could function as an indicator that determines the requirement for muscle training within pulmonary rehabilitation programs.

Abbreviations

BMI	Body mass index
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
DLCO	Carbon monoxide diffusing capacity
HSG	Handgrip strength
MEP	Maximal expiratory pressure
MEF 25–75	Maximum expiratory flow between 25 and 75%
MIP	Maximal inspiratory pressures
MQI	Muscle quality index
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SMI	Skeletal muscle mass index

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To LGA.

Authors' contributions

Conceptualization: G-I D., F-C L., and O-T A.; Data curation: H-L N., S-S R., and G-H JC; Formal analysis; G-I D., and F-C L.; Investigation; O-T A., R-H R., and V-M MI.; Resources: G-A S., and S-S R.; Methodology: G-I D., F-C L., O-T A., and H-L N.; Project administration: R-H R., V-M MI, and C-M A.; Supervision; R-H R., G-A S., G-HJC., and C-M A.; Roles/Writing: original draft; G-I D., F-C L., O-T A., R-H R., G-Ar S., H-L N., S-S R., G-H JC., G-H JC., V-M MI, and C-M A.; Writing: review and editing; G-I D., F-C L.,O-T A., R-H R., G-A S., H-L N., S-S R., V-M MI, G-H JC., and C-M A.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the fact that individual privacy could be compromised but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics and Research Committee for Biomedical Research in Humans at the Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas" (approval number C57–21). All participants provided informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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