Efficacy of Inspiratory Muscle Training on Respiratory Muscle Strength in Hematopoietic Stem Cell Recipients: A Systematic Review and Meta-analysis

Larissa Melo Sampaio, PT[1]*; Helen Kerlen Bastos Fuzari, PT, PhD*[2]

[1]Physiotherapist, Specialist in Oncology, Hospital Instituto Nacional de Cancer (INCA), Rio de Janeiro, Brazil; and
[2]Physiotherapist, Master and PhD in Physiotherapy, Physiotherapist at the Hospital Instituto Nacional de Cancer (INCA), Rio de Janeiro, Brazil.

Objective: To investigate whether inspiratory muscle training improves respiratory muscle strength and function and reduces dyspnea and fatigue in hematopoietic stem cell recipients. **Design:** A systematic review and meta-analysis of randomized controlled trials. **Participants:** People with hematological neoplasms who underwent hematopoietic stem cell transplantation. **Intervention:** Inspiratory muscle training with POWER breath Plus, POWERbreathe, Classic, and Threshold devices, with a load of 40% of the maximum inspiratory pressure. **Outcome Measures:** The primary outcomes were maximal inspiratory pressure, maximal expiratory pressure, forced expiratory volume in the first second of expiration (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio. Secondary outcomes were dyspnea, fatigue, respiratory rate, peripheral O_2 saturation, quality of life, and functional capacity. **Results:** The search identified 3 eligible studies with a sample of 108 participants. Maximal inspiratory pressure was higher in the intervention group in the 3 studies reviewed, with an average difference of −9.3 cm H_2O, −31.94 cm H_2O, and −16 cm H_2O in relation to the control group after inspiratory muscle training. One study found an improvement in the distance covered in the 6-minute walk test (34.22 m) and in the distance covered in the modified incremental shuttle walking test (66.43 m) in the intervention group. **Limitation:** This systematic review includes only 3 randomized controlled clinical trials. **Conclusion:** Inspiratory muscle training is effective in increasing inspiratory muscle strength and functional capacity in bone marrow transplant recipients. However, its effects on fatigue and dyspnea

Rehabilitation Oncology

POWER breath Plus: Provides a variable level of load setting (weight lifted) in increments of 16/17cmH2O, from 23cmH2O to 186cmH2O; POWERbreathe Classic: Provides a level of load setting (weight lifted) in increments of 10cmH2O, from 10cmH2O to 90cmH2O; and Threshold: One-way valve independent of flow, easy to set and dependent pressure (2 cm increments of H2O).

This was a systematic review study, so no ethics committee approval was required, just a PROSPERO registration (PROSPERO registration no. CRD 42020206178). All participants gave written informed consent before data collection began.

The authors declare no conflicts of interest.

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Correspondence: *Larissa Melo Sampaio, PT, PhD, Cancer Hospital I, National Cancer Institute, Praça Cruz Vermelha, 23, Centro, Rio de Janeiro, RJ, 20230-130, Brazil (larissamelosampaio97@gmail.com).*

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remain uncertain. **(Rehab Oncol 2022;40:96–104)** *Key words: bone marrow transplant, breathing exercises, hematological neoplasms, hematopoietic stem cell transplantation, inspiratory muscle training, maximum respiratory pressures, specialty in physiotherapy*

Hematological neoplasms predominantly affect adults between 18 and 65 years of age and have an insidious onset. The most prevalent are leukemias (lymphoid and myeloid, acute and chronic), lymphomas (Hodgkin's and non-Hodgkin's), and myelomas.[1] Although they are different, their clinical manifestations are similar: anemia, thrombocytopenia, neutropenia, fatigue, anorexia, hemorrhage, dyspnea, fever, and recurrent infections.[2]

Cancer treatments for these types of neoplasms are chemotherapy, radiotherapy, and immunotherapy. Chemotherapy may or may not be combined with radiation therapy. Both are designed to destroy malignant cells and restore normal bone marrow function.[3] Immunotherapy stimulates the immune system to act against cancer cells with a series of techniques such as CART (chimeric antigen receptor) cells.[4]

However, bone marrow transplantation (BMT) is indicated[5] when chemotherapy and radiotherapy fail to induce complete remission of the disease and there is a high risk of recurrence. Bone marrow transplantation is a procedure in which hematopoietic cells are infused into the recipient via venous access, similar to a blood transfusion process that lasts from 1 to 6 hours. Prior to marrow infusion, the patient undergoes the conditioning regimen (destruction of blood cells through chemotherapy and total body irradiation, which is called aplasia generated by the conditioning regimen). The objective is to replace diseased hematopoiesis with healthy cells from the donor.[5]

A study of patients who developed hematologic malignancies showed that they had reduced cardiovascular fitness, as measured by cardiopulmonary exercise testing with a measure of peak oxygen consumption (peak $\dot{V}O_2$) and a 6-minute walk test (6MWT), and increased fatigue, as measured by a simple numerical rating from 0 to 10.[6] Physical inactivity resulting from pretransplant isolation and during hospitalization, chemotherapy, and corticosteroids in high doses and total body irradiation causes muscle damage,[7,8] which impacts on muscle strength and cardiorespiratory conditioning. Physical and cardiorespiratory deconditioning increase fatigue and make it more difficult to perform activities of daily living.[8]

On the other hand, randomized controlled clinical trials with transplant patients have shown that an exercise program can be beneficial in this population. A study from Denmark[9] evaluated the effects of a multimodal exercise program (aerobic exercises, such as cycling, resistance, and stretching) and psychoeducation in patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) compared with a control group, which underwent standard physical therapy. They assessed the severity of symptoms divided into 5 groups: mucositis, cognitive, gastrointestinal, affective, and functional using the Stem Cell Transplant Symptom Assessment Scale, elaborated by the authors. The intervention group had lower scores after the intervention in all groups, with statistical significance, except for affective symptoms.

In another study,[10] the authors assessed muscle strength using the Chatillon Inc extensometer dynamometer in participants before transplantation, after marrow infusion, and 6 weeks after infusion. After marrow infusion, they were divided into 2 groups, an intervention group and a control group. The intervention group performed an active exercise program, muscle stretching, and treadmill walking. The intervention group showed increased muscle strength in most muscle groups compared with the control group.

Inspiratory muscle training (IMT) increases the muscle strength of the inspiratory muscles, which facilitates alveolar ventilation and, consequently, increases exercise tolerance and improves the performance of activities of daily living.[11]

There is evidence in the literature[10] about the effectiveness of aerobic and strength exercises in transplant patients; however, there are still no systematic reviews on the effectiveness of IMT in adults who underwent hematopoietic stem cell transplantation, although randomized clinical trials already exist.[12-14] This study aims to investigate the effectiveness of IMT in increasing inspiratory muscle strength and reducing fatigue and dyspnea in adults with hematologic malignancies undergoing BMT. This systematic review is registered in PROSPERO under registration number CRD42020206178.

METHODS

Search Strategy and Study Selection

Searches for randomized clinical trials were performed in the PubMed, LILACS, SciELO, PEDro, Scopus, Web of Science, and CINAHL databases, and in the IBICT (database of theses and dissertations) in the period between September 1 and October 14, 2020. The terms "Hematopoietic Stem Cell Transplantation," "Inspiratory muscle training," "Breathing exercises," "Bone Marrow Transplantation," "Respiratory muscle training," and "Clinical Trials" were used to identify studies. The search is in accordance with Supplemental Digital Content Appendix 1, available at: http://links.lww.com/REHABONC/A31. No date or language restrictions were applied. A search was also carried out in the references of the selected articles.

The articles were analyzed by title and abstract by 2 independent reviewers and a third reviewer was asked to make a decision in case of disagreement. The articles selected by title and abstract were read in full, and studies that met the inclusion criteria were searched in their references. Contacts were made with authors to obtain

additional data through email, and 2[12,14] responded with some additional data.

Inclusion Criteria

Only randomized controlled clinical trials that included adult volunteers between 18 and 65 years of age with hematologic neoplasms who received hematopoietic stem cell transplantation and underwent IMT were included. Among the selected studies, 2 of them were carried out in Brazil (1 in the state of São Paulo,[14] the other in the state of Minas Gerais,[12] and 1 in Turkey, province of Ankara.[13]

Exclusion Criteria

Studies on a pediatric population that are not randomized controlled trials (cohort, observational, etc) or whose study population did not undergo IMT with hematopoietic stem cell transplantation were excluded.

Intervention

The intervention analyzed in this review was the IMT with a linear load device, as it is easy to apply in clinical practice, inexpensive, and has evidence of its effectiveness in increasing inspiratory muscle strength in other pathologies, such as chronic obstructive pulmonary disease.[11] The load value and the training duration were extracted.

Outcomes Measured

In all 3 studies, outcomes were measured by physical therapists. The primary outcomes of this review were respiratory muscle strength by the maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) variables measured using manovacuometry, and lung function measured using the variables of forced expiratory volume in the first second of expiration (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio as measured by spirometry in liters.

The secondary outcomes measured were respiratory rate (Rr), peripheral oxygen saturation (SPO_2), fatigue assessed using the Modified Fatigue Impact Scale, dyspnea measured using the Medical Research Council questionnaire, and quality of life assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) questionnaire.

Study Quality Evaluation

The study quality evidence was measured by the GRADE[15] tool, which assesses the following criteria: study limitations, inconsistencies, existence of direct evidence, and imprecision. Based on these criteria, the evidence level can be classified as high, moderate, low, or very low.

Risk of Bias

The risk of bias was analyzed according to the Cochrane document "Cochrane risk of bias,"[16] which lists 6 analysis criteria: generation of the allocation sequence, allocation secrecy, blinding of participants and professionals, blinding of the outcome evaluators, if there were incomplete data on the outcome, and the presence or absence of a selective outcome. The risk of bias was considered high if there were any flaws in the methodological process, low if the methodology was well described and adequate, and uncertain if details were missing in the description.

Data Analysis

The data were extracted using a standard form, according to Table 1. The continuous variables of the outcomes were analyzed using the mean difference within a 95% confidence interval. Data from 2[12,13] similar studies were analyzed using meta-analysis for the MIP outcome, which was constructed using the Review Manager 5.4 software program.[17] The heterogeneity tests (*P* value), Higgins and Thompson I^2, and the "overall effect" test were calculated by the same software.

RESULTS

Identification and Selection of the Results

A total of 25 808 results were found, 19 of which were duplicates. Next, 25 786 were excluded by title and abstract as they did not meet the inclusion and exclusion criteria. Thus, 3 studies[12-14] were selected, read in full, and included in this systematic review. Figure 1 shows the selection steps according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[18] flowchart.

Characteristics of the Included Studies

The included studies[12-14] had a number of participants between 31 and 39, totaling 108. The age in the 2 studies[12,13] ranged from 18 to 65 years, and between 18 and 60 years of age in the other study.[14] All underwent hematopoietic stem cell transplantation as a treatment for hematological neoplasms.

The 3 studies[12-14] had IMT intervention with a linear load device—POWER breath and Threshold.[12-14] Aerobic, strength, and breathing exercises were applied in the control groups, in addition to IMT with minimum load. Table 1 presents the characteristics of the included studies.

Intervention

The 3 studies[12-14] used an IMT intervention with a linear load device and 40% of the MIP was applied as resistance, calculated by means of a manovacuometer. Participants in a study in Brazil[12] used the POWERbreathe Plus (IMT Technologies Ltd., Birmingham, UK) device with 12 to 16 diaphragmatic breaths per minute for 10 to 20 min/d, 5 d/wk. The participants in a 2016

TABLE 1

Summary of Included Studies

Study	Design	Participants	Intervention	Outcome Measures
Almeida et al[12] (2020)	RCT	n = 31 Age = 18-65 y Gender = 18 M, 13 F	Exp = Conventional rehabilitation: mobilization (stretching, strengthening, balance, and coordination + breathing exercises + moderate-intensity aerobic exercises, 10-20 min, 5 times a week, 50%-70% of HR_{max}) + inspiratory muscle training: 12-16 breaths diaphragms per minute at 40% of the maximum inspiratory pressure (MIP) for 10-20 min/d for 5 d/wk Con = Conventional rehabilitation	• IMT safety and viability • Respiratory muscle strength (MIP and MEP) • Lung function • Respiratory rate • Oxygen saturation and frequency of patients with oxygen desaturation • Bleeding, dyspnea, and acute lung edema
Barğı et al[13] (2016)	RCT	n = 38 Age = 18-65 y Gender = 24 M, 14 F	Exp = Diaphragmatic breathing, fractional inspiration, and exercises with the Respiron incentive spirometer (3 series of 10 repetitions), standard ventilation with short expiration (2 series of 5 repetitions), muscle strengthening with the Threshold device—40% of MIP (3 series of 15 repetitions, 3 times a day); Shaker exercises (3 sets of 15 repetitions); spontaneous cough at the end of the exercises. Con = IMT 5% MIP, 25-30 diaphragmatic breaths, 30 min/d, 7 d/wk, for 6 wk.	• Lung function • Respiratory muscle strength • Peripheral muscle forces (quadriceps femoral and handgrip strength) • Maximum exercise capacity (modified incremental MISWT test) • Submaximal exercise capacity 6MWT • Fatigue • Depression • Quality of life
BOM et al[14] (2012)	RCT	n = 39 Age = 18-60 y Gender = 20 M, 19 F	Exp = Diaphragmatic breathing, fractional inspiration, and exercises with the Respiron incentive spirometer (3 series of 10 repetitions), standard ventilation with short expiration (2 series of 5 repetitions), muscle strengthening with the Threshold device—40% of MIP (3 series of 15 repetitions, 3 times a day); Shaker exercises (3 sets of 15 repetitions); spontaneous cough at the end of the exercises. Con = only exercises with the Respiron incentive spirometer (in 3 sets of 10 repetitions).	• Tidal volume • Minute volume • Respiratory muscle strength • Heart rate • Respiratory rate • Peripheral oxygen saturation

Abbreviations: Con, control group; Exp, experimental group; HRmax, maximal heart rate; IMT, inspiratory muscle training; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MISWT, modified incremental shuttle walking test; RCT, randomized controlled clinical trial; 6MWT, 6-minute walk test.

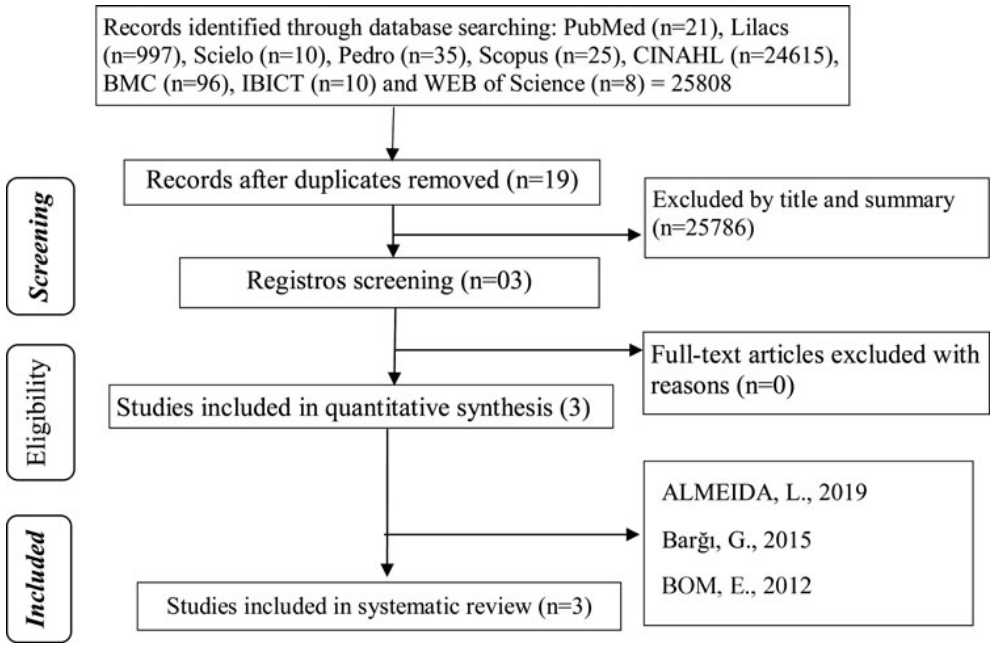

Fig. 1. Search and selection of studies for systematic review in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

study[13] also used POWERbreathe, but from the Classic line, 25 to 30 diaphragmatic breaths, 30 min/d, 7 d/wk, for 6 weeks. Finally, the Threshold device used in another study also carried out in Brazil,[14] with 3 series of 15 repetitions, 3 times a day, for 7 days. The sessions took place in the immediate period after hematopoietic stem cell transplantation.

The control group had different activities in each study. A 2012 study[14] chose to perform only exercises with an incentive spirometer, 3 sets of 10 repetitions; another study[13] had the same IMT regimen as the intervention group, except for the low resistance load (only 5% of the MIP). And finally, the control group in the study by Almeida et al[12] performed stretching, strengthening, balance and coordination exercises, breathing exercises, and aerobic exercises of moderate intensity, 50% to 70% of the maximum heart rate, 5 times a week, each session lasting from 10 to 20 minutes, as described in Table 1.

Outcome Measures

The 3 studies[12-14] had MIP and MEP as the outcome measures measured by a manovacuometer. Only 1 study[19] evaluated lung function by the FEV_1%, FVC%, FEV_1/FVC ratio, peak expiratory flow (PEF), and PEF from 25% to 75% variables by spirometry.[14] Two studies[13,14] evaluated Rr by observing respiratory incursions and SPO_2 through a pulse oximeter. Dyspnea was one of the outcomes evaluated in 2 studies[13,14] using the Medical Research Council Scale and through the reports of patients collected from medical records.

Functional capacity estimated by measuring submaximal exercise capacity and maximum exercise capacity was assessed in one study.[13] Submaximal exercise capacity was assessed by the 6MWT. In this test, the patient walks on a flat surface of 30 m in 6 minutes. The distance covered is measured and vital signs are monitored. The participants performed the test twice with an interval of 30 minutes, and the longest distance covered was recorded in meters and as the percentage of normal predicted values.[20] Maximum exercise capacity was assessed using the modified incremental shuttle walk test (MISWT), in which participants were instructed to ascend and descend at a distance of 10 m, increasing their gait speed every minute in 12 stages. The distance covered was also recorded in meters and as a percentage of the predicted normal values.[19]

Fatigue was measured in the same study[13] using the Fatigue Impact Scale, which ranges from 0 to 63 points[21] and quality of life using the EORTC QLQ Scale, divided into the Global Health Scale, Functional Scale, and Symptoms Scale.[22] Tidal volume was measured only in the 2012 study[21] with an Oxigel 953 ventilometer, and the minute volume was calculated by the product of tidal volume with Rr. Peripheral muscle strength was assessed only in one study,[13] in which muscle strength of the quadriceps femoris and handgrip strength were measured by a portable dynamometer (JTECH Commander; JTECH Medical, Midvale, Utah) on the nondominant side.[13] A single study[13] assessed the degree of depression among the participants using the Montgomery-Åsberg Depression Rating Scale.[23] It comprises 10 questions, each with a score ranging from 0 to 6. The higher the score, the greater the degree of depression. Table 2 shows the results of the outcomes found in the 3 selected studies.

Effects of IMT

Respiratory Muscle Strength. Respiratory muscle strength was assessed in the 3 studies.[12-14] The mean difference in MIP in the control and intervention groups after IMT between 2 studies[13,14] was −24.02 cm H_2O, with a 95% confidence interval. This can be seen in the forest plot, Figure 2 and in Table 3. The variables in the constructed meta-analysis are continuous: mean and standard deviation of MIP between the control and intervention groups after IMT. The measure of association between them was the mean difference. A random effects model was adopted. It is observed that the first study[12] had less weight because it was a smaller sample. In addition, the confidence interval crosses the null line, which means that there is no statistically significant difference between the groups. The second study[13] presented greater weight and high statistical significance in its results. The final result of the meta-analysis corroborates that IMT increases MIP in patients after undergoing hematopoietic stem cell transplantation with hematological neoplasms compared with the control group, which did not undergo IMT.

The Higgins and Thompson I^2 test was equal to 34% in the statistical tests of heterogeneity, which indicates low heterogeneity between the studies. Cochran's Q heterogeneity test ($P = .22$) shows the probability that the difference found between the studies is not due to chance. In others words, this means that a P value greater than .05 indicates low heterogeneity. In the test for overall effect ($P = .03$, well below 1), it means that the final result of the meta-analysis is statistically relevant. Another study[14] also found greater MIP in the group that underwent IMT, with a difference in the mean of −16 cm H_2O after the intervention ($P = .035$). In addition, the control group showed a reduction in MIP (−90 cm H_2O to −82 cm H_2O).

Regarding MEP, 2 studies[13,14] showed an increase in the intervention group after IMT: in 1 study[14] a difference of 20 cm H_2O was found between the 2 groups ($P = .033$), and in the other study,[13] an average difference of 14.35 cm H_2O ($P \leq .05$) was found. However, one study found no statistically significant difference between the intervention and control groups in relation to the MEP values ($P > .05$).[12]

Functional Capacity. Only one study[13] assessed functional capacity in which the treatment group showed better results on the 6MWT; they walked 44.53 m more on average than the control group, 34.22 m more than the distance covered in the initial assessment before the intervention was applied ($p < 0.001$), and an increase of 4.6% in the percentage of the distance covered as normal values—from 80.13% to 84.68% ($P < .001$).

TABLE 2

Results of Included Studies[a]

Outcome	Almeida et al[12] (2020)		Barğı et al[13] (2016)		Bom et al[14] (2012)	
	Sham	IMT	Sham	IMT	Sham	IMT
MIP MÁX (cm H_2O)	A = 100.6 (40.8)/D = 93.8 ± 42.8	A = 86.4 (34.9)/D = 103.1 (44.6)	A = 115.67 (28.91)/D = 120.61 (27.92)	A = 111.65 ± (27.31)/D = 152.55 (31.55)	A = −90/D = −82	A = −95/D = −98
MEP MÁX(cm H_2O)	A = 116.4 (40.3)/D = 109.0 (40.6)	A = 102.5 (37.5)/D = 102.2 (26.1)	A = 133.72 (27.35)/145.50 ± 33.13	A = 135.35 (38.34)/D = 159.85 (43.84)	A= 88/D = 79	A = 97/D = 99
Frequency of patients with dyspnea (%)	F = 25.0	F = 13.3	…	…	…	…
Frequency of patients with acute lung edema (%)	F = 6.20	F = 0	…	…	…	…
Frequency of patients with epistaxis (%)	F = 12.5	F = 6.6	…	…	…	…
Need for oxygen therapy (%)	F = 18.7	F = 6.6	…	…	…	…
FEV_1, %	…	…	A = 87.94 (18.86)/D = 88.06 (19.24)	A = 97.75 (18.53)/D = 96.50 (14.29)	…	…
FVC	…	…	A = 91.89 (14.88)/D = 93.17 (14.14)	A = 99.65 (16.04)/D = 100.40 (12.29)	…	…
FEV_1/FVC	…	…	A = 79.28 (9.48)/D = 78.39 (8.69)	A = 83.05 (8.71)/D = 81.90 (7.92)	…	…
PEF, %	…	…	A = 98.65 (17.77)/D = 100.15 (16.47)	A = 88.11 (21.76)/D = 92.56 (20.49)	…	…
6MWT, m	…	…	A = 574.89 (69.33)/D = 580.07 (67.44)	A = 590.61 (65.19)/D = 624.60 (71.84)	…	…
Δ HR, beats/min (after 6MWT)	…	…	50.83 ± 16.8752.61 ± 16.14	62.55 ± 13.8764.65 ± 17.34	…	…
Δ Modified Borg dyspnea (após o T C6')	…	…	A = 0.72 (1.23)/D = 1.36 (1.79)	A = 1.85 (1.69)/D = 1.48 (1.62)		
MISWT, m	…	…	A = 692.73 (151.53)/D = 697.27 ± 150.41	A = 751.11 (218.01)/D = 811.11 ± 198.25	…	…
Δ HR, beats/min (after o MISWT)	…	…	A = 84.80 (11.93)/D = 81.30 ± 15.19	A = 87.58 (19.11)/D = 91.95 (16.50)	…	…
Fatigue Impact Scale (0-63)	…	…	A = 38.94 (33.02)/D = 32.89 (25.16)	A = 35.30 (30.19)/D = 26.80 (32.86)	…	…
EORTC QLQ : Global health status (0-100)	…	…	A = 72.22 (16.67)/D = 77.32 (19.97)	A = 72.92 (23.24)/D = 82.08 (17.99)		
EORTC QLQ: Functional scale (0-100)	…	…	80.74 ± 14.5482.35 ± 9.23	80.67 ± 14.9485.89 ± 12.11		
EORTC QLQ: Symptom scale (0-100)	…	…	A = 20.79 (13.34)/D = 17.52 (9.92)	A = 14.49 (14.05)/D = 13.21 (9.68)		
Strength of quadriceps femoris	…	…	A = 314.72 (109.81)/D = 317.94 ± 97.21	266.40 ± 82.13295.05 ± 99.57		
Hand grip (L), N	…	…	A = 186.83 (53.19)/D =192.66 ± 58.43	A = 176.91 (66.33)/D = 186.49 (66.19)		
TV	…	…	…	…	A700/D = 740	A666/D = 633
MV	…	…	…	…	A14.5/D = 16.3	A15.06/D = 14.3
HR, bpm	…	…	…	…	A = 90/D = 93	A = 90/D = 96
F	A = 18.5 (4.5)/D = 20.0 (3.3)	A = 17.0 (3.7)/D = 16.7 (4.3)	…	…	A = 21/D = 22	A = 23/D = 22
SpO_2	A = 97.4 (1.9)/D = 97.5 ± 1.2	A = 97.4 (1.7)/D = 98.7 (1.6)	…	…	A = 98/D = 97	A = 97/D = 97

Abbreviations: A, average before intervention; D, average after intervention; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; F, frequency of patients with a certain characteristic as a percentage of the total number of participants; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; IMT, inspiratory muscle training; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MISWT, modified incremental shuttle walking test; MV, minute volume; PEF, peak expiratory flow; 6MWT, 6-minute walk test; TV, tidal volume.
[a]Values within parentheses indicate standard deviation. Ellipses indicate without registration in the article.

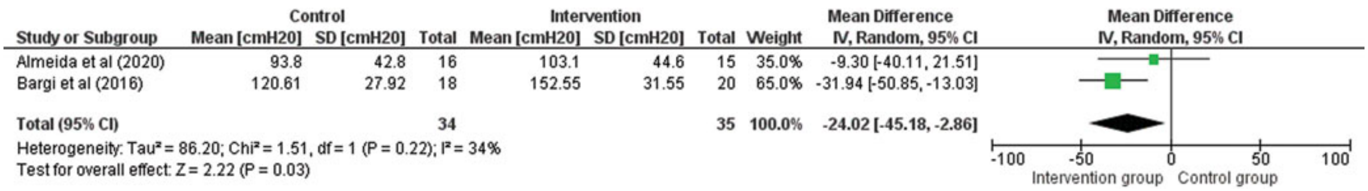

Fig. 2. Mean difference (95% CI) in maximum inspiratory pressure after inspiratory muscle training in 2 studies (n = 69). CI indicates confidence interval; mean difference IV, weighted average difference. This figure is available in color online (www.rehabonc.com).

The treatment group had an average of 113.84 more meters traveled on the MISWT compared with the control group after IMT and had an average gain of 62.46 m compared with the distance covered in the initial test ($P < .001$). The percentage of the predicted value in the treatment group had an average difference of 6.48%—from 69.95% to 76.40% ($P < .001$).

Lung Function. The study that evaluated lung function using spirometry[18] found no statistically significant differences in FEV_1%, FVC%, PEF, and PEF values from 25% to 75%. The FEV_1/FVC ratio decreased in the treatment group after IMT ($P = .051$) and in the control group ($P = .030$).

In the only study that assessed tidal volume,[14] a difference of 107 mL was observed in the mean tidal volume in the intervention group compared with the control group at the end of the study ($P = .004$). The intervention group had a 40-mL increase in tidal volume after IMT, while the control group had a 33-mL drop. The minute volume did not present a statistically significant difference between the groups.

Quality of Life. The study that assessed quality of life[13] found no statistically significant difference in the EORTC QLQ questionnaire scores, or in the Global health status, functional, and symptom subscales ($P > .05$).

Fatigue. In the only study in which fatigue was measured,[13] there was no statistically significant difference between the 2 groups after the intervention ($P > .05$). However, there was an average reduction of 8.98 in the fatigue scores within the intervention group, as assessed by the Fatigue Impact Scale ($P = .041$).

Dyspnea. Two studies[12,13] evaluated dyspnea. In one of them,[12] the frequency of dyspnea among the participants after the intervention was 25% in the control group and 13% in the intervention group but without statistical significance ($P = .41$). Another study[13] assessed the degree of dyspnea using the MMRC scale, which ranges from 0 to 4, in which no statistical difference was found between the groups ($P = .041$), but there was a significant reduction within the intervention group (−0.29, $P = .021$).

Respiratory Signs and Symptoms. The mean Rr of the participants before and after the IMT was reported in 2 studies[12,14] with no statistical difference between the groups ($P = .35$ and $P = .46$, respectively). In addition, the SPO_2 also did not present statistical significance ($P = .07$ and $P = .79$, respectively). Heart rate was compared between groups in one study[14] before and after IMT, also without statistical significance ($P = .38$).

The need for oxygen therapy, the presence of epistaxis, and acute lung edema between the groups were reported in one study[13] during the follow-up period. There was a higher prevalence of negative symptoms for the control group but also without statistical significance: 18.7% against 6.6% of participants who needed oxygen therapy ($P = .31$), 12.5% versus 6.6% had epistaxis ($P = .58$), and 6.2% versus 0% had acute lung edema ($P = .51$).

Peripheral Muscle Strength. Peripheral muscle strength was assessed in one study.[13] There was no difference in the muscle strength of the quadriceps femoris and in the handgrip strength between the intervention group and the control group ($P = .461$ and $P = .639$).

Depression. The difference in the scores of the Montgomery-Åsberg Depression Rating Scale[13] questionnaire came close to statistical significance ($P = .057$) in favor of the treatment group, and this had a reduction of 3.45 points in the scores after the IMT ($P < .001$).

Grade Analysis

The MIP results were evaluated for the evidence degree quality according to the GRADE tool. The evidence quality found was high, as shown in Figure 3.

TABLE 3

Results of the Meta-analysis Between 2 Studies: Mean Difference in Maximum Inspiratory Pressure After Inspiratory Muscle Training[a]

Study	Control Mean ($cm H_2O$)	Control SD ($cm H_2O$)	Control Total Sample	IMT Mean ($cm H_2O$)	IMT SD ($cm H_2O$)	IMT Total Sample	Weight (%)	IV, Random, 95% CI
Almeida et al[12] (2020)	93.8	42.8	16	103.1	44.6	15	35.0	− 9.30 (−40.11 to 21.51)
Barği et al[13] (2016)	120.61	27.92	18	152.55	31.55	20	65.0	− 31.94 (50.85 to −13.03)
Total			34			35	100	− 24.02 (45.18 to −2.86)

Abbreviations: CI, confidence interval; IMT, inspiratory muscle training; IV, weighted average difference.
[a]Heterogeneity: Tau^2: 86.20; $df = 1$ ($P = .22$); $I^2 = 34\%$. Test for overall effect: $Z = 2.22$ ($P = .03$).

Quality assessment							Participants		Effect	Quality	Importance
Studies (n)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IMT (n)	Con (n)	Absolute effect (95% CI)		
IMT (2)	RCT	Not serious	Not serious	Not serious	Not serious	None	34	35	AD 24,02 cmH2O maior	High ⊕⊕⊕⊕	Important

Fig. 3. Quality of evidence using the GRADE approach (inspiratory muscle training vs control/sham). AD indicates average difference; CI, confidence interval; Con, no intervention; IMT, inspiratory muscle training; RCT, randomized controlled clinical trial.

Risk of Bias

The studies[12-14] rarely showed methodological flaws. The 3 studies were randomized with a control group and only 1 study[14] did not describe how the allocation secrecy was done. Participants were not blinded in any of the studies, and the evaluators were blinded in only 1 study,[13] configuring a high risk of bias. Regarding the presence of incomplete data, 2 of the studies[12,13] presented a risk of uncertain bias because the variation in the outcome values (the lowest and highest values) was not demonstrated, only the mean.

DISCUSSION

This review aimed to determine whether IMT is effective for increasing inspiratory muscle strength, improving respiratory function, and reducing dyspnea and fatigue in patients with HSCT. However, the studies included in this review varied widely in terms of the assessed outcomes. Dyspnea was assessed by 2 studies[12,13] and fatigue by only 1 study.[13]

Only inspiratory muscle strength was unanimous: the 3 studies[12-14] all evaluated MIP and MEP. There was also agreement regarding the IMT load when the same load was used, which corroborates more with the similar results found in relation to the increase in MIP in the intervention group. The randomized controlled clinical trials included in this review had good methodological quality, except for the blinding of the evaluators, which did not occur in 2 studies.[12-14] The studies reviewed herein generally have a high degree of evidence and a low risk of bias.

Functional capacity is a very important outcome that directly interferes with the quality of life of patients with hematological neoplasms undergoing BMT.[24] It was found that a group of patients in an observational study receiving HSCT who had their functional capacity increased after aerobic and strength exercises also improved their quality of life.[24] However, there is still insufficient evidence to state that IMT also has this effect. This was only evaluated in one study[13] with the 6MWT and the MISWT test.

Because of the high degree of heterogeneity between the studies, it was possible to perform a meta-analysis of 2 studies[12,14] with IMT with the same load, similar duration and with higher methodological quality, and with the analyzed outcome being MIP as it was analyzed in both studies,[12,14] in addition to being a critical outcome. In this meta-analysis, it was found that IMT increased MIP in patients with hematological malignancies who are HSCT recipients, providing evidence of a high degree and low heterogeneity (Figure 3).

Fatigue is a common symptom in patients receiving HSCT, which reduces quality of life.[6,25,26] There is evidence that aerobic and strength exercises can reduce fatigue in transplant recipients.[24] It is not possible to conclude through this review whether IMT brings any direct benefit to reducing fatigue in this population, since only 1 study investigated the effects of IMT on fatigue.[13] The same can be said for dyspnea, which was evaluated only in 2 studies[12,13] and its results are not statistically significant ($P > .05$). Even more uncertain is the effect of IMT on quality of life. The assessment of quality of life was carried out only in 1 study,[12] which found no difference.

The limitations of the studies include the absence of blinding the participants and evaluators of the outcomes, which characterizes a high risk of bias and the absence of some data in the studies, only presenting the average of the outcomes. This gap was not remedied even by contacting the authors by email.

Inspiratory muscle training is effective in increasing MIP in HSCT recipients, with high-quality evidence. However, it is unclear what the effect of this result will be on patients' lives, as it is not proven whether dyspnea and fatigue are reduced, nor whether there is an improvement in quality of life. More randomized clinical trials are needed to clarify these points.

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