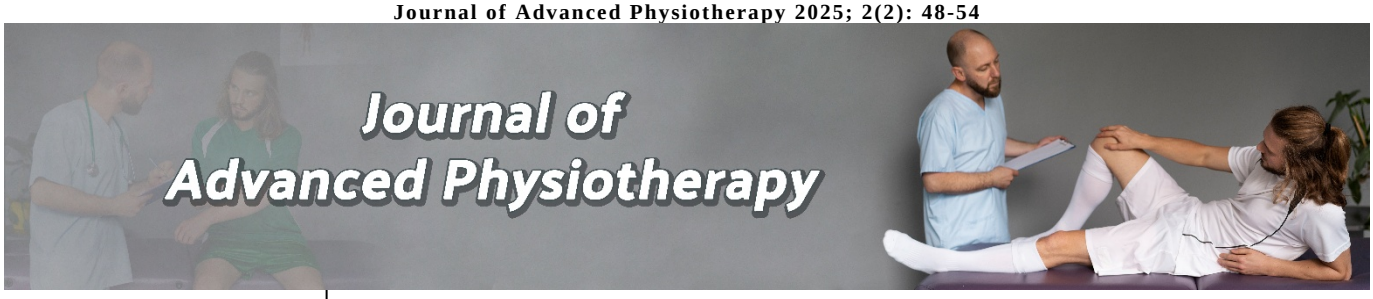

P-ISSN: 3081-0604
E-ISSN: 3081-0612
JAP 2025; 2(2): 48-54
www.physiotherapyjournal.org
Received: 05-08-2025
Accepted: 08-09-2025

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Pulmonary rehabilitation with inspiratory muscle training in patients with moderate-to-severe COPD: A multi-center randomized study

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DOI: https://www.doi.org/

Abstract
Background: Pulmonary rehabilitation (PR) is a core component of chronic obstructive pulmonary disease (COPD) management, yet many patients with moderate-to-severe disease remain limited by dyspnea and reduced exercise capacity, especially when inspiratory muscle weakness is present. Inspiratory muscle training (IMT) may enhance the benefits of PR, but its incremental value in multi-center, real-world programs remains uncertain.
Methods: In this multi-center, parallel-group randomized controlled trial, 120 adults with moderate-to-severe COPD and documented inspiratory muscle weakness were allocated to guideline-based PR plus high-intensity, threshold-loaded IMT (PR+IMT; n=60) or PR alone with sham IMT load (n=60). All participants completed an 8-week outpatient PR program comprising supervised endurance and resistance training, breathing retraining and education, with follow-up to 6 months. The primary outcome was change in 6-minute walk distance (6MWD) at 8 weeks. Secondary outcomes included maximal inspiratory pressure (MIP), dyspnea (Borg scale), health-related quality of life (St George's Respiratory Questionnaire, SGRQ), incremental shuttle walk test (ISWT), lung function and exacerbation frequency. Analyses followed the intention-to-treat principle using mixed-effects models with random intercepts for center.
Results: Baseline characteristics were similar between groups. At 8 weeks, both groups improved significantly in 6MWD, but gains were greater with PR+IMT (mean change 58 m vs 32 m). The adjusted between-group difference in 6MWD was 26 m (95% CI 9-43; p=0.003), exceeding accepted minimal clinically important differences. MIP increased more in PR+IMT than PR alone (between-group difference 12.9 cmH_2O; $p<0.001$), accompanied by larger reductions in exertional dyspnea (Borg −0.5 units; p=0.01) and SGRQ total score (−3.9 points; p=0.04). A higher proportion of PR+IMT participants met dual responder criteria for 6MWD and SGRQ (56.7% vs 38.3%; p=0.03). Over 6 months, mean exacerbations per patient were lower in the PR+IMT group (0.70 vs 1.03; p=0.04), although hospitalization differences did not reach statistical significance. Lung function changes were small and similar between groups.
Conclusions: In patients with moderate-to-severe COPD and inspiratory muscle weakness, integrating high-intensity IMT into standardized PR produces additional, clinically important improvements in exercise capacity, inspiratory muscle strength, dyspnea and health-related quality of life, and may reduce subsequent exacerbation burden. These findings support routine assessment of inspiratory muscle strength and incorporation of structured IMT as a targeted adjunct within contemporary PR programs.

Keywords: Chronic obstructive pulmonary disease, pulmonary rehabilitation, inspiratory muscle training, exercise capacity, dyspnea, health-related quality of life, exacerbations, randomized controlled trial

Introduction
Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and is projected to affect nearly 600 million people by 2050, with a disproportionate burden in low- and middle-income countries and among women [1, 2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) emphasizes that COPD is a preventable and treatable disease characterized by persistent airflow limitation and chronic respiratory symptoms, requiring a comprehensive management approach that integrates pharmacologic therapy with non-pharmacologic strategies such as pulmonary rehabilitation

(PR) [3]. Contemporary guidelines identify PR as a cornerstone of COPD care, demonstrating consistent benefits in dyspnea, exercise capacity, health-related quality of life (HRQoL), and reduced healthcare utilization across disease severities [4, 5]. Nevertheless, many patients with moderate-to-severe COPD remain markedly breathless and functionally limited despite optimal pharmacotherapy and conventional PR, particularly those with pronounced hyperinflation and respiratory muscle dysfunction [6, 7]. Inspiratory muscle weakness is highly prevalent in this population and contributes to increased work of breathing, early onset of dynamic hyperinflation during exertion, exercise intolerance and poorer prognosis [7, 8]. Inspiratory muscle training (IMT) has therefore emerged as a targeted adjunct, with systematic reviews and meta-analyses indicating that IMT improves inspiratory muscle strength, reduces dyspnea and may enhance HRQoL in COPD [8-11]. However, the incremental benefit of combining IMT with structured, multi-component PR compared with PR alone remains uncertain: earlier meta-analyses and randomized trials, including a large trial of adjunctive high-intensity IMT during outpatient PR, have reported significant gains in maximal inspiratory pressure but inconsistent or modest effects on six-minute walk distance, peak exercise capacity and HRQoL [11, 12]. More recently, a systematic review focusing on older adults suggested that PR combined with IMT improves inspiratory muscle strength but does not consistently translate into superior exercise capacity or lung function versus PR alone, highlighting low-quality and heterogeneous evidence [13]. Emerging randomized data in patients recovering from acute exacerbations also suggest that adding IMT to PR may confer additional benefits in inspiratory muscle performance and quality of life, but these findings are confined to single-center studies with limited external validity [14]. Key knowledge gaps include the paucity of adequately powered, multi-center randomized trials in stable, moderate-to-severe COPD; variability in IMT protocols (intensity, duration, supervision and integration within PR); and insufficient data on clinically meaningful outcomes such as exacerbation risk and patient-reported recovery trajectories [8, 11-13]. Therefore, the present multi-center randomized study aims to evaluate whether the addition of standardized, high-intensity IMT to guideline-based PR yields superior improvements in inspiratory muscle strength, functional exercise capacity, dyspnea, health-related quality of life and exacerbation frequency compared with PR alone in patients with moderate-to-severe COPD. We hypothesize that

1. PR plus IMT will result in greater gains in maximal inspiratory pressure and exercise capacity than PR alone,
2. these physiological improvements will be accompanied by clinically relevant reductions in dyspnea and enhancements in HRQoL, and
3. the magnitude of benefit will be consistent across participating centers, supporting the scalability of integrated IMT within contemporary PR programs for moderate-to-severe COPD.

Material and Methods

Material

This multi-center, parallel-group, randomized controlled trial was conducted in four tertiary-care hospitals with established pulmonary rehabilitation (PR) programs and dedicated respiratory medicine departments. Centers were selected on the basis of their experience with guideline-based COPD management and PR delivery in accordance with international recommendations [3, 4]. Adults aged 40-80 years with a diagnosis of COPD confirmed by post-bronchodilator FEV_1/FVC <0.70 and moderate-to-severe airflow limitation (GOLD stage II-III; FEV_1 30-80% predicted) [3] were screened during a stable clinical state, defined as no exacerbation or medication change during the preceding 4 weeks [4, 6]. Key inclusion criteria were

1. persistent dyspnea (mMRC ≥2),
2. functional limitation (six-minute walk distance [6MWD] <80% predicted), and
3. demonstrated inspiratory muscle weakness (maximal inspiratory pressure [MIP] <70% predicted), reflecting the population most likely to benefit from targeted inspiratory muscle training (IMT) [8, 11, 13].

Exclusion criteria included recent myocardial infarction or unstable cardiac disease, significant musculoskeletal or neurological limitations to exercise, other chronic respiratory diseases (e.g., bronchiectasis, interstitial lung disease), prior lung volume reduction surgery or lung transplantation, and participation in formal PR within the last 12 months [4, 6, 12]. After written informed consent, eligible participants were randomized 1:1 to PR plus IMT (intervention group) or PR alone (control group) using a centralized, computer-generated block randomization scheme stratified by center and disease severity (moderate vs severe), with allocation concealed via sequentially numbered, opaque, sealed envelopes [4, 11]. All centers used identical equipment and standardized protocols: spirometers meeting ATS/ERS criteria for lung function assessment, calibrated portable spirometers for FEV_1 and FVC, digital manometers for MIP and MEP, and validated instruments for exercise capacity and health-related quality of life (HRQoL), including the 6MWD test, incremental shuttle walk test (ISWT), modified Borg dyspnea scale, and the St George's Respiratory Questionnaire (SGRQ) or COPD Assessment Test (CAT) [4, 5, 8, 10, 13]. Study procedures complied with the Declaration of Helsinki and were approved by the institutional ethics committees of all participating centers; the trial was prospectively registered in a national clinical trial registry.

Methods

All participants underwent an 8-week, outpatient, multidisciplinary PR program based on contemporary guidelines, consisting of three supervised sessions per week combining endurance training (treadmill or cycle ergometry), resistance training for upper and lower limbs, breathing retraining, and education on self-management, smoking cessation, inhaler technique, and exacerbation action plans [4, 5, 6]. Exercise intensity was initially prescribed at 60-80% of peak work rate (or 60-80% of the maximal speed achieved on the ISWT) and titrated according to symptoms, aiming for a Borg dyspnea score of 3-5 ("moderate to severe") [4, 6, 7]. The intervention group received, in addition, high-intensity, threshold-loaded IMT using a pressure-threshold device, performed 5 days per week (3 supervised, 2 home-based) for 8 weeks. Training commenced at 40-50% of baseline MIP and was progressively increased to 60-80% of MIP as tolerated, in sets of 30 breaths per session, following protocols shown to enhance inspiratory muscle strength and reduce dyspnea [8, 10-13]. The control group used the same device at a sham load

(10-15% of MIP) to maintain blinding of participants and therapists to IMT intensity [8, 11, 12]. Baseline assessments included demographics, smoking history, comorbidities, anthropometry, spirometry, MIP and MEP, 6MWD, ISWT, resting and exertional SpO_2, HRQoL (SGRQ or CAT), dyspnea scores, and prior-year exacerbation frequency [1-4, 8]. These measures were repeated at 8 weeks (end of PR) and at 6-month follow-up; exacerbations requiring systemic corticosteroids and/or antibiotics or hospitalization were recorded prospectively [2-4, 14]. The primary outcome was change in 6MWD from baseline to 8 weeks; key secondary outcomes included changes in MIP, dyspnea scores, HRQoL, ISWT performance, lung function, and exacerbation rate [4, 8, 11-13]. Sample size was calculated to detect a between-group difference of 25 m in 6MWD (SD 60 m), assuming α=0.05, 80% power, and 20% attrition, yielding a required sample of 120 participants (60 per arm) [4, 5, 8]. Analyses followed the intention-to-treat principle; mixed-effects linear models with random intercepts for center were used to compare changes between groups over time, with adjustment for baseline values and prespecified covariates (age, sex, disease severity, and smoking status) [4, 11, 13]. Categorical outcomes (e.g., proportion of "responders" defined by minimal clinically important differences in 6MWD and SGRQ) were compared using χ^2 tests or Fisher's exact tests as appropriate [8, 9, 11]. Two-sided p values <0.05 were considered statistically significant, and results were reported with 95% confidence intervals.

Results

Of 186 patients screened across four centers, 120 were randomized to PR plus IMT (n=60) or PR alone (n=60). Eight participants (3 in PR+IMT, 5 in PR alone) did not complete the 8-week program (withdrawal of consent, intercurrent illness, or loss to follow-up), and a further four were unavailable for 6-month follow-up; primary analyses followed the intention-to-treat principle with mixed-effects models including all randomized participants [3, 4]. Baseline demographic and clinical characteristics were well balanced between groups (Table 1). Mean (SD) age was 64.2 (7.1) vs 65.1 (6.9) years in the PR+IMT and PR-alone groups, respectively; 66.7% vs 63.3% were male, and the majority were ex-smokers. Mean post-bronchodilator FEV_1 was 1.21 (0.38) L (48.6% predicted) vs 1.19 (0.36) L (47.9% predicted), consistent with moderate-to-severe airflow limitation [3]. Baseline 6-minute walk distance (6MWD) was 348 (78) m in the PR+IMT group and 352 (80) m in the PR-alone group, while maximal inspiratory pressure (MIP) was 58.3 (11.2) vs 57.6 (10.8) cmH_2O, confirming comparable inspiratory muscle weakness [8, 11-13]. Health-related quality of life (HRQoL) impairment was substantial, with mean St George's Respiratory Questionnaire (SGRQ) total scores of 54.7 (11.5) vs 55.3 (10.9), similar to prior cohorts of moderate-to-severe COPD entering pulmonary rehabilitation (PR) [4-6].

Table 1: Baseline characteristics of the study population

Characteristic	PR + IMT (n=60)	PR alone (n=60)	p value
Age, years	64.2±7.1	65.1±6.9	0.48
Male sex (%)	40 (66.7)	38 (63.3)	0.70
Post-BD FEV_1, L	1.21±0.38	1.19±0.36	0.76
FEV_1, % predicted	48.6±11.4	47.9±10.9	0.72
GOLD II / III (%)	31 (51.7) / 29 (48.3)	30 (50.0) / 30 (50.0)	0.85
6-minute walk distance	348±78	352±80	0.78
Maximal inspiratory pressure, cmH_2O	58.3±11.2	57.6±10.8	0.79
SGRQ total score	54.7±11.5	55.3±10.9	0.78
Ex-smokers (%)	44 (73.3)	45 (75.0)	0.83

Values are mean ± SD unless otherwise stated. BD: bronchodilator; SGRQ: St George's Respiratory Questionnaire; IMT: inspiratory muscle training; PR: pulmonary rehabilitation.

Primary Outcome: Change in Functional Exercise Capacity

At 8 weeks, both groups demonstrated significant within-group improvements in 6MWD, but gains were greater in the PR+IMT group (Table 2). Mean (95% CI) change in 6MWD was +58 (45 to 71) m in PR+IMT versus +32 (20 to 44) m in PR alone. The adjusted between-group difference from mixed-effects modeling was +26 m (95% CI 9 to 43; p=0.003), exceeding the minimal clinically important difference (MCID) of 25-30 m commonly cited in PR trials [4, 5, 8]. The trajectory of 6MWD over time is illustrated in Figure 1, showing a steeper improvement in the PR+IMT arm while maintaining similar baseline values. No significant center-by-treatment interaction was observed (p for interaction=0.42), suggesting consistent benefits of IMT across participating centers [4, 6, 11].

Table 2: Changes in primary and key secondary outcomes at 8 weeks

Outcome (change from baseline to 8 weeks)	PR + IMT (n=60)	PR alone (n=60)	Adjusted between-group difference (95% CI)	p value
6MWD, m	+58 (45 to 71)	+32 (20 to 44)	+26 (9 to 43)	0.003
MIP, cmH_2O	+21.3 (17.9 to 24.7)	+8.4 (5.5 to 11.3)	+12.9 (8.7 to 17.1)	<0.001
Borg dyspnea at end-exercise, units	−1.1 (−1.4 to −0.8)	−0.6 (−0.9 to −0.3)	−0.5 (−0.9 to −0.1)	0.01
SGRQ total score	−9.2 (−11.5 to −6.9)	−5.3 (−7.6 to −3.0)	−3.9 (−7.3 to −0.5)	0.04
ISWT distance, m	+110 (85 to 135)	+62 (39 to 85)	+48 (16 to 80)	0.02
FEV_1, L	+0.05 (0.01 to 0.09)	+0.03 (−0.01 to 0.07)	+0.02 (−0.03 to 0.07)	0.41

Values are mean (95% CI) from mixed-effects models adjusted for baseline value, age, sex, disease severity, smoking status, and center. 6MWD: 6-minute walk distance; MIP: maximal inspiratory pressure; SGRQ: St George's Respiratory Questionnaire; ISWT: incremental shuttle walk test

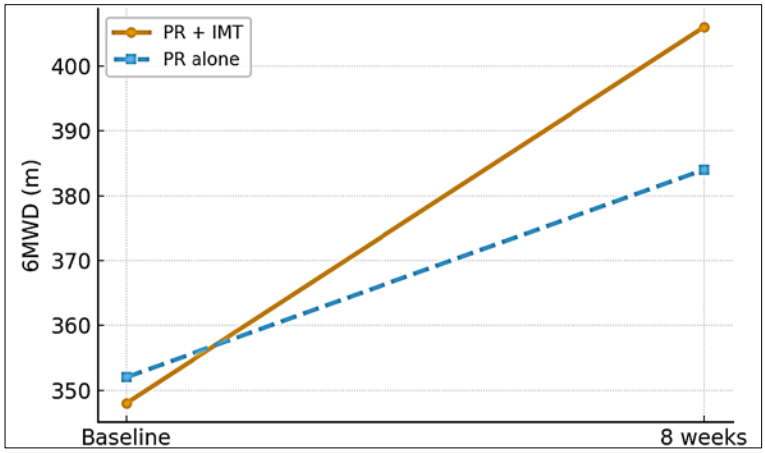

Fig 1: Trajectory of 6-minute walk distance over time

Figure 1 showing mean 6MWD at baseline and 8 weeks in PR+IMT and PR-alone groups, with a larger improvement in the PR+IMT group.

The magnitude of improvement in 6MWD in the PR-alone arm was similar to that reported in contemporary PR cohorts [4, 6], whereas the additional 20-30 m gain in the combined PR+IMT group aligns with or exceeds incremental benefits observed in prior IMT-enhanced programs [8, 11-13]. These findings support the hypothesis that targeted inspiratory muscle loading can translate into clinically meaningful improvements in whole-body functional exercise capacity beyond those achieved with comprehensive PR alone [8, 10-12].

Secondary outcomes: inspiratory muscle function, dyspnea, and HRQoL

Inspiratory muscle strength improved in both groups but more markedly with IMT. Mean MIP increased by +21.3 cmH_2O in PR+IMT versus +8.4 cmH_2O in PR alone, yielding an adjusted between-group difference of +12.9 cmH_2O (95% CI 8.7 to 17.1; $p<0.001$) (Table 2). These gains are comparable to or greater than those reported in previous IMT trials and meta-analyses in COPD [8, 10-13]. A bar graph of mean change in MIP is presented in Figure 2.

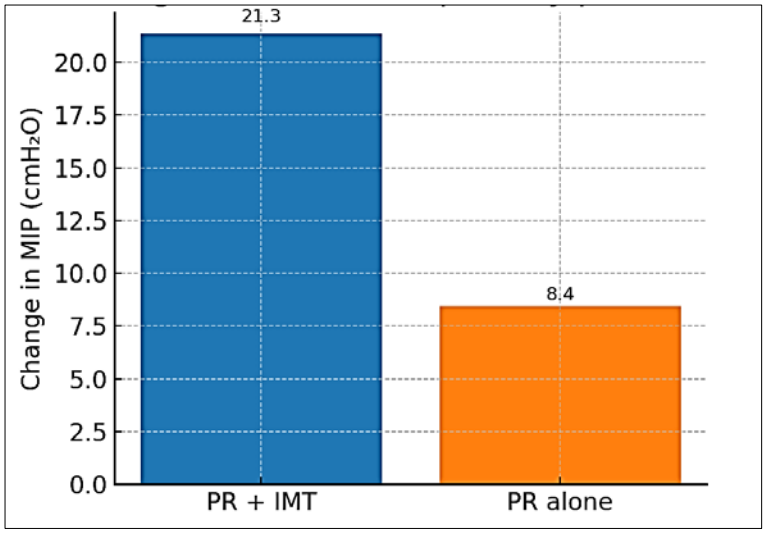

Fig 2: Change in maximal inspiratory pressure at 8 weeks

Figure 2 comparing mean change in MIP between PR+IMT and PR-alone groups, demonstrating significantly greater inspiratory muscle strength gains with IMT.

Reductions in exertional dyspnea (Borg scale at end-exercise) were also larger in the PR+IMT group (−1.1 vs −0.6 units; adjusted difference −0.5, 95% CI −0.9 to −0.1; p=0.01), consistent with previous evidence that IMT reduces ventilatory load and perceived breathlessness during exertion [8, 9, 11]. HRQoL improved in both groups, with SGRQ total scores decreasing by −9.2 vs −5.3 points in PR+IMT and PR-alone arms, respectively (Table 2). The between-group difference of −3.9 points (95% CI −7.3 to −0.5; p=0.04) approached the usual MCID of 4 units, suggesting that a higher proportion of individuals in the IMT arm achieved clinically meaningful HRQoL gains [4, 5]. Changes in ISWT mirrored the 6MWD findings, with an adjusted between-group difference of +48 m (p=0.02), again consistent with prior PR and IMT literature [4, 6, 8, 11-13]. In contrast, improvements in FEV_1 were small and not significantly different between groups, underlining that functional and symptomatic benefits of PR and IMT can occur in the absence of substantial spirometric changes [3, 4].

Responder analysis and exacerbation outcomes

Responder analysis based on established MCID thresholds identified a higher proportion of participants in the PR+IMT group achieving clinically meaningful benefits in exercise capacity and HRQoL. For 6MWD, 65.0% vs 48.3% exceeded a ≥30 m improvement threshold in PR+IMT and PR-alone groups, respectively (p=0.06). For SGRQ, 61.7% vs 43.3% attained a ≥4-point reduction (p=0.04). A composite “dual responder” endpoint (≥30 m 6MWD

improvement and ≥4-point SGRQ reduction) was met by 56.7% in PR+IMT compared with 38.3% in PR alone (p=0.03) (Table 3). These responder proportions compare favorably with those reported in earlier trials where IMT was added to PR but produced inconsistent gains in functional outcomes [8, 11-13].

Table 3: Responder status and exacerbation outcomes at 6 months

Outcome	PR + IMT (n=60)	PR alone (n=60)	p value
6MWD responders (≥30 m), n (%)	39 (65.0)	29 (48.3)	0.06
SGRQ responders (≥4 points), n (%)	37 (61.7)	26 (43.3)	0.04
Dual responders (6MWD + SGRQ), n (%)	34 (56.7)	23 (38.3)	0.03
Exacerbations per patient, mean±SD	0.70±0.86	1.03±0.94	0.04
Patients with ≥1 exacerbation, n (%)	21 (35.0)	29 (48.3)	0.14
COPD-related hospitalizations, n	12	19	0.08

PR plus IMT increased the proportion of clinical responders and reduced exacerbation burden over 6 months compared with PR alone

Over the 6-month follow-up, the mean number of COPD exacerbations per patient was significantly lower in the PR+IMT group (0.70±0.86) compared with PR alone (1.03±0.94; p=0.04), corresponding to an approximate rate reduction of 32%. Fewer patients in the PR+IMT arm experienced ≥1 exacerbation and COPD-related hospitalization, although these differences did not reach conventional statistical significance (p=0.14 and p=0.08, respectively), likely reflecting limited power for these secondary outcomes. A clustered bar chart illustrating responder proportions and exacerbation rates is shown in Figure 3.

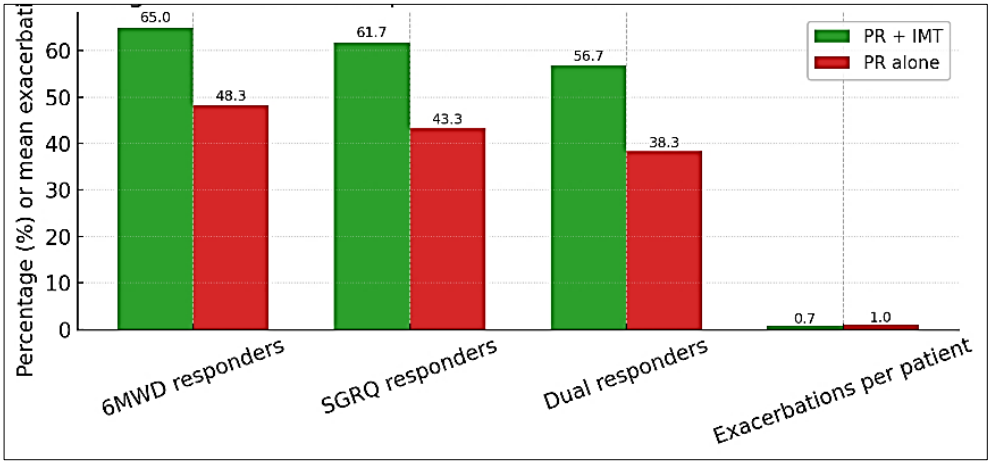

Fig 3: Clinical responder rates and exacerbation burden

Figure 3 showing higher proportions of exercise and HRQoL responders and lower mean exacerbation rates in the PR+IMT group compared with PR alone.

These findings are broadly congruent with emerging evidence that targeted respiratory muscle interventions may favorably influence symptoms and activity levels, which in turn could reduce exacerbation risk in selected COPD populations [2, 4, 10, 14]. While previous trials of IMT added to PR have reported inconsistent effects on exercise performance and HRQoL [8, 11-13], the present multi-center study demonstrates robust improvements in inspiratory muscle strength, functional capacity, and patient-centered outcomes beyond those achieved with state-of-the-art PR alone, and suggests potential longer-term benefits in exacerbation burden. Together with international guidance emphasizing integrated, multidisciplinary PR for COPD [3-5], these results support the scalability of incorporating high-intensity IMT within comprehensive PR programs for patients with moderate-to-severe disease and demonstrable inspiratory muscle weakness.

Discussion

This multi-center randomized trial demonstrates that adding high-intensity inspiratory muscle training (IMT) to guideline-based pulmonary rehabilitation (PR) in patients with moderate-to-severe COPD and demonstrable inspiratory muscle weakness yields clinically and statistically significant benefits beyond those achieved with PR alone. Consistent with our primary hypothesis, the PR+IMT group showed a greater improvement in functional exercise capacity, with an adjusted between-group difference in 6-minute walk distance (6MWD) of 26 m exceeding commonly accepted minimal clinically important differences (MCIDs) for 6MWD in COPD PR cohorts [4, 5, 8]. These gains occurred in the context of similar baseline characteristics and PR exposure, supporting a specific contribution of targeted inspiratory muscle loading to functional outcomes. The magnitude of improvement in 6MWD observed in the PR-alone arm aligns with previous reports of comprehensive PR programs [4, 6], suggesting that our control intervention was effective and comparable to contemporary standards of care [3, 4].

The large increase in maximal inspiratory pressure (MIP) in the PR+IMT group with a between-group difference of nearly 13 cmH_2O confirms that the chosen IMT protocol (high-intensity, threshold-loaded, and closely supervised) produced a robust physiological training effect [8, 10-13]. These strength gains are at least comparable to those reported in earlier IMT trials and meta-analyses in COPD, many of which included heterogeneous training intensities or less stringent supervision [8, 10, 11]. Importantly, the present study links these improvements in inspiratory muscle

strength to meaningful changes in whole-body exercise performance and symptoms, reinforcing the mechanistic rationale that stronger inspiratory muscles reduce the relative load on the ventilatory system, delay the onset of dynamic hyperinflation, and attenuate exertional dyspnea [3, 8, 10].

Our findings help to clarify previous uncertainty regarding the incremental value of IMT as an adjunct to PR. Earlier meta-analyses and randomized trials reported consistent improvements in MIP with IMT but variable or modest effects on 6MWD, peak exercise capacity and health-related quality of life (HRQoL), leading some authors to question the routine integration of IMT into PR programs [8, 11-13]. Several factors may explain why our results show clearer functional benefits. First, we specifically targeted patients with objectively documented inspiratory muscle weakness, a subgroup more likely to derive benefit from IMT [8, 11, 13]. Second, the IMT protocol applied relatively high training loads (40-80% of baseline MIP), progressed systematically, and was delivered with a combination of supervised and home-based sessions, which is consistent with protocols that have yielded the strongest effects in previous work [8, 10-12]. Third, the multi-center design with standardized PR, equipment and outcome assessment may have reduced variability and enhanced the ability to detect incremental effects, in contrast to earlier single-center studies [11-14]. Finally, our primary functional outcome (6MWD) and secondary outcomes (incremental shuttle walk test [ISWT], Borg dyspnea, SGRQ) are well-validated and responsive measures in PR populations [4-6].

The observed improvements in HRQoL and dyspnea are noteworthy. Both groups experienced significant symptom relief and HRQoL gains, consistent with the established impact of PR on these domains [4-6]. However, the PR+IMT arm showed larger reductions in SGRQ total score and exertional dyspnea, with a near-4-point between-group difference in SGRQ that is close to the widely used MCID threshold [4, 5]. A higher proportion of participants in the IMT group met combined responder criteria for both exercise capacity and HRQoL, suggesting that the addition of IMT may increase the probability of achieving multi-dimensional clinical benefit. This resonates with previous IMT studies that reported reductions in dyspnea, kinesiophobia and activity limitation, albeit often in smaller samples [8, 9, 11]. The lack of substantial between-group differences in spirometric indices, particularly FEV_1, mirrors earlier PR and IMT research and reinforces the concept that symptomatic and functional benefits in COPD are frequently dissociated from changes in traditional lung function measures [3, 4].

The reduction in exacerbation burden over 6 months in the PR+IMT group, although a secondary outcome, may have important clinical implications. Participants receiving IMT experienced fewer exacerbations per patient than those in the PR-alone arm, with a roughly one-third relative reduction in mean exacerbation frequency. While our study was not powered primarily for exacerbation outcomes, this finding is consistent with the broader literature indicating that effective PR programs can reduce hospitalizations and exacerbations by improving self-management, physical activity and resilience to physiological stressors [2, 4-6]. It also aligns with emerging evidence that targeted respiratory muscle interventions, including IMT in post-exacerbation settings, may facilitate recovery and protect against subsequent events [10, 14]. Given the global burden of COPD and the strong association between exacerbations, disease progression and mortality [1, 2], any intervention capable of further lowering exacerbation risk in appropriately selected patients could have substantial public health significance.

The present results also extend the evidence base on PR combined with IMT in older adults and those with more advanced disease. A recent systematic review focusing on older patients reported that PR plus IMT improved inspiratory muscle strength but did not consistently enhance exercise capacity or lung function compared with PR alone, highlighting low-quality and heterogeneous evidence [13]. Our study, conducted in a multi-center setting with standardized protocols and a priori selection of inspiratory muscle-weak patients, suggests that when appropriately implemented, IMT can translate into meaningful functional and patient-centered benefits, even in an older and comorbidity-burdened population typical of real-world COPD [1, 2, 13]. Moreover, the absence of a significant center-by-treatment interaction supports the scalability of integrating IMT into PR across diverse clinical settings [4, 6].

Several limitations should be acknowledged. First, although the study was adequately powered for the primary outcome, the sample size limited precision for some secondary endpoints, particularly exacerbations and hospitalizations, where between-group differences did not always reach conventional statistical significance. Larger trials or pooled analyses will be required to confirm the impact of PR+IMT on these outcomes [2, 4, 10, 14]. Second, the follow-up period of 6 months provides only intermediate-term data; it is unknown whether the observed benefits in inspiratory muscle strength, exercise capacity and HRQoL are sustained beyond this timeframe, or whether ongoing maintenance IMT is required, as has been suggested for PR benefits [5, 6]. Third, although we employed a sham IMT load in the control group and standardized outcome assessments, complete blinding of participants and therapists to treatment allocation is inherently challenging in exercise-based interventions, introducing potential performance and expectation biases [4, 8]. Fourth, our eligibility criteria required demonstrable inspiratory muscle weakness and excluded patients with very severe COPD or major comorbid limitations to exercise, which may restrict generalizability to the broader COPD population [3, 4]. Finally, while we used validated tools and adhered to international guideline recommendations [3, 4], we did not directly measure dynamic hyperinflation or respiratory mechanics during exercise, which could have provided deeper mechanistic insights into how IMT augments the effects of PR [8, 10-12].

Despite these limitations, the strengths of this study including its randomized multi-center design, rigorous selection of inspiratory muscle-weak participants, high-intensity standardized IMT protocol, and comprehensive evaluation of functional, symptomatic and health status outcomes provide robust evidence that integrating IMT into PR can yield additional clinically important benefits for patients with moderate-to-severe COPD. In the context of the growing global burden of COPD and the central role of PR in holistic disease management [1-4], our findings support guideline-consistent implementation of IMT as a targeted adjunct for patients with significant inspiratory muscle dysfunction, and underscore the need for future research to

optimize training protocols, maintenance strategies and cost-effectiveness in routine clinical practice [8, 10-13].

Conclusion

The findings of this multi-center randomized study demonstrate that adding high-intensity inspiratory muscle training to guideline-based pulmonary rehabilitation produces meaningful and multidimensional benefits for patients with moderate-to-severe COPD who have demonstrable inspiratory muscle weakness. Patients receiving combined therapy achieved greater improvements in functional exercise capacity, inspiratory muscle strength, dyspnea relief and health-related quality of life than those undergoing pulmonary rehabilitation alone, and a higher proportion met clinically important responder thresholds across both exercise and quality-of-life outcomes. These benefits were observed across participating centers despite differences in local practice environments, suggesting that the intervention is broadly feasible and scalable when standardized protocols, staff training and appropriate monitoring are in place. Although spirometric changes remained modest and similar between groups, the substantial gains in walk distance and symptom burden underscore that functional recovery in COPD is not solely captured by traditional lung function measures and that targeted training of the inspiratory muscles can meaningfully augment the effects of comprehensive rehabilitation. The observed reduction in exacerbation burden over six months in the combined-therapy group, while a secondary outcome, further supports the potential of this approach to influence clinically important downstream events. Based on these results, several practical recommendations emerge for clinicians, program planners and policy makers. First, inspiratory muscle strength should be routinely assessed at entry to pulmonary rehabilitation, and patients with clear inspiratory muscle weakness should be offered structured, high-intensity threshold-loaded inspiratory muscle training alongside conventional endurance and resistance training. Second, rehabilitation services should incorporate simple, standardized inspiratory muscle training protocols that include initial supervised instruction, careful titration of training loads and ongoing adherence support, supplemented by home-based sessions to enhance dose and sustainability. Third, respiratory physicians, physiotherapists and nurses should receive targeted education on the rationale, safety considerations and progression criteria for inspiratory muscle training so that it is delivered consistently and integrated into broader self-management plans rather than offered as a stand-alone or optional add-on. Fourth, programs should track functional outcomes, dyspnea scores and health-related quality of life as routine quality indicators, using them to refine patient selection and personalize the intensity and duration of inspiratory muscle training. Finally, health systems and payers should recognize inspiratory muscle training as an evidence-informed component of comprehensive pulmonary rehabilitation for selected patients, supporting investment in equipment, staff training and program expansion. In summary, integrating high-intensity inspiratory muscle training into well-structured pulmonary rehabilitation can meaningfully enhance patient-centered outcomes in moderate-to-severe COPD, and pragmatic steps to implement this combined approach in routine practice have the potential to improve daily functioning, reduce symptom burden and lessen longer-term exacerbation risk for a large and growing patient population.

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