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Effect of Supervised Exercise Training on Oxidative Stress Markers and Inflammatory Profile in Patients with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition characterized by progressive lung dysfunction, chronic oxidative stress and systemic inflammation, which impair exercise capacity and quality of life. This study compared the effect of a 12-week supervised combined aerobic and resistance training program with a 12-week home-based aerobic training on pulmonary function, oxidative stress and inflammatory markers in COPD patients.

Methods: This was a single blind, two arm parallel randomized controlled trial conducted at the Department of Physical Therapy, Dow University of Health Sciences, Ojha Campus, Karachi from February to October 2025. 106 COPD patients who were diagnosed by a pulmonologist were randomly divided into two groups of 53. Group A did supervise combined aerobic and resistance training 5 times a week for 12 weeks, while Group B did aerobic exercises at home, at the same frequency. Pulmonary function tests (VC, TLC, FEV1/VC), oxidative stress indicators (SOD, MDA), and inflammatory cytokines (IL-6, TNF-α) were used as outcome measures. Paired and independent t-tests were used to analyze data, and p values < 0.05 were considered statistically significant.

Results: Within-group improvements were significant for both groups for all variables measured ($p < 0.05$). But Group A showed a significantly better increase in VC, FEV1/VC ratio, SOD, MDA reduction and decrease in IL-6 and TNF-α compared to Group B ($p < 0.05$).

Conclusion: Group A shows greater improvement in pulmonary function, oxidative balance and inflammation than home-based AT, and should be considered as a preferred method for pulmonary rehabilitation in COPD patients.

Keywords: *COPD, Inflammatory Markers, Pulmonary Function Test, Vital Capacity*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a huge health problem in the 21st century and is one of the most important causes of morbidity and mortality in the world. It affects approximately 10% of adults aged 30–79 years and is currently ranked as the third leading cause of death globally[1]. There are a number of significant systemic changes associated with COPD and the burden of COPD is also regionally variable, largely due to smoking prevalence, environmental pollution and access to health care[2]. Effective non-pharmacological management strategies are needed to address COPD beyond the respiratory changes.

Chronic oxidative stress and systemic inflammation are one of the hallmarks of COPD pathogenesis. Superoxide dismutase (SOD) is an important antioxidant enzyme and malondialdehyde (MDA) is a marker of lipid peroxidation and oxidative damage from a biochemical point of view[3]. Watson et al.

observed that few studies with suboptimal data were available in a systematic review on the effect of pulmonary rehab on redox status, and they believed this was due to the lack of well-designed studies[4]. In COPD patients' systemic inflammation, driven by cytokines like interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), also plays a role in muscle dysfunction, exercise capacity and pulmonary function[5]. Pulmonary rehabilitation (PR) is an important part of COPD treatment. Aerobic exercise increases antioxidant defenses and decreases inflammation, oxidative stress and apoptosis, and resistance training increases antioxidant defenses and mitochondrial function[6-8], combined training has been shown to have synergistic effects such as decreased protein carbonyl and improved functional outcomes[9].

There is a lack of research on the role of supervision in the delivery of exercise. There was greater improvement in exercise capacity with supervised rehabilitation programs than with home-based programs[10], but the effect of these programs on oxidative stress and inflammatory markers remains uncertain, and lung function parameters such as VC, TLC, and FEV1/VC have not been extensively studied. A structured progression and monitoring of rehabilitation may be suboptimal at home and can be achieved through supervised rehabilitation[11].Furthermore, supervised resistance training has been associated with a decrease in inflammatory markers and improvement in pulmonary function in elderly people with COPD[12]. Thus, a randomized controlled trial was performed to compare the effect of 12 weeks of supervised combined aerobic and resistance training, and home-based aerobic training on oxidative stress markers (SOD, MDA), inflammatory cytokines (IL-6, TNF-α) and pulmonary function indices (VC, TLC, FEV1/VC).

METHODOLOGY

Study Design and Setting

This single-blind, two-arm parallel randomized controlled trial (RCT) was conducted at the DUHS F&SRC, Dow University of Health Sciences, Ojha Campus. The study was carried out over a period of nine months, from January 2025 to December 2025.

Sample Size

A total sample of n=106 participants was enrolled in this study, calculated using G*Power software (version 3.1) at a significance level of α = 0.05, statistical power of 80%, and based on the value of FEV1/ FVC of second research period 67.43±15.31 for study group and 58.023±19.12 for control group[9]. Participants were randomly allocated into two equal groups of 53 each: Group A (Supervised Combined Training) and Group B (Home-Based Aerobic Training) using a computer-generated randomization sequence with sequentially numbered sealed opaque envelopes to ensure allocation concealment.

Selection Criteria

Inclusion Criteria: Participants were included if they (i) had a confirmed diagnosis of COPD established by a registered pulmonologist based on spirometric criteria (post-bronchodilator FEV1/FVC < 0.70) in accordance with GOLD guidelines; (ii) were in clinical remission with no acute exacerbation in the preceding four weeks; (iii) were aged between 40 and 60 years; (iv) were medically stable and cleared by their treating pulmonologist to participate in an exercise program; and (v) were able to provide written informed consent and commit to the 12-week intervention period.

Exclusion Criteria: Participants were excluded if they (i) had a concurrent diagnosis of uncontrolled cardiovascular disease, musculoskeletal disorder, or neurological condition that would contraindicate exercise participation; (ii) had a history of exacerbation requiring hospitalization within the previous four weeks; (iii) were currently enrolled in any other formal pulmonary rehabilitation program; (iv) had any significant comorbidity that would independently affect oxidative stress or inflammatory markers, such as active malignancy or autoimmune disease; (v) were using systemic corticosteroids or immunosuppressive therapy at the time of enrollment; or (vi) were unable to perform spirometry reliably.

Data Collection Procedure

Baseline assessment was carried out in less than one week before the start of the intervention. A trained assessor who was blinded to group assignment recorded all outcome measures at the point of baseline (Week 0) and post-intervention (Week 12).

Pulmonary Function Testing (PFT):

Spirometric testing was done using a calibrated spirometer in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) standardization guidelines. Three measures were documented: Vital Capacity (VC), Total Lung Capacity (TLC) and FEV1/VC ratio. The best of three acceptable maneuvers was recorded for each participant.

Oxidative Stress Markers:

Each of the participants was placed under fasting conditions and the venous blood sample (5 mL) was collected. The amount of SOD activity in serum samples was determined using a colorimetric assay kit of enzyme activity, and the level of Malondialdehyde (MDA) was measured through the thiobarbituric acid reactive substances (TBARS) technique. The samples were centrifuged, aliquoted and stored at -80 o C until batch analysis.

Inflammatory Markers:

The serum levels of Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) were measured using commercially made enzyme-linked immunosorbent assay (ELISA) kits in accordance with the manufacturer instructions.

Intervention Protocol

Group A: Supervised Combined Aerobic and Resistance Training:

Group A participants had a structured 12 weeks supervised combined aerobic and resistance exercise program which was conducted at the physical therapy outpatient department, OJHA Campus, 5 sessions a week. The program consisted of three aerobic sessions and two sessions on resistance training per week.

The aerobic sessions were done on a motorized treadmill or stationary cycle ergometer, with the intensity of the training being prescribed as 70% of the Maximum Heart Rate (MHR) and calculated using the formula: MHR = 220- age. Each session, the pulse oximeter was constantly used to monitor heart rate. All aerobic exercises took 30-40 minutes with warm-up (5 minutes low intensity) and cool-down (5 minutes low intensity).

The resistance training was performed on two nonconsecutive days in a week. The individualization of the training load was done using the One-Repetition Maximum (1RM) method, which was measured at baseline in each relevant exercise. The participants were trained at 60-70 % of their own 1RM with progressive overload every two weeks. The first day of resistance was focused on upper limbs and back, including the exercises of seated dumbbell shoulder press, seated cable row, and bicep curls. Day 2 Resistance was dedicated to low limbs; leg press, knee extension, and seated leg curl were all incorporated. The resistance sessions were divided into 2-3 sets of 10-12 repetitions of exercises separated by a one-to-two-minute relaxation period. The sessions were directly supervised by a qualified physical therapist who observed technique, progression of load, and tolerance in the participants during the intervention.

Group B: Home-Based Aerobic Training:

Home-Based Aerobic Training: Group B participants completed 12 weeks of aerobic training at home, five sessions per week, and at a prescribed intensity of 70% of their MHR. The participants were trained on how to use a personal pulse oximeter to self-monitor the heart rate. Modality of exercise entailed walking or stationary cycling of 30-40 minutes per session. Participants were given a standardized written exercise guide and a weekly supervisory phone call with the research physical therapist to monitor compliance, address concerns and reinforce compliance. No formal resistance training was included in this group.

Statistical Analysis

The entered and analyzed data were SPSS version 26 (IBM Corp., USA). Shapiro-Wilk test was used to determine the normality of data. A frequency and percentage were used for descriptive analyses. Within group analyses paired t test was run and for between group comparison independent t-test was performed. Values were significant at <0.05.

Ethical Consideration

The study was approved by the Ethical Review Committee of the Foundation of Medical Research and Laboratories (IRB Protocol No.: FMRL-IRB/2025/033) before the beginning of the study. All participants gave informed written consent prior to enrolment. The trial was carried out in compliance with the

principles of the Declaration of Helsinki.

RESULTS

A total of 106 participants with confirmed COPD were enrolled and randomized into two groups of 53 each. No significant dropouts were recorded during the 12-week intervention period. The two groups were comparable at baseline with respect to all demographic and clinical variables, as shown in Table 1.

The mean age of participants in Group A was 52.4 ± 5.8 years and in Group B was 51.8 ± 6.2 years. Males constituted the majority in both groups (66% and 62% respectively). No statistically significant between-group differences were observed for age, sex, BMI, smoking status, or GOLD staging (all $p > 0.05$), confirming successful randomization.

Table 1. Baseline Demographic and Clinical Characteristics of Participants

Variable	Group A (n=53)	Group B (n=53)	p-value
Age (years)	52.4 ± 5.8	51.8 ± 6.2	0.611
Gender	35 (66%)	33 (62%)	0.720
BMI (kg/m²)	24.6 ± 3.1	25.1 ± 3.4	0.432
Smoking Status	38 (71.7%)	36 (67.9%)	0.721
GOLD Stage II	28 (52.8%)	27 (50.9%)	0.845
GOLD Stage III	25 (47.2%)	26 (49.1%)	0.845
Disease Duration (years)	6.2 ± 2.4	6.5 ± 2.7	0.558

Group A = Supervised Combined Aerobic a Resistance Training; Group B = Home-Based Aerobic Training; BMI = Body Mass Index; GOLD = Global Initiative for Chronic Obstructive Lung Disease. Mean±; n (%)

Pulmonary function test parameters at baseline and post-intervention for both groups are presented in Table 2. Within-group analysis revealed statistically significant improvements in VC, TLC, and FEV1/VC in both groups following the 12-week intervention (all $p < 0.05$). However, between-group analysis demonstrated that Group A achieved significantly greater.

Table 2. Within and Between Group Comparison of Pulmonary Function Test Parameters

Parameter	Group A		Within-Group p	Group B		Within-Group p	Between-Group p
	Pre	Post		Pre	Post		
VC (L)	2.81 ± 0.42	3.24 ± 0.38	<0.001	2.78 ± 0.45	2.97 ± 0.41	<0.001	0.002
TLC (L)	6.84 ± 0.71	6.52 ± 0.64	<0.001	6.79 ± 0.68	6.66 ± 0.71	0.023	0.018
FEV1/VC (%)	56.8 ± 8.2	63.4 ± 7.6	<0.001	57.1 ± 7.9	60.2 ± 8.1	<0.001	0.014

VC = Vital Capacity; TLC = Total Lung Capacity; FEV1/VC = Forced Expiratory Volume in one second to Vital Capacity ratio. Within-group comparison by paired samples t-test; between-group comparison by independent samples t-test. Significance set at $p < 0.05$, Mean ± SD

The results of oxidative stress markers are presented in Table 3. At baseline, both groups demonstrated comparable levels of SOD and MDA ($p > 0.05$). Following the 12-week intervention, Group A showed a significantly greater increase in SOD activity (0.88 ± 0.21 to 1.34 ± 0.28 U/mL; $p < 0.001$) and a significantly greater reduction in MDA levels (4.38 ± 0.82 to 2.74 ± 0.61 µmol/L; $p < 0.001$) compared to Group B, which showed more modest within-group changes (SOD: 0.91 ± 0.19 to 1.08 ± 0.22 U/mL; MDA: 4.42 ± 0.79 to 3.51 ± 0.73 µmol/L). Between-group differences for both SOD and MDA were highly significant ($p < 0.001$), indicating superior attenuation of oxidative burden in the supervised combined training group. Improvements across all three spirometric parameters compared to Group B (all $p < 0.05$). The FEV1/VC ratio improved from 56.8 ± 8.2% to 63.4 ± 7.6% in Group A, compared to an

Table 3. Within and Between Group Comparison of Oxidative Stress Markers

Parameter	Group A		Within-Group p	Group B		Within-Group p	Between-Group p
	Pre	Post		Pre	Post		
SOD (U/mL)	0.88 ± 0.21	1.34 ± 0.28	<0.001	0.91 ± 0.19	1.08 ± 0.22	<0.001	<0.001
MDA (µmol/L)	4.38 ± 0.82	2.74 ± 0.61	<0.001	4.42 ± 0.79	3.51 ± 0.73	<0.001	<0.001

SOD = Superoxide Dismutase; MDA = Malondialdehyde. Within-group comparison by paired samples t-test; between-group comparison by independent samples t-test. Significance set at $p < 0.05$, Mean ± SD

improvement from 57.1 ± 7.9% to 60.2 ± 8.1% in Group B, with the between-group difference reaching statistical significance (p = 0.014).

Inflammatory marker results are presented in Table 4. Both groups demonstrated significantly elevated baseline concentrations of IL-6 and TNF-α consistent with established systemic inflammation in COPD, with no significant between-group difference at baseline ($p > 0.05$). Following the intervention, statistically significant within-group reductions were observed in both IL-6 and TNF-α concentrations in both groups (all $p< 0.001$). Group A exhibited substantially greater reductions in IL-6 (16.42 ± 4.21 to 9.18 ± 3.14pg/mL) and TNF-α (22.36 ± 5.14 to 13.74 ± 4.28pg/mL) compared to Group B (IL-6: 16.87 ± 4.53 to 13.24 ± 3.87 pg/mL; TNF-α: 23.01 ± 5.62 to18.42 ± 4.91 pg/mL). Between-group comparisons for both inflammatory markers were statistically significant ($p < 0.001$), demonstrating the superior anti-inflammatory effect of the supervised combined training protocol.

Table 4. Within and Between Group Comparison of Inflammatory Markers

Parameter	Group A		Within-Group p	Group B		Within-Group p	Between-Group p
	Pre	Post		Pre	Post		
IL-6 (pg/mL)	16.42 ± 4.21	9.18 ± 3.14	<0.001	16.87 ± 4.53	13.24 ± 3.87	<0.001	<0.001
TNF-α (pg/mL)	22.36 ± 5.14	13.74 ± 4.28	<0.001	23.01 ± 5.62	18.42 ± 4.91	<0.001	<0.001

IL-6 = Interleukin-6; TNF-α = Tumour Necrosis Factor-alpha. Comparison within a group by paired samples t-test; between groups by independent samples t-test. Significance level of $p < 0.05$.

DISCUSSION

The current randomized controlled trial compared the effects of 12 weeks of supervised combined aerobic and resistance exercise versus home-based aerobic exercise alone on pulmonary function, oxidative stress markers, and systemic inflammatory cytokines in patients with COPD. The main conclusion of the given study is that both of the interventions resulted in statistically significant within-group improvements in all of the measured outcomes; nevertheless, the supervised combined training group was characterized by significantly better gains in VC, FEV1/VC, SOD, MDA, IL-6 and TNF-alpha in comparison with the home-based aerobic training group. All these findings contribute to the argument that the modality, structure, and supervision of the exercise delivery is a critical determinant of the therapeutic effect of the intervention in COPD management, and that combined training under professional supervision is a more effective intervention than is the aerobic exercise performed independently at home.

The high rates of improvement in pulmonary functioning in both groups are aligned with the expanding literature that exercises-based pulmonary rehabilitation is a modifier of ventilatory mechanics in COPD. Group A, as represented in the current work, showed a more significant increase in VC and an increase in the

FEV1/VC, in addition to a significant decrease in TLC - the latter to reflect a clinically significant attenuation of pulmonary hyperinflation, which is one of the cardinal pathophysiological processes of COPD. These results support earlier evidence that graded exercise rehabilitation of COPD patients results in significant improvements in lung volumes and airflow indices, attributing the effect to improved function of respiratory muscles and reduced dynamic hyperinflation[13].

The relatively lesser spirometric improvements recorded in Group B though statistically significant, imply that aerobic exercise performed at home without resistance training is not adequate to maximally rehabilitate respiratory mechanics. This is biologically plausible, where resistance training of upper limb and trunk musculature included in the protocol of Group A directly trains accessory respiratory musculature, thereby enhancing thoracic compliance and expiratory flow. It has further been demonstrated through lung transcriptomic analysis that aerobic training upregulates gene pathways governing pulmonary remodeling and inflammation resolution in COPD, providing a molecular basis for the spirometry improvements observed in both groups[6].

With respect to oxidative stress, Group A exhibited substantially greater increases in SOD activity and reductions in MDA concentrations relative to Group B. SOD, as the primary enzymatic antioxidant defense against superoxide radicals, is notably depleted in COPD, and its restoration following exercise reflects an upregulation of endogenous antioxidant capacity[3]. The significant increase in SOD activity in Group A is consistent with evidence that resistance training induces mitochondrial biogenesis and enhances the expression of antioxidant enzymes within skeletal muscle tissue[7]. MDA, as a terminal product of lipid peroxidation, is widely used as a surrogate marker of oxidative membrane damage, and its significant reduction in Group A supports the premise that combined modality training exerts a superior protective effect against ROS-mediated cellular injury compared to aerobic training alone[4]. It has similarly been reported that reductions in oxidative stress biomarkers, including lipid peroxidation indices, following structured exercise rehabilitation in patients with compromised pulmonary function are dose-dependent, with higher exercise volumes and multi-modal training producing greater biochemical responses[14]. The more modest but still significant reductions in MDA observed in Group B confirm that aerobic exercise independently contributes to redox modulation, as previously demonstrated in experimental COPD models[8]. However, the magnitude of benefit conferred by the addition of resistance training in Group A through its specific stimulation of skeletal muscle antioxidant enzyme systems appears to account for the statistically significant between-group difference observed in the present study.

The changes in the levels of IL-6 and TNF-a observed in both groups after the 12-week intervention are clinically significant, as the high levels of these cytokines are central to the maintenance of systemic inflammation, skeletal muscle catabolism and progression of the disease in COPD[5]. Group A showed significantly greater decreases in both of the markers, indicating that the combination of aerobic and resistance exercise has a synergistic anti-inflammatory effect that was greater than the effect of aerobic training alone. It has been documented that structured pulmonary rehabilitation in COPD patients produces significant reductions in circulating inflammatory markers over time, with the magnitude of the anti-inflammatory response correlating with the intensity and regularity of exercise sessions[15]. The proposed mechanisms underlying exercise-induced attenuation of systemic inflammation in COPD include the reduction of adipose tissue-derived cytokine production, modulation of skeletal muscle myokine signaling particularly through the release of anti-inflammatory IL-6 from contracting muscle fibers during acute exercise bouts and downregulation of NF-κB-mediated inflammatory pathways with chronic training adaptation[16]. The progressive resistance component of Group A's protocol likely contributed additional anti-inflammatory benefit through its capacity to preserve and rebuild skeletal muscle mass, thereby reducing the systemic pro-inflammatory milieu associated with sarcopenia, which is prevalent and pathologically significant in COPD[12].

The superiority of supervised outpatient combined training over home-based aerobic exercise is a finding of direct clinical relevance. In Group B, while participants received weekly supervisory phone calls and standardized

written instructions, the absence of direct professional oversight, individualized load progression, and resistance training modalities appears to have limited the magnitude of physiological adaptation. This is congruent with evidence demonstrating that institute-based supervised pulmonary rehabilitation produces significantly greater functional and clinical improvements compared to conventional home-based exercise, a difference attributed to the precision of exercise prescription, real-time feedback, and the motivational environment of supervised sessions[11]. The inclusion of resistance training in a progressive, 1RM-guided protocol in Group A further distinguishes this intervention from standard home-based walking programs, as progressive overload which is difficult to implement safely without professional supervision is the principal driver of neuromuscular adaptation and antioxidant enzyme upregulation in skeletal muscle.[7] It has further been highlighted that structured, supervised non-pharmacological interventions in COPD produce improvements in exercise tolerance and systemic responses that home-based strategies frequently fail to replicate at equivalent intensity, underscoring the importance of the supervised setting as an independent therapeutic variable[15]. Evidence from concurrent exercise training in older COPD patients has also demonstrated reductions in plasma protein carbonyls of approximately 26.9% following combined supervised training compared to no change in controls, providing further mechanistic support for the oxidative benefits of combined supervised exercise observed in the current trial[17].

The sample size of the present study was derived from prior work reporting measurable changes in oxidative stress parameters following exercise in COPD patients, supporting the reliability of these biomarkers as sensitive indicators of training-induced biochemical adaptation[9]. Evidence from eccentric and concentric cycling protocols in stable COPD patients has further corroborated that multi-modal training modalities differentially affect pulmonary and plasma oxidative stress indices, with supervised protocols consistently producing larger effect sizes than unsupervised comparators[18]. Additionally, findings from endurance versus resistance training comparisons in COPD have demonstrated that resistance training uniquely upregulates skeletal muscle antioxidant enzyme expression, including SOD2, independent of the aerobic stimulus[19], which is consistent with the superior biochemical outcomes observed in Group A of the present trial. The current results further extend the current evidence of pulmonary rehabilitation by confirming that structured combined exercise, when delivered in accordance with ATS/ERS rehabilitation principles,[20,21] produces measurable and statistically significant improvements across pulmonary, oxidative, and inflammatory domains, concurrently, in a South Asian COPD population that remains underrepresented in the global rehabilitation literature.

The current study has a number of methodological strengths such as its randomized controlled design, blinded outcome assessment, allocation concealment, and the use of a multidomain outcome panel. However, there are some constraints that need to be recognized. The single-center design involving a tertiary academic institution can be limiting to the generalizability of the study to the community-based COPD populations with different disease severity profiles or access to healthcare. Even though the subjects in Group B were called once a week to take supervisory telephone calls, home exercise adherence could not be objectively measured in the absence of accelerometry or continuous heart rate monitoring, and self-reported compliance may be subject to social desirability bias. The 12-week follow-up period, even though it is consistent with the standard duration of pulmonary rehabilitation courses, does not permit making any conclusion about the sustainability of the observed biochemical and functional improvements beyond the active intervention phase. Moreover, no control or recording was done regarding the dietary intake of antioxidants which could independently regulate the levels of SOD and MDA. Multi-center trials with longer follow up periods, objective measures of adherence, dietary evaluation and dose response analyses are justified to further define the best exercise prescription to alter oxidative and inflammatory pathways in COPD.

CONCLUSION

The results of this randomized controlled trial show that 12 weeks of supervised combined aerobic and resistance training produces significantly more improvements in pulmonary function, oxidative stress markers and systemic inflammatory cytokines than home based

aerobic training alone in patients with COPD. The supervised combined protocol through its combination of progressive resistance training, individualized prescription of loads, and professional supervision had a superior and clinically significant therapeutic response in all outcome domains. These findings support the priority of supervised, multi-modal exercise training in the framework of pulmonary rehabilitation in patients with COPD and indicate the insufficiency of home-based aerobic exercise as a standalone intervention to achieve optimal biochemical and functional rehabilitation outcomes.

Author Contributions

MS: Conception & Design, Data Collection, Manuscript Writing, Final Approval
YKL: Data Analysis & Interpretation, Critical Revision
HBN: Data Collection, Data Analysis & Interpretation, and Final Approval
D: Data Analysis, Manuscript Writing, Final Approval
MH: Data Analysis, Manuscript Writing, Critical Revision and Final Approval
MN: Critical Revision and Final Approval

Conflict of Interests

No conflict of interest.

Data Availability

Data will be available upon request.

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No sources

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