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CLINICAL TRIAL REPORT

Severity-Stratified Pulmonary Rehabilitation Modulates Diaphragm Function and Oxidative Stress in Hospitalized AECOPD Patients: A Randomized Controlled Trial

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Objective: Diaphragmatic dysfunction and oxidative stress are central pathophysiological alterations in patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Evidence is lacking regarding early pulmonary rehabilitation protocols stratified by objective disease severity and their physiological effects. This study aimed to evaluate the impact of an individualized, severity-graded exercise rehabilitation program on diaphragmatic function and oxidative stress biomarkers in these patients.

Methods: In this single-center randomized controlled trial, 132 AECOPD patients were first stratified into three severity grades (I, II, III) based on predefined clinical and physiological criteria, then randomly assigned to either a study group (n=66, receiving severity-graded rehabilitation) or a control group (n=66, receiving conventional rehabilitation).Diaphragmatic function was assessed by bedside ultrasonography measuring excursion (DE), end-inspiratory thickness (DTei), and end-expiratory thickness (DTee). Serum levels of malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (TAOC) were determined. All measurements were taken before and after the intervention. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR2500106687).

Results: Compared to the control group, the study group showed significant improvements in all diaphragmatic function parameters (all $p<0.001$). Furthermore, increases in SOD and TAOC levels were significantly greater in the study group (p=0.005 and p=0.025, respectively). Subgroup analysis revealed that patients with mild disease exhibited the most pronounced improvement in DE (p=0.044), and oxidative stress responses were heterogeneous across severity grades. Partial correlation analysis indicated that improvements in DE were significantly negatively correlated with improvements in all oxidative stress biomarkers only in the study group (r range: −0.314 to −0.331, all $p<0.05$).

Conclusion: Severity-graded exercise rehabilitation effectively improves diaphragmatic function and enhances endogenous antioxidant capacity in hospitalized AECOPD patients. The improvement in diaphragmatic excursion was significantly correlated with favorable changes in oxidative stress biomarkers, suggesting a potential physiological association. These findings support the efficacy of severity-graded rehabilitation but warrant further mechanistic studies.

Keywords: acute exacerbation of chronic obstructive pulmonary disease, graded exercise rehabilitation, diaphragmatic function, oxidative stress

Introduction

Chronic obstructive pulmonary disease (COPD) poses a substantial global burden, driven by factors such as smoking and aging, and is a leading cause of mortality worldwide.[1–4] Beyond airflow limitation, extrapulmonary manifestations like respiratory muscle dysfunction—particularly of the diaphragm are central to its pathophysiology.[5] In COPD, the

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diaphragm undergoes maladaptive remodeling due to chronic overload, hypoxia, inflammation, and oxidative stress, leading to contractile impairment and increased fatigability.[6] This dysfunction worsens acutely during exacerbations (AECOPD), exacerbating dyspnea, reducing exercise tolerance, and elevating the risk of respiratory failure.[7]

Oxidative stress is a key driver of diaphragmatic atrophy and functional decline.[8] During AECOPD, systemic inflammation further amplifies oxidative damage, which impairs contractility and promotes muscle loss via pathways such as protein oxidation and proteasome activation.[9,10] From a clinical perspective, mitigating oxidative stress during AECOPD is potentially important because enhanced antioxidant capacity may protect diaphragmatic myocytes from damage, thereby preserving muscle contractility and potentially improving patient outcomes such as exercise tolerance and recovery from respiratory failure.[11] However, direct evidence linking changes in oxidative stress to functional recovery remains limited, and this study aims to explore that relationship.Although pulmonary rehabilitation (PR) improves outcomes in stable COPD,[12,13] its application during acute hospitalization remains challenging due to clinical heterogeneity and the lack of severity-stratified, individualized protocols. Evidence is notably scarce on how early rehabilitation differentially affects diaphragmatic function and oxidative stress across severity grades, and on the interrelationship between these physiological parameters.[14,15] Diaphragmatic ultrasound parameters, including excursion and thickness, were selected as the primary outcomes for this study because they provide a direct, non-invasive, and real-time assessment of diaphragmatic contractility and structure, which are critically compromised during AECOPD and are specifically targeted by exercise rehabilitation.[16]

To address this gap, the severity-graded exercise rehabilitation program used in this study was developed based on our previous work. Briefly, the Triangle model was adopted as the theoretical framework to stratify patients by disease severity,[17] and a comprehensive literature synthesis was conducted to summarize available evidence on exercise rehabilitation in AECOPD.[18] The protocol was then refined through a two-round Delphi expert consultation,[19] resulting in a scientifically robust and clinically applicable graded rehabilitation framework.

Therefore, this study aimed to implement and evaluate a severity-graded exercise rehabilitation program in hospitalized AECOPD patients. We sought to assess: 1) its overall effects on diaphragmatic function and oxidative stress biomarkers; 2) its differential benefits across disease severity strata (Grades I–III); and 3) the correlation between improvements in oxidative stress and diaphragmatic function, thereby exploring potential mechanisms of rehabilitation efficacy. We hypothesized that a graded rehabilitation approach would safely improve physiological outcomes, with efficacy moderated by baseline severity and mediated in part by attenuated oxidative stress.

Methods

Study Design

This study was a single-centre, randomised controlled trial(RCT). Following baseline assessment, all eligible participants were randomly assigned by a research assistant, using a sealed envelope method, to either the study group or the control group. Group allocation was concealed from the investigators. Data were collected on the first day of the intervention and on the day of hospital discharge. Participant recruitment details are presentedin Figure 1.

Randomisation and Blinding

The random allocation sequence was generated by computer in a 1:1 ratio. Eligible patients were first classified into one of three severity grades (I, II, and III) based on the predefined clinical and physiological criteria shown in Table 1. Then, within each severity grade, patients were randomly assigned (1:1) to either the study group or the control group. An independent researcher, who was not involved in participant recruitment, implemented allocation concealment using sealed, opaque envelopes. The study employed a single-blind design, whereby the sonographers and personnel responsible for data collection and analysis remained blinded to group assignment throughout the trial.

Participants

A total of 150 potential subjects were assessed for eligibility. Of these, 18 were excluded (13 did not meet the inclusion criteria and 5 declined to participate). Consequently, 132 hospitalised patients with AECOPD were recruited from the

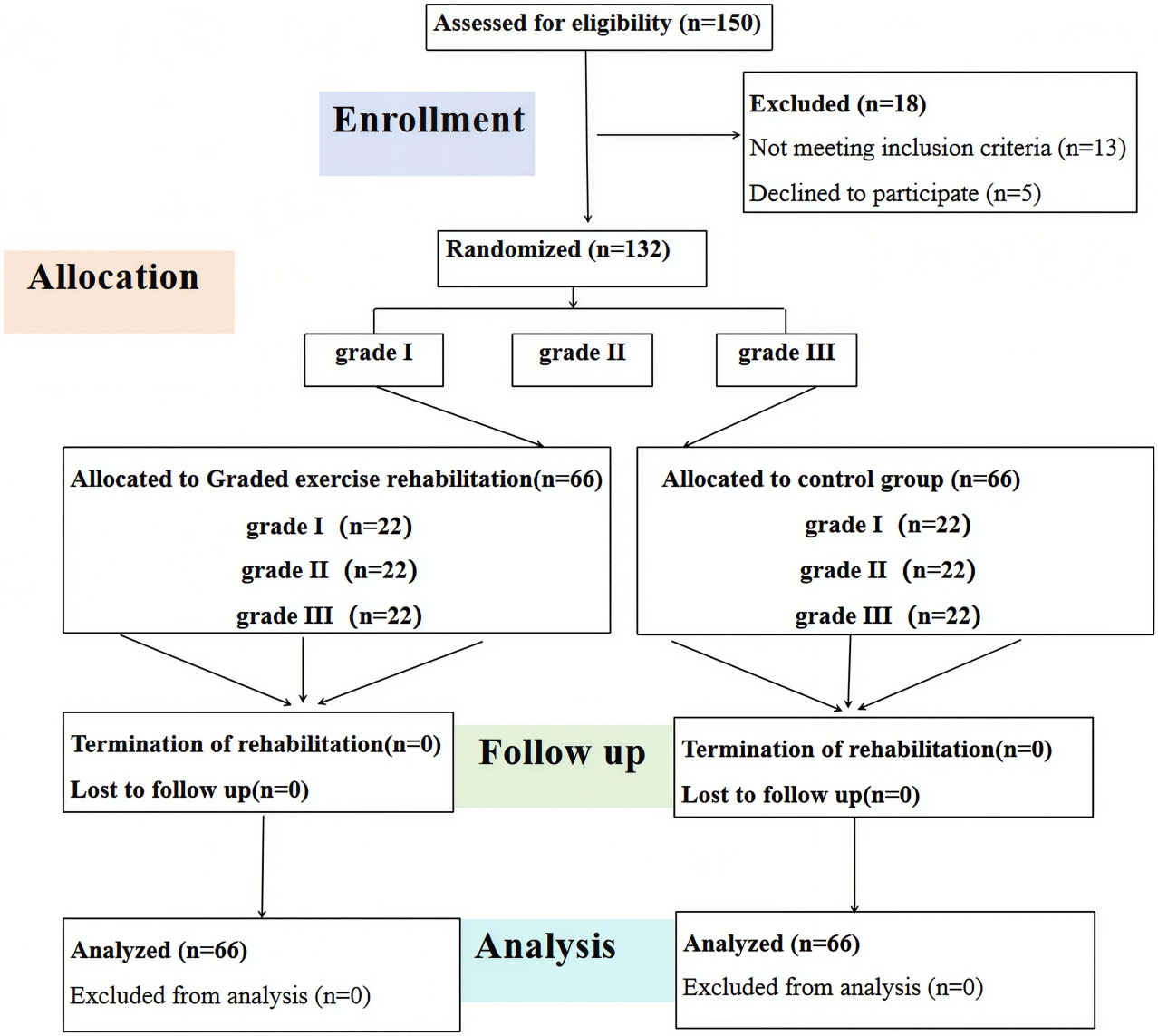

Figure 1 Consort diagram of the study.

Department of Respiratory and Critical Care Medicine of a tertiary hospital in Zunyi and were randomly assigned to two groups: the study group (n=66) and the control group (n=66). All participants provided written informed consent. The sample size was calculated a priori using G*Power software. Assuming a medium effect size (Cohen's d = 0.5), α=0.05, and power=0.80, a minimum of 64 patients per group was required. Therefore, we enrolled 66 patients per group (132 in total).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) diagnosis of COPD according to theGlobal Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 criteria, with the patient experiencing an acute exacerbation; 2) meeting at least one of the diaphragmatic dysfunction criteria defined by the 2022 EXODUS (EXpert consensus On Diaphragm Ultra Sonography in the critically ill): diaphragmatic excursion < 2 cm, diaphragmatic thickness < 2.2 mm, or diaphragmatic thickening fraction<20%; 3) age between 40 and 80 years; 4) clear consciousness, unimpaired verbal communication ability, and willingness to cooperate with the study procedures.

Table 1 Severity-Graded Exercise Rehabilitation Programme for AECOPD Patients

Exercise Grade	Stratification Criteria	Intervention Content
Grade I Exercise	• Patient Severity Level: III • Respiratory Rate: >24 breaths/min • Breathing Pattern: Use of accessory muscles • Oxygenation: Requires>40% FiO_2 • Ventilation: $PaCO_2$ >60 mmHg or pH ≤7.25 • Mental Status: Acutely altered but cooperative	Respiratory training guides patients to close their mouths and relax their breathing regularly, to achieve human-machine coordination and improve the effectiveness of ventilator treatment.Exercise training: mainly passive exercise, gradually transitioning to active exercise according to the patient's condition. (1) Multi-sensory motor stimulation: massage and pat the limbs to enhance sensory input. (2) Upper limb training. ① Joint relaxation: flexion and extension of the wrist, elbow, and shoulder joints in both upper limbs. ② Fist-making exercise: Make a firm fist for 5 seconds, then release it for another 5 seconds. ③ Arm raising exercise: Assist the patient in taking a supine or sitting position, placing both hands flat on both sides of the body, and lifting both upper limbs 180° (3) Lower limb training. ① Joint relaxation: Bend the hip and knee joints of both lower limbs by 90 degrees, and practice alternating legs. ② Straight leg lifting exercise: Keep one limb with the knee joint straight, flex the back of the foot to lift the heel off the bed by about 15 cm, and alternate between legs. ③ Ankle pump exercise: The patient performs toe flexion, dorsiflexion, and wrap-around movements of the ankle joint, all for 5–10 seconds. Exhale when exerting force and inhale when relaxing. Each action is completed 2–3 times per set, 8–12 times per set.
Grade II Exercise	• Patient Severity Level: II • Respiratory Rate: >24 breaths/min • Breathing Pattern: Use of accessory muscles • Oxygenation: Requires >35% FiO_2 • Ventilation: $PaCO_2$ 50–60 mmHg • Mental Status: No acute alteration	**Respiratory muscle training**: pursed lip abdominal breathing: Take a sitting or lying position, place your hands on your chest and abdomen respectively, and when inhaling through the nose, expand your abdomen as much as possible outward to make it bulge while keeping your chest still. When exhaling, close your lips slightly while your abdomen naturally sinks, and contract your abdomen as much as possible towards the spine while keeping your chest still. The ratio of inhalation to exhalation is 1:2 or 1:3. 5–10 minutes/time **Exercise training**: (1) Upper limb training. ① Elbow extension exercise: Take a supine position, straighten the elbow joint, then flex the elbow joint to bring the hand as close to the shoulder joint as possible, and alternate the practice with both hands. ② Stretching up and down: Hold the bed railing with both hands, use the strength of the upper limb muscles to slowly sit up, exhale when getting up forcefully, and slowly lie down and inhale normally. ③ Grip strength exercise: Use grip strength devices, clench fists with hands, and other methods to train the forearm muscles, pectoralis major muscles, biceps brachii muscles, and triceps brachii muscles. (2) Lower limb training. ① Straight leg lifting exercise: Take a supine position, straighten the knee joint, flex the back of the foot to lift the heel of the foot about 15 cm off the bed surface, exhale when lifting the leg with force, inhale slowly when lowering it, and practice alternating legs. ② Bridge movement: Lie in a supine position, bend the knee joints, place both soles of the feet flat on the bed surface, lift the buttocks 10–15 cm off the bed surface with force, hold for 5–10 seconds as much as possible, and then slowly lower them down. ③ Riding a bicycle in the air: take a flat position, keep your upper body still, bend your knees and raise your legs, and alternate between short and short legs while riding a bicycle in the air. Each action is completed 2–3 times per set, 8–12 times per set. **Transfer training**: After the patient's condition improves, assist the patient in getting out of bed, holding onto the bed railing, standing at the foot or beside the bed, walking in place, and moving around the bed.

(*Continued*)

Table 1 (Continued).

Exercise Grade	Stratification Criteria	Intervention Content
Grade III Exercise	• Patient Severity Level: I • Respiratory Rate: ≤24 breaths/min • Heart Rate: <95 beats/min • Breathing Pattern: No use of accessory muscles • Oxygenation: Requires 24–35% FiO_2 • Ventilation: No increase in $PaCO_2$ • Mental Status: No acute alteration	**Respiratory muscle resistance training** (1) Pursed lip abdominal resistance training: take a supine position, and place sandbags on the abdomen based on pursed lip abdominal breathing for abdominal muscle resistance training. The weight of the sandbags gradually increases from 0.5 kg to 2 kg according to the patient's tolerance level, 3–5 minutes per time. (2) Artificial resistance breathing training: using methods such as blowing balloons, taking a deep breath, holding your breath slightly, and then blowing hard to inflate the balloon, reducing residual air in the lungs, maintaining a certain pressure in the trachea, and preventing premature collapse of the bronchi and bronchioles, 3–5 minutes/time **Exercise resistance training** (1) Upper limb resistance training: Open both feet shoulder-width apart, lift sandbags with both hands or tie sandbags with wrists, perform front/side horizontal lifts, neck and back arm flexion and extension, arm bending exercises, etc. to train upper limb muscle groups. (2) Lower limb resistance training: Stand firmly on an armchair or wall, keep your body neutral, tighten your abdomen and hips, straighten your knee joints, tie sandbags to your calves, and perform exercises such as backward extension, outward extension, and knee flexion on your thighs; Sit in a chair and perform straight and bent leg movements. The weight of sandbags gradually increases from 0.5 kg to 2 kg according to the patient's tolerance level. Each movement is completed 2–3 times and 8–12 times per group **Aerobic exercise** (1) Walking training: Starting with a 40% intensity walking distance in a 6-minute walking test, when the Borg score decreases by 1 point from baseline, the distance increases by 10%. (2) Stair climbing training: Up and down stair training, climb 25 stairs for the first time, and add 5 stairs each time if the patient can tolerate it

The exclusion criteria were as follows: 1) presence of any contraindication to exercise, including uncontrolled hypertension (>180/110 mmHg) or hypotension (<90/60 mmHg), severe cardiovascular disease, concurrent acute asthma attack, pulmonary embolism, pneumothorax, or any neuromuscular or osteoarticular disorder affecting exercise capacity; 2) chest deformity, known diaphragmatic paralysis, or chronic neuromuscular disease.

Establishment of the Research Team

A multidisciplinary research team was established to implement the study protocol. The core composition and responsibilities of the team are summarized in Figure 2.

Study Group Allocation

As most patients with AECOPD experience rapid and significant disease progression, pulmonary function tests could not be completed in the majority of cases and were therefore not used as a criterion for severity stratification. Consequently, the 132 eligible AECOPD patients were classified into three severity grades (I, II, and III) according to the predefined stratification criteria (see Table 1 for eligibility criteria). Patients within each severity grade were then randomly allocated to either the study group or the control group.

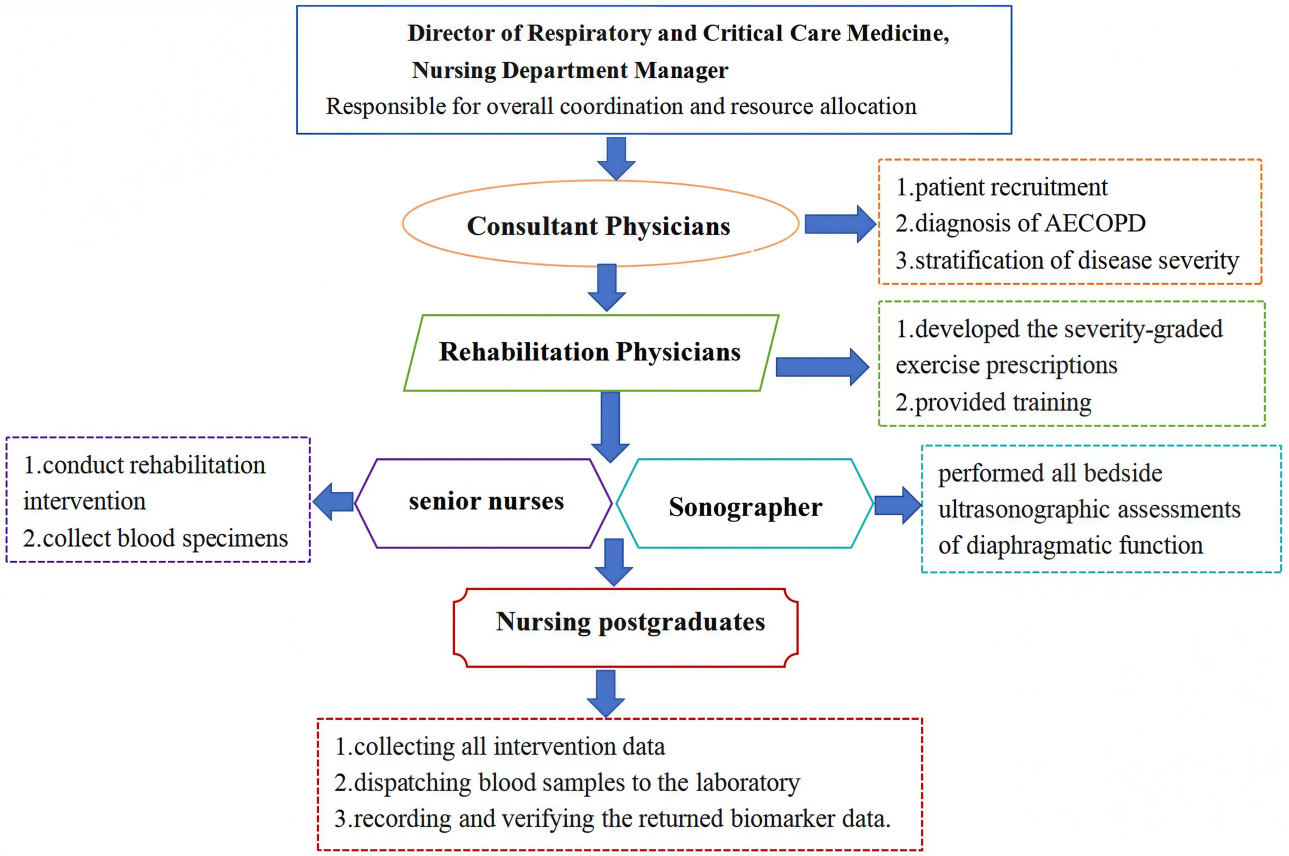

Figure 2 Composition and responsibilities of the multidisciplinary research team.

Intervention Protocol

The intervention was initiated within 24 hours of hospital admission and continued until the day of discharge, without interruption, and was administered twice daily.The hospitalization-based intervention period was chosen because the acute phase of AECOPD is characterized by rapid physiological changes, and previous studies have demonstrated that early, short-term rehabilitation can induce measurable improvements in diaphragmatic function and oxidative stress biomarkers within this timeframe.[18,20]

Standardization, Adherence, and Safety

To ensure standardization, all treating physiotherapists received a detailed manual outlining the procedures for each severity grade and attended training session before the study. Adherence was monitored by a daily log completed by the treating therapist after each session, documenting the exercises performed andtheir duration.

During each exercise session, a trained physiotherapist was present to directly supervise the patient, monitor vital signs and symptoms, and ensure adherence to the safety criteria. Overall safety was overseen by the attending physician. Predefined safety pause criteria included: SpO_2 <85% for >3 minutes; heart rate exceeding the target range for >3 minutes; respiratory rate <5 or >30 breaths/min; systolic blood pressure >180 mmHg or <90 mmHg; mean arterial pressure <65 mmHg; a drop or rise of ≥20% from baseline blood pressure lasting >3 minutes; new need for or increased dose of vasoactive drugs; arrhythmia, acute heart failure, or suspected myocardial infarction; severe dyspnea, chest pain, dizziness, profuse sweating, pallor, intolerance to activity, or patient refusal. Emergency response protocols were established for severe dyspnea, acute myocardial infarction, soft tissue injury, muscle spasm, and falls. If any safety criterion was met, the exercise session was interrupted immediately, and the patient was assessed by the attending physician before considering resumption.

Control Group

In addition to standard medical treatment, the control group received conventional exercise rehabilitation, which comprised the following:

(1) Airway Management: Position turning, directed effective coughing.
(2) Chest Physiotherapy: Manual percussion and vibration, mechanical vibration.
(3) Breathing Exercises: Pursed-lip breathing, diaphragmatic breathing.
(4) Limb Training: Upper limb exercises with light dumbbells and seated lower limb exercises.

All sessions were administered twice daily.

Study Group

In addition to standard medical treatment, the study group received theseverity-graded exercise rehabilitation programme as detailed in Table 1.

Outcome Measures and Assessment

Timing of Assessment

Measurements and assessments were performed for all participants in both groups within 24 hours of enrolment and on the day of hospital discharge.

Outcome Measures

Diaphragmatic Function

Diaphragmatic function was assessed on the right hemidiaphragm using a portable colour Doppler ultrasonography system (Mindray UMT-200). DE was measured with a low-frequency convex array probe, while DTei and DTee were measured with a high-frequency linear array probe. All measurements were obtainedby the same sonographer using an identical measurement protocol to ensure consistency. Representative still images illustrating the ultrasonographic measurement of DE, DTei, and DTee are presented in Figures 3–5.

Oxidative Stress Biomarkers

A 5 mL blood sample was collected from the median cubital vein. MDA levels, indicating the degree of cellular damage under oxidative stress, SOD activity,reflecting the body's capacity to scavenge free radicals and a strong independent

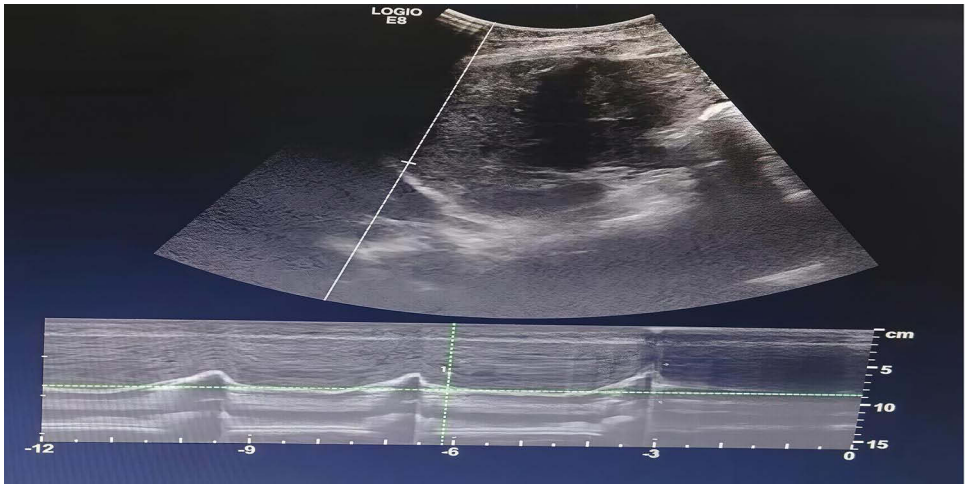

Figure 3 Ultrasonographic measurement of DE. The liver is used as an acoustic window. The M-mode sampling line is directed toward the diaphragmatic dome. The white undulating wave line indicates the amplitude of diaphragmatic movement.

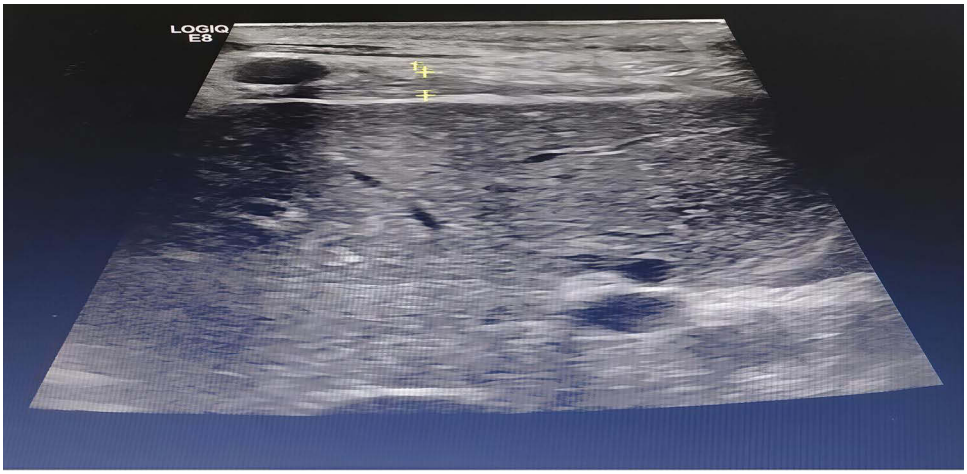

Figure 4 Ultrasonographic measurement of DTei. The diaphragm is visualized as a hypoechoic layer between two hyperechoic lines: the pleural line (superior) and the peritoneal line (inferior). Thickness is measured as the distance between these two lines at the end of inspiration.

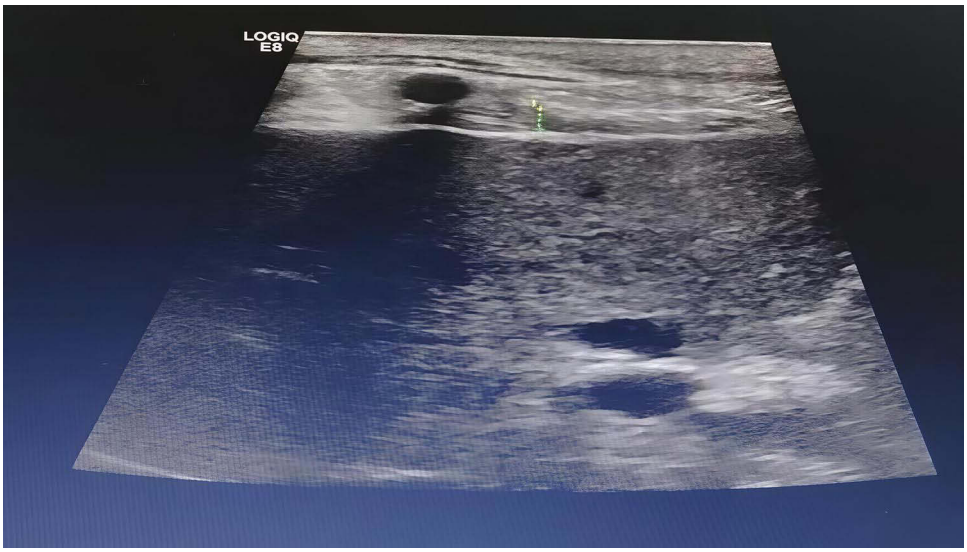

Figure 5 Ultrasonographic measurement of DTee. The same anatomical landmarks as in Figure 4 are used (pleural line and peritoneal line as hyperechoic boundaries). Thickness is measured at the end of expiration, when the diaphragm is at its most relaxed position. Table 1. Severity-Graded Exercise Rehabilitation Programme for AECOPD Patients.

predictor of one-year all-cause mortality in AECOPD patients, and TAOC, representing the plasma's overall antioxidant capability, were measured. All biomarkers were analysed using commercially available ELISA kits purchased from Shanghai Jingkang Bioengineering Co., Ltd.These biomarkers are widely recognized indicators of systemic oxidative stress, and the ELISA method is a standard, validated approach for their quantification. All assays were performed by trained laboratory technicians who were blinded to group allocation, following the manufacturer's protocols. Standard curves were generated for each plate, and samples were measured in duplicate. Internal quality controls were included in each run to ensure reliability.

Data and Statistical Analysis

Data were analyzed using IBM SPSS 29.0. Continuous and categorical variables are presented as mean±SD and frequencies (percentages), respectively. Baseline characteristics were compared using independent t-tests and Chi-square tests. The primary intervention effects on diaphragm function and oxidative stress biomarkers were assessed with

repeated-measures ANOVA (evaluating time, group, and interaction effects). Differences in improvements across severity subgroups (Grades I–III) were compared via one-way ANOVA with LSD post-hoc tests. Additionally, partial correlation analyses examined relationships between changes in diaphragm function and oxidative stress, controlling for severity, age, sex, and disease duration. Statistical significance was set at a two-tailed $p<0.05$.

Before conducting repeated-measures ANOVA and partial correlation analyses, the underlying assumptions (normality, sphericity, homogeneity of variances, and linearity) were formally assessed using Shapiro-Wilk, Mauchly's, and Levene's tests, respectively. Violations of sphericity were adjusted using the Greenhouse-Geisser correction.

Results

Comparison of Baseline Characteristics

A total of 132 patients were enrolled, with 66 allocated to the study group and 66 to the control group. No significant differences were observed in baseline characteristics between the two groups, including age, sex, body mass index (BMI), disease duration, educational level, comorbidities, and history of prior rehabilitation training (all $p > 0.05$), confirming their comparability.See Table 2 for details.

Changes and Effects on Diaphragmatic Function

Statistical analysis revealed that the graded exercise rehabilitation significantly improved diaphragmatic function in COPD patients (see Table 3). Repeated-measures analysis of variance confirmed significant time-by-group interaction effects for all three diaphragmatic parameters-DE, DTei, and DTee (all p<0.001), with medium to large effect sizes. Post-intervention measures were significantly improved compared to baseline in the study group (all $p<0.001$), whereas no significant changes were observed in the control group. Furthermore, the study group demonstrated significantly better outcomes than the control group across all measures at post-intervention (all $p<0.001$). These findings indicate that the improvements in diaphragmatic function are attributable to the graded exercise rehabilitation intervention rather than natural recovery.

Changes and Effects in Oxidative Stress Biomarkers

Repeated-measures analysis of variance was used to evaluate the impact of the graded exercise rehabilitation on oxidative stress markersAs presented in Table 4, significant time-by-group interaction effects were observed for both SOD (p=0.001) and TAOC (p=0.024), but not for MDA (p=0.965).Simple effects analysis indicated that, compared to the

Table 2 Comparison of Baseline Characteristics Between the Two Groups

Characteristic	Study Group (n=66)	Control Group (n=66)	Test Statistic	p-value
Age (years)	68.92±7.216	67.91±8.954	0.7171[a)]	0.475
Sex (n)			0.148[b)]	0.701
Male	48 (72.7)	46 (69.7)		
Female	18 (27.3)	20 (30.3)		
Body mass index	22.249±2.995	23.112±3.793	−1.450[a)]	0.149
Disease duration (years)	9.267±6.492	9.247±9.824	0.014[a)]	0.989
Education level			1.803[b)]	0.406
Primary school or below	53 (80.3)	50 (75.8)		
Junior high school	7 (10.6)	12 (18.2)		
Secondary school or above	6 (9.1)	4 (6.1)		
Comorbidities			0.433[b)]	0.511
Yes	62 (93.9)	60 (90.9)		
No	4 (6.1)	6 (9.1)		
Previous rehabilitation training			0.553[b)]	0.457
Yes	8 (12.1)	11 (16.7)		
No	58 (87.9)	55 (83.3)		

Note: a) t-value; b) χ2-value.

Table 3 Changes in Diaphragmatic Function Before and After Intervention (n=66/Group, $\bar{x} \pm s$)

Measure	Group	Before Intervention	After Intervention	Within-Group (*p*-value)	Between-Group (*p*-value)
DE (cm)	Study	1.556±0.260	1.800±0.303	<0.001	$p < 0.001$
	Control	1.501±0.272	1.497±0.300	0.245	
DTei (mm)	Study	3.161±0.460	3.561±0.526	<0.001	$p < 0.001$
	Control	3.027±0.503	3.175±0.680	0.112	
DTee (mm)	Study	2.660±0.571	2.987±0.633	<0.001	$p < 0.001$
	Control	2.498±0.508	2.578±0.539	0.09	

Note: p-value for between-group comparison at post-intervention (independent *t*-test). Significant time×group interactions were observed for all three parameters (p<0.001, repeated-measures ANOVA), indicating that improvements were attributable to the intervention. Detailed statistics (t-values, F-values, partial η^2) are available from the corresponding author upon request.

Table 4 Changes in Oxidative Stress Biomarkers Before and After Intervention (n=66/Group, $\bar{x} \pm s$)

Measure	Group	Before Intervention	After Intervention	Within-Group (p-value)	Between-Group (p-value)
MDA	Study	6.015±1.372	5.777±1.463	0.316	p=0.703
(nmol/mL)	Control	5.956±1.330	5.875±1.407	0.316	
SOD	Study	13.921±3.770	16.263±4.767	<0.001	p=0.005
(ng/mL)	Control	13.6584±3.358	14.087±3.483	0.073	
TAOC (U/mL)	Study	16.785±4.201	19.504±3.911	<0.001	p=0.025
	Control	16.817±4.084	17.816±4.372	0.094	

Notes: p-value for between-group comparison at post-intervention (independent *t*-test). Significant time×group interactions were observed for SOD (p=0.001) and TAOC (p=0.024) but not for MDA (p=0.965), indicating that the intervention enhanced antioxidant capacity. Detailed statistics (t-values, F-values, partial η^2) are available from the corresponding author upon request.

control group, the study group demonstrated significant post-intervention increases in SOD activity and TAOC levels (all $p<0.05$). However, no significant changes were observed in MDA levels, a marker of lipid peroxidation, in either group. These results suggest that the rehabilitation programme effectively enhanced the body's antioxidant defence capacity, but its effect on mitigating oxidative damage was not significant.

Heterogeneity in Improvements of Diaphragmatic Function and Oxidative Stress Biomarkers Across Severity Subgroups Within the Study Group

To further evaluate patient heterogeneity in rehabilitation response, we analysed the differential benefits among patients stratified by disease severity. The results demonstrated that the intervention effects varied depending on the specific outcome and baseline severity: Regarding diaphragmatic function, the improvement in DE was significantly greater in patients with mild (Grade I) disease (0.295±0.218) compared to those with moderate (Grade II) disease (p=0.018), suggesting they derived the greatest benefit in diaphragmatic contractile function. In contrast, for oxidative stress, although a significant difference in MDA change was observed across severity groups (p=0.001), thetrendwas severity-specific-MDA levels decreased in patients with mild and moderatedisease (improvement values: −1.506 and −0.421, respectively), whereas they increased in patients with severe (Grade III) disease (0.853±1.298), a change significantly worse than in the mild and moderate groups (all $p< 0.05$). This indicates that while the graded protocol ameliorated oxidative damage in patientswith mild-to-moderate disease, it failed to reverse the pre-existing oxidative stress burden in severe patients, demonstrating that severity-graded rehabilitation achieves differential physiological effects.Detailed results are presented in Table 5.

Table 5 Comparison of Improvements in Diaphragmatic Function and Oxidative Stress Biomarkers by Disease Severity

Measure	Disease Severity	N	Improvement Value ($\bar{x} \pm s$)	F-Value	*P*-value	Post-hoc Comparisons
DE	I	22 per grade	0.295 ± 0.218	3.293	0.044*	I vs II: p=0.018*
	II		0.171 ± 0.150			I vs III: p=0.608
	III		0.269 ± 0.128			II vs III: p=0.060
DTei	I	22 per grade	0.380 ± 0.235	0.517	0.599	No significant differences
	II		0.436 ± 0.198			
	III		0.382 ± 0.180			
DTee	I	22 per grade	0.251 ± 0.164	1.482	0.235	No significant differences
	II		0.356 ± 0.260			
	III		0.379 ± 0.339			
MDA	I	22 per grade	−1.506±2.447	7.513	0.001*	I vs II:p=0.020*I vs III: p<0.001*
	II		−0.421±2.187			II vs III: p=0.150
	III		0.853±1.298			
SOD	I	22 per grade	0.614±8.974	1.724	0.187	No significant differences
	II		3.400±4.284			
	III		2.167±2.766			
TAOC	I	22 per grade	0.867±7.497	1.084	0.345	No significant differences
	II		2.347±8.028			
	III		−0.886±6.298			

Note: *1) Improvement value = Post-intervention value - Pre-intervention value; 2) Data are presented as mean±standard deviation ($\bar{x} \pm s$); 3) *indicates p < 0.05, considered statistically significant; 4) Post-hoc comparisons were performed using the LSD test; 5) I = mild, II = moderate, III = severe.

Table 6 Specific Effects of Graded Exercise Rehabilitation on the Relationship Between Diaphragmatic Function and Oxidative Stress

Measure Association		Study Group (n=66)		Control Group (n=66)		Correlation Indication
		R-value	p-value	r-value	p-value	
DE	MDA	−0.314	0.013*	0.002	0.987	1
	SOD	−0.331	0.009*	0.002	0.987	1
	TAOC	−0.304	0.016*	0.059	0.650	1
DTei	MDA	−0.124	0.336	0.171	0.184	2
	SOD	−0.071	0.583	0.042	0.744	2
	TAOC	−0.161	0.211	−0.093	0.474	2
DTee	MDA	−0.141	0.273	0.138	0.286	2
	SOD	−0.002	0.987	0.092	0.475	2
	TAOC	−0.060	0.645	−0.014	0.913	2

Notes: *1) r: partial correlation coefficient; p: significance level; 2) * indicates < 0.05, statistically significant; 3) 1 indicates intervention-specific correlation, 2 indicates no significant difference; 4) All analyses were controlled for disease severity, sex, age, and disease duration.

Specific Effects of Graded Exercise Rehabilitation on the Diaphragm-Oxidative Stress Relationship

Partial correlation analysis revealed a significant specific effect of the graded exercise rehabilitation (see Table 6). Only in the study group were improvements in DE significantly correlated with improvements in all oxidative stress biomarkers (MDA, SOD, TAOC; r = −0.314 to −0.331, all p< 0.05). In contrast, none of thesecorrelations were statistically significant in the control group. This indicates that the rehabilitation intervention did not uniformly improve all aspects of diaphragmatic function, but rather specifically and significantly enhanced the negativeassociation between diaphragmatic excursion (DE) and systemic oxidative stressstatus. This implies that, post-intervention, a greater amelioration of oxidative stress was associated with better recovery of diaphragmatic mobility. Furthermore,no

Table 7 Specificity of Interrelationships Among Oxidative Stress Biomarkers

Measure Association	Study Group (n=66)		Control Group (n=66)		Correlation Indication
	R-value	p-value	r-value	p-value	
MDA-SOD	0.332	0.008*	0.338	0.007*	a
MDA-TAOC	0.486	<0.001*	0.391	0.002*	a
SOD-TAOC	0.410	<0.001*	0.398	0.001*	a

Notes: 1) r: partial correlation coefficient; *p*: significance level; 2) * indicates < 0.05, statistically significant; 3) a indicates consistent correlations across groups; 4) All analyses were controlled for disease severity, sex, age, and disease duration.

significant associations were observed between the diaphragmatic thickness measures (DTei, DTee) and oxidative stress biomarkers in either group, suggesting that the rehabilitation intervention likely exerts its effects primarily by improving diaphragmatic contractile function and efficiency, rather than by altering static structural thickness.

Interrelationship Analysis of Oxidative Stress Biomarkers

Internal correlation analysis revealed that the improvement values of MDA, SOD, and TAOC exhibited significant positive correlations in both the study and control groups (r = 0.332–0.486, $p< 0.01$). This indicates an intrinsic coordinated relationship between the oxidative damage and antioxidant defense systems, irrespective of rehabilitation intervention. This consistent pattern across groups reflects an inherent physiological linkage within the oxidative stress system, independent of the intervention, thereby providing a stable biological reference context for the study.Detailed results are presented in Table 7.

Discussion

Graded Exercise Rehabilitation Significantly Improves Diaphragmatic Function in AECOPD Patients

Our study robustly demonstrates that a severity-graded rehabilitation program during hospitalization yields significant, clinically meaningful improvements in diaphragmatic function among AECOPD patients. Compared to usual care, the intervention group exhibited greater increases in diaphragmatic excursion (DE: 1.556±0.260 cm to 1.800±0.303 cm), end-inspiratory thickness (DTei), and end-expiratory thickness (DTee), with medium to large effect sizes and significant time-by-group interactions (all $p<0.001$). The most pronounced improvement was observed in DE, a dynamic marker of contractile efficiency. This finding confirms that early, personalized exercise is safe and effective even in the acute phase, extending benefits previously observed in stable COPD to a more vulnerable inpatient population.[21–23] The rapid gain in DE, as opposed to thickness parameters which may reflect slower structural adaptation, likely stems from enhanced neuromuscular drive, fatigue resistance, and local perfusion, which are crucial for alleviating dyspnea and maintaining respiratory stability.

Differential Modulation of the Oxidative Stress Response

Our results reveal a dual effect on oxidative stress. The intervention significantly enhanced the endogenous antioxidant defense system, evidenced by a greater increase in serum superoxide dismutase (SOD: $p=0.005$ vs. control) and total antioxidant capacity (TAOC: $p=0.025$). This aligns with the exercise hormesis concept, whereby moderate physiological stress upregulates cytoprotective pathways.[24,25] Conversely, no significant between-group difference was found in malondialdehyde (MDA), a marker of lipid peroxidation ($p=0.965$). This indicates that while short-term rehabilitation effectively bolsters antioxidant capacity, it may be insufficient to rapidly clear pre-existing oxidative damage during an acute exacerbation. The primary therapeutic effect on oxidative stress thus appears to be the augmentation of defense mechanisms rather than the reversal of accumulated damage.

Heterogeneity in Intervention Effects: The Role of Disease Severity

Subgroup analysis underscores that intervention benefits are severity-dependent. Patients with mild (Grade I) disease derived the greatest functional benefit, showing a superior improvement in DE (0.295±0.218 cm) compared to those with moderate disease (0.171±0.150 cm; p=0.018). At the molecular level, a concerning divergence was observed: MDA levels decreased in mild and moderate patients (improvement values: −1.506 and −0.421) but increased in severe (Grade III) patients (0.853±1.298; p<0.05 vs. mild). This indicates that while the graded protocol alleviates oxidative damage and improves function in mild-to-moderate disease, patients with severe AECOPD may have an overwhelming oxidative stress burden that is not mitigated by short-term exercise alone. This dissociation validates the necessity of severity-stratified rehabilitation protocols.

Correlation Between Diaphragmatic Function and Oxidative Stress

A pivotal finding is the specific correlation, observed only in the intervention group, between improved diaphragmatic function and attenuated oxidative stress. Partial correlation analysis revealed that the increase in DE was significantly associated with favorable changes in all oxidative biomarkers (MDA: r = −0.314, p=0.013; SOD: r = −0.331, p=0.009; TAOC: r = −0.304, p=0.016). No such correlations were found in the control group or for diaphragmatic thickness indices. This suggests that exercise-induced enhancement of antioxidant defenses may protect diaphragmatic myocytes, potentially improving calcium handling and mitochondrial function,[8,26] thereby translating into better contractile performance. This evidence chain links molecular adaptation to organ-level recovery, deepening our understanding of pulmonary rehabilitation. However, it is important to note that these findings are correlational and do not prove causality. The proposed mechanistic interpretation remains hypothesis-generating and requires further experimental validation.

Clinical and Mechanistic Implications

Clinical relevance of short-term improvements – Although the intervention period was limited to the hospital stay, the observed improvements in diaphragmatic excursion and antioxidant markers are clinically relevant. Enhanced diaphragmatic excursion is a direct indicator of improved contractility and has been associated with reduced dyspnea and better exercise capacity in AECOPD patients. Furthermore, serum SOD is a strong independent predictor of one-year all-cause mortality in AECOPD, and increased TAOC has been linked to better survival. Therefore, the short-term improvements observed in our study may translate into meaningful clinical benefits, including better symptom control and potentially improved prognosis, though longer-term follow-up studies are needed to confirm this.

Robustness of the correlation and influence of baseline heterogeneity – The intervention-specific partial correlations between improvements in diaphragmatic excursion and oxidative stress biomarkers remained significant after controlling for disease severity, age, sex, and disease duration, supporting their robustness. However, the magnitude of these correlations varied across severity subgroups, likely due to baseline heterogeneity. Patients with mild (Grade I) disease showed the greatest improvement in DE and a reduction in MDA, whereas patients with severe (Grade III) disease did not exhibit MDA reduction despite some improvement in DE. This suggests that the association between enhanced diaphragmatic mobility and attenuated oxidative stress is most evident in mild-to-moderate AECOPD, where the endogenous antioxidant system retains some capacity to respond to exercise. In severe patients, the overwhelming oxidative burden may overwhelm the protective effects of short-term rehabilitation, highlighting the need for adjunctive therapies in this population.

Clinical guidance for severity-stratified rehabilitation – Our findings offer concrete guidance for clinical decision--making based on disease severity. For patients with mild (Grade I) AECOPD, early initiation of progressive resistance and aerobic exercise is recommended. For moderate (Grade II) AECOPD, moderate-intensity exercise focusing on respiratory muscle training and resistance exercises should be prioritized. For severe (Grade III) AECOPD, exercise should be started at low intensity with close safety monitoring, and adjunctive strategies such as nutritional support or antioxidant supplementation should be considered.

Limitations

This study has several limitations: (1) Single-center design may affect generalizability. (2) Lack of post-discharge follow-up limits assessment of long-term outcomes. (3) While antioxidant capacity improved, no significant reduction in oxidative damage (MDA) was observed. (4) The study did not investigate downstream cellular mechanisms linking oxidative stress to diaphragmatic dysfunction. (5) Due to the inherent differences in exercise intensity and content between the study group and the control group, it was not possible to blind the treating physiotherapists or the patients to group allocation, which may introduce performance bias. However, outcome assessors (sonographers, laboratory technicians, and statisticians) were kept blinded to group assignment throughout the trial to minimize detection bias, and the primary outcomes were objective measurements.Future research should focus on multi-center validation, long-term follow-up, optimized intervention strategies (eg., combining exercise with antioxidants), and mechanistic studies to elucidate underlying pathways.

Conclusion

This study demonstrates that a severity-graded exercise rehabilitation program is a safe and effective strategy for improving diaphragmatic function and endogenous antioxidant capacity in hospitalized patients with AECOPD, with treatment responses varying according to baseline disease severity. These findings provide a practical, evidence-based framework for implementing early, individualized pulmonary rehabilitation in the inpatient setting, supporting a severity-stratified approach to clinical decision-making. It is important to note that these conclusions are based on short-term, in-hospital physiological outcomes and do not directly address long-term prognosis. Future multicenter studies with extended follow-up are warranted to confirm these physiological benefits and evaluate their impact on long-term clinical outcomes, as well as to optimize intervention strategies for patients with severe AECOPD, in whom exercise alone may be insufficient.

Trial Registration

This study was a single-centre, randomised controlled trial (RCT). It has been registered with the Chinese Clinical Trial Registry (Registration number: ChiCTR2500106687; Registration date: 2025-07-28). This registration was completed retrospectively following the conclusion of the study, and all research data are available upon reasonable request. The study received approval from the Ethics Committee of The Second Affiliated Hospital of Zunyi Medical University (Approval No. KYLL-2025-040) and was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki.

Abbreviations

AECOPD, Acute exacerbation of chronic obstructive pulmonary disease; COPD, Chronic obstructive pulmonary disease; DE, Diaphragmatic excursion; DTei, Diaphragmatic thickness at end-inspiration; DTee, Diaphragmatic thickness at end-expiration; MDA, Malondialdehyde; SOD, Superoxide dismutase; TAOC, Total antioxidant capacity; ELISA, Enzyme-linked immunosorbent assay.

Data Sharing Statement

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request. Data requests should include a brief description of the intended use and relevant research credentials. All data sharing will be conducted in accordance with applicable ethical guidelines and institutional policies.

Consent to Participate

This study was approved by the local ethics committee and written informed consent was obtained from all participants before enrollment.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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