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CLINICAL RESEARCH ARTICLE

Effects of Dog-Assisted Occupational Therapy on Upper Limb Functions in ALS and Other Neuromuscular Disorders: A Randomized Controlled Pilot Study

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ABSTRACT

Introduction/Aims: The beneficial effects of animal-assisted therapy (AAT) on balance, walking endurance, and mood symptoms in amyotrophic lateral sclerosis (ALS) have been previously demonstrated. In this study, we aimed at expanding upon these findings by further evaluating its effects on upper limb (UL) functions and mood symptoms both in ALS and other neuromuscular disorders (NMDs).

Methods: Sixty-eight patients participated in a regular 2-week occupational therapy program once a day. For three days a week, in place of the traditional treatment, the AAT group ($N = 34$) performed a session in interaction with the therapy dog. Outcome measures included hand grip strength, manual dexterity, and mood symptoms. Differences between baseline and post-treatment values were assessed using the Wilcoxon Signed-Rank Test, and one-way analysis of covariance was used to examine between-group differences in post-treatment values, adjusting for baseline measurements.

Results: Both groups improved in hand grip strength ($p = 0.004–0.03$), whereas mood symptoms improved exclusively in the AAT group ($p = 0.0003–0.03$). Post-treatment values were significantly better in the AAT group ($p = 0.01–0.03$). When ALS patients were analyzed separately, the improvement of hand grip strength and mood symptoms was observed only in the AAT group ($p = 0.001–0.04$), which accordingly showed better post-treatment values ($p = 0.0007–0.05$).

Discussion: Our findings indicate that AAT has greater beneficial effects than traditional treatments on UL strength and mood symptoms. These findings have the potential to facilitate more effective rehabilitation strategies both in ALS and other NMDs.

Abbreviations: AAT, Animal-assisted therapy; ALS, Amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale revised; ANCOVA, Analysis of covariance; HADS, Hospital Anxiety and Depression scale; LL, Lower limb; MNDs, Motor neuron diseases; MRC, Medical Research Council; NHPT, Nine-Hole Peg Test; NMDs, Neuromuscular disorders; OT, Occupational therapy; UL, Upper limb.

1 | Introduction

Many neuromuscular disorders (NMDs), particularly amyotrophic lateral sclerosis (ALS), continue to lack treatments that improve muscle strength and function. It is therefore essential to optimize existing symptomatic interventions, such as physical and occupational therapy (OT).

Balance and lower limb (LL) symptoms may be improved through physical therapy, while OT represents an effective tool for enhancing upper limb (UL) strength and dexterity, which are frequently affected in these conditions. Therefore, it is recommended that these characteristics be evaluated in clinical trials [1].

UL function is a key determinant of independence in daily life activities. Recent studies have demonstrated significant correlations between objective grip strength measures and the associated ALS Functional Rating Scale revised (ALSFRS-R) domains of physical function, as well as the patient-perceived quality of life [2].

Despite these considerations, OT studies on NMDs are rare and have significant methodological limitations. With regard to ALS, although preliminary investigations have suggested that OT may be beneficial in reducing perceived fatigue and improving manual dexterity [3–5], these studies have largely been limited to small clinical samples and have employed non-controlled pre-to-post designs [6]. This underscores the need for more rigorous studies to ascertain therapeutic efficacy.

Alongside traditional treatments, novel approaches such as animal-assisted therapy (AAT) are gaining increasing attention for their additional benefits. The co-therapist role of animals in AAT interventions has been shown to improve alertness and concentration [7] and enhance mental and behavioral health [8]; this suggests the utility of such treatment for further improving non-motor symptoms in various neurological conditions. In ALS it has recently been shown that AAT—specifically dog-assisted physical therapy—has greater beneficial effects than traditional treatments on balance, walking endurance, and mood symptoms [9].

In this study, we therefore aimed to build upon previous findings by comparing the effects of dog-assisted and traditional OT on UL functions and the psychological status of patients with ALS and other NMDs.

2 | Methods

2.1 | Study Design

The study protocol was approved by the Regional Ethics Committee for Research and Trials in Genoa (CER Liguria n. 004/2018).

All study procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

2.2 | Participants

Eligible patients were recruited at the NEuroMuscular Omnicentre (NEMO) Inpatient Rehabilitation Unit of Arenzano from June 2018 to June 2019.

The Unit is a clinical centre devoted to the functional assessment, clinical management, and rehabilitation of patients with ALS and other NMDs. To achieve these objectives, patients are periodically admitted for a multimodal functional assessment of motor, respiratory, and cognitive/psychological symptoms. After the initial evaluations, all patients participate in a physical therapy program (consisting of daily 1-h morning and 1-h afternoon sessions) and an OT program (consisting of daily 1-h morning sessions). Depending on the presence of additional symptoms, the patients may also undergo non-invasive ventilation adaptation, cognitive rehabilitation, and/or psychological support sessions.

Inclusion criteria for this study were: (1) a confirmed diagnosis of either ALS (possible, probable, probable laboratory-supported or definite according to the revised El Escorial criteria [10]) or other NMD, (2) the ability to perform all baseline motor examinations, and (3) the capacity to understand and sign the informed consent for participation in the study.

Exclusion criteria were: (1) any medical condition that could interfere with physical activity, including active malignancy, severe heart, lung, renal, and liver failure, (2) cognitive impairment sufficient to prevent understanding the study or complying with the study requirements (including frontotemporal dementia in ALS cases) [11], and (3) allergy to animals.

2.3 | Allocation and Blindness

Based on the case–control design, participants were assigned to either the AAT group or the control group, with matching criteria including age, sex, frequency of ALS diagnoses, and UL muscle strength as assessed using the Medical Research Council (MRC) Scale. Additionally, for ALS patients, matching criteria included the degree of disability evaluated using the ALSFRS-R.

Outcome assessors and statistical analysts were both blinded to the allocation sequences. Independent therapists were assigned to measure the outcomes and were instructed not to participate in any training sessions. Unrelated codes, such as A and B, were used to represent the groups during the evaluation and statistical analyses.

2.4 | Intervention Procedure

All patients (AAT and control groups) participated in a regular OT program at the NEMO Inpatient Rehabilitation Unit of Arenzano. This program consisted of daily one-hour sessions, which included: (a) UL strengthening activities, and (b) manual dexterity and fine motor skills training.

The total duration of the training program was two weeks. All sessions were adapted to the fatigability and autonomy of each patient according to the Borg rating scale of perceived exertion [12] and were interrupted if patients reported a score of 15 (indicating hard exertion).

UL strengthening activities included the following exercises: (a) using a stick to trace lines drawn on a board positioned on a reclinable desk, both with gravity (vertical position of the desk) and without gravity (horizontal position of the desk); (b) hand gripping using a gripper; (c) pinching a small soft ball; and (d) placing a small ball into the occupational therapist's hand and then holding the arm raised with an open hand to retrieve the ball.

Manual dexterity and fine motor skills training included the following exercises: (a) picking up small objects and handing them to the occupational therapist; (b) opening and closing a backpack and adjusting its straps; (c) knotting and untying a bandana from the occupational therapist's arm; and (d) creating drawings by connecting points with a fine pen.

2.5 | AAT Group

In place of the traditional morning session, for three days a week, patients in the AAT group performed an OT session focusing on UL strength and dexterity with a simultaneous interaction with a therapy dog.

AAT exercises were developed by a team comprising a physiatrist as the project manager, occupational therapists with 8 years of experience working with ALS and other NMDs patients, an AAT-expert dog handler and veterinary surgeon, and two therapy dogs, according to the National Guidelines and IAHAIO. All team members received specific academic training in AAT, and the therapy dogs underwent advanced education training, as detailed in the Supporting Informations.

The AAT session was performed by experienced occupational therapists who carried out rehabilitation work through the interaction of the patient with the therapy dogs (always supervised by their handler). Occupational therapists worked with each patient during interactions with the therapy dog.

The UL strengthening activities consisted of regular UL strengthening exercises (as detailed in the regular session paragraph), but with simultaneous interaction with the therapy dog, in particular: (a) caressing and massaging the dog from head to tail and back; (b) brushing the dog using two brushes with different resistances; (c) decorating the dog's bandana using clothespins; and (d) placing a small ball in the dog's mouth and keeping the arm raised with an open hand to get the ball back.

Manual dexterity and fine motor skills training included the following tasks in interaction with the therapy dog: (a) grabbing dog kibbles and leaving them on a table ready for the dog; (b) putting on and taking off the harness and leash from the dog; (c) knotting and unknotting a bandana from the dog's neck; and (d) using cotton swabs to clean the dog's paws.

2.6 | Outcome Measurements

Clinical outcome assessments for all patients were conducted at baseline and after the 2-week treatment. To prevent fatigue from the assessments, there was a 10-min interval between tests. The total duration of the evaluation was 30 min, including rest periods.

To evaluate UL muscle strength, hand grip was assessed using a dedicated digital dynamometer. This movement involves 35 forearm and hand muscles, including both agonists (flexors) and stabilizers (extensors), providing a comprehensive yet common and simple measure of muscle strength [13].

Manual dexterity was evaluated using the Nine-Hole Peg Test (NHPT) [14]. Mood symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS), a questionnaire consisting of two subscales, each with seven questions; this scale evaluates both anxiety and depressive symptoms [15].

2.7 | Statistical Analyses

Differences in demographic and baseline clinical characteristics between the AAT and control groups were evaluated using the Wilcoxon signed-rank test (for numeric data) and the chi-squared test (for categorical data), as appropriate.

To examine the effect of AAT treatment, intragroup differences between baseline and post-treatment values were evaluated separately for each group using the Wilcoxon signed-rank test. Finally, a one-way analysis of covariance (ANCOVA) was used to compare post-treatment values between the AAT and control groups, using baseline measurements as covariates.

All data were analyzed using CRAN R Version 3.4.1 (https://cran.r-project.org/, accessed on 16 May 2022), with the statistical significance threshold set at $p \leq 0.05$.

3 | Results

3.1 | Analyses of All Patients

A total of 68 patients were enrolled in this study. The demographic and baseline clinical features of the AAT ($N = 34$) and control ($N = 34$) groups are presented in Table 1. According to the matching criteria, the frequency of ALS diagnoses and the MRC UL strength scores did not differ significantly between the AAT and control groups.

As regards the ALS diagnoses, these were respectively 25 in the AAT and 26 in the control group. Among other NMDs diagnoses, the AAT group included 5 patients with genetically confirmed myotonic dystrophy type 1 (DM1) [16], 2 patients with cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) [17], and 2 patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [18]. The control group comprised 2 patients with Guillan-Barrè syndrome [19],

TABLE 1 | Demographic and clinical features of the control and AAT groups.

	Control group ($n = 34$)	AAT group ($n = 34$)	p
Demographic features			
Age (years)	68.32 ± 10.73	65.69 ± 12.10	0.10
Sex (M/F)	20/14	16/18	0.46
Diagnosis (ALS/other NMDs)	26/8	25/9	1.00
Motor UL features			
MRC R UL	27.18 ± 6.20	27.27 ± 5.56	0.67
MRC L UL	27.29 ± 6.45	27.70 ± 6.02	1.00
HAND GRIP R UL	9.66 ± 6.91	11.03 ± 6.95	0.70
HAND GRIP L UL	10.00 ± 7.41	12.14 ± 6.60	0.29
NHPT R UL	0.06 ± 0.12	0.05 ± 0.10	0.73
NHPT L UL	0.06 ± 0.13	0.03 ± 0.05	0.80
Mood features			
HADS Total score	12.11 ± 3.98	13.36 ± 6.11	0.34
HADS Anxiety score	6.64 ± 2.91	7.63 ± 4.16	0.41
HADS Depression score	5.47 ± 1.97	5.77 ± 2.59	0.43

Note: Values are given as means ± standard deviations and absolute frequencies. Abbreviations: ALS, amyotrophic lateral sclerosis; F, females; HADS, Hospital Anxiety and Depression Scale; L, left; M, males; MRC, Medical Research Council Scale; NHPT, Nine-Hole Peg Test; NMDs, neuromuscular diseases; R, right; UL, upper limb.

4 patients with CIDP, 1 patient with DM1, and 1 patient with inclusion body myositis [20].

No statistically significant differences were observed between the two groups in terms of the baseline clinical motor and mood features.

The results of the Wilcoxon signed-rank test and ANCOVA are presented in Table 2. Regarding intragroup differences in motor features, a significant improvement from baseline to post-treatment values was observed in both groups for the right- and left-hand grip, whereas no significant changes were observed for the NHPT.

Concerning mood measures, significant improvements in the HADS total, anxiety, and depression scores from baseline to post-treatment were observed exclusively in the AAT group.

ANCOVA showed statistically significant between-group differences in post-treatment values for right- and left-hand grip, as well as the HADS anxiety domain, with the AAT group showing better motor and mood scores.

3.2 | Analyses of the ALS Subgroup

The demographic and baseline clinical features of the ALS-only AAT and control groups are presented in Table 3. According to the matching criteria, the MRC UL strength and ALSFRS-R scores do not differ between the AAT and control groups.

No statistically significant differences were observed between the two groups in terms of baseline clinical motor and mood features.

The results of the Wilcoxon signed-rank test and ANCOVA of the ALS-only AAT and control groups are presented in Table 4. Regarding the intragroup differences in motor features, significant improvements from baseline to post-treatment values were observed only in the AAT group for the right- and left-hand grip, while no significant differences were observed for the NHPT.

Regarding mood measures, significant improvements from baseline to post-treatment in the HADS total and anxiety scores were observed exclusively in the AAT group.

ANCOVA showed statistically significant post-treatment differences between the two groups in right- and left-hand grip, as well as the HADS total and anxiety scores, with the AAT group showing better motor and mood outcomes.

4 | Discussion

By comparing traditional and dog-assisted OT in patients with ALS and other NMDs, this study demonstrated that: (a) while both programs improved muscle strength, post-treatment values were significantly better in the AAT group; (b) patients undergoing the AAT program also showed a significant improvement in mood symptoms that was not observed in the control group; and (c) these results were even more pronounced in the ALS subgroup analyses.

Taken together, these observations suggest that AAT has greater beneficial effects on UL strength and mood symptoms than traditional treatments, particularly in patients with ALS.

Studies evaluating the effects of exercise on muscle strength in patients with ALS and other NMDs have yielded conflicting results. Some studies have reported either no effect or, at most, maintenance effects [21, 22], while others have demonstrated positive effects [23, 24].

In this context, the added value of AAT can be explained by at least two main factors. The first is attentional focus, which has been shown to improve both muscular endurance and force production [25]. AAT is indeed known to exert beneficial effects on alertness and concentration [7]. The therapy dog acts as an external attentional focus, which in turn leads to an enhanced

TABLE 2 | Intragroup differences between baseline and post-treatment values, and differences in post-treatment values between the control and AAT groups.

	Group	Baseline	Post-treatment	*p**	*p***
Motor UL features					
HAND GRIP R UL	AAT	11.03 ± 6.95	12.85 ± 6.92	**0.004**	**0.03**
	Control	9.66 ± 6.91	10.72 ± 7.09	**0.02**	
HAND GRIP L UL	AAT	12.14 ± 6.60	13.27 ± 7.00	**0.009**	**0.01**
	Control	10.00 ± 7.41	11.33 ± 7.64	**0.03**	
NHPT R UL	AAT	0.05 ± 0.10	0.07 ± 0.13	0.18	0.41
	Control	0.06 ± 0.12	0.05 ± 0.10	0.97	
NHPT L UL	AAT	0.03 ± 0.05	0.08 ± 0.14	0.42	0.45
	Control	0.06 ± 0.13	0.06 ± 0.12	0.94	
Mood features					
HADS Total score	AAT	13.36 ± 6.11	10.81 ± 5.30	**0.0003**	0.09
	Control	12.11 ± 3.98	11.94 ± 3.83	0.72	
HADS Anxiety score	AAT	7.63 ± 4.16	5.68 ± 3.41	**0.0004**	**0.03**
	Control	6.64 ± 2.91	6.64 ± 2.47	0.88	
HADS Depression score	AAT	5.77 ± 2.59	5.18 ± 2.48	**0.03**	0.75
	Control	5.47 ± 1.97	5.29 ± 1.82	0.49	

Note: Values are given as means ± standard deviations. Bold values are those with $p < 0.05$.
Abbreviations: HADS, Hospital Anxiety and Depression Scale; L, left; NHPT, Nine-Hole Peg Test; R, right; UL, upper limb.
*Wilcoxon signed rank analysis results.
**ANCOVA analysis results.

economy of movement associated with greater force production and reduced muscular activity compared to an internal focus [26].

The second factor concerns stress response and emotional well-being. It is well established that ALS and other NMDs exert a profound impact on physical and emotional well-being [27], with a significant proportion of patients experiencing psychological distress of various types [28].

Therefore, a growing number of studies have focused on possible changes in stress response systems such as the hypothalamic–pituitary–adrenal (HPA) axis. Roozendaal et al. previously observed a lower cortisol awakening response (CAR) in patients with ALS than in caregiver controls, which was further correlated with reduced muscular strength and more severe depressive symptoms [29]. As a low CAR is generally observed in burnout, fatigue, and post-traumatic stress conditions, these findings suggest that reducing stress-associated activity may have beneficial effects on motor and mood disturbances. In this context, dog-assisted therapy is known to reduce stress hormone levels [30]; accordingly, we observed that the AAT group was the only one showing a significant improvement in mood measures after treatment, particularly in the anxiety domain.

While previous AAT studies in elderly individuals and patients with dementia have demonstrated selective improvements in depressive symptoms, both our previous and current studies have shown that this type of treatment has additional positive effects on anxiety symptoms [9]. These findings have important clinical implications, as mood disturbances significantly influence quality of life and are related to disease progression in both ALS and other NMDs [31–33].

A relevant finding is the absence of significant treatment effects on manual dexterity. While muscle weakness is widely recognized as the core symptom of ALS and other NMDs, manual dexterity impairment is another relevant feature that is frequently targeted by exercise interventions. In this regard, it should be noted that hand dexterity is a complex function that requires not only the integrity but also the synergy of various muscles, including both prime movers and those stabilizing the limb during skilled movements [34]; moreover, dexterity has been shown to rely on sensorimotor and corticomotoneuronal connectivity, suggesting a key role of cortical components in maintaining its integrity [35]. Given these considerations, the lack of dexterity improvements observed in our study may be due to several factors, including the variability in muscle group involvement often observed at the onset of disease in NMDs, as well as the greater effect of treatment on peripheral rather than central motor system components. Alternatively, this finding might be related to the short duration of the rehabilitation program. Multiple studies of other neurological conditions, such as stroke, have reported that improvements in strength are not always associated with

TABLE 3 | Demographic and clinical features of the ALS control and AAT groups.

	Control group ($n = 26$)	AAT group ($n = 25$)	p
Demographic features			
Age (years)	68.53 ± 11.23	67.92 ± 10.34	0.71
Sex (M/F)	15/11	14/11	1.00
Motor UL features			
ALSFRS-R	29.30 ± 10.67	28.29 ± 9.97	0.80
MRC R UL	27.95 ± 5.32	27.65 ± 5.63	0.65
MRC L UL	27.67 ± 6.31	28.74 ± 5.93	0.66
HAND GRIP R UL	9.93 ± 6.88	11.75 ± 7.25	0.64
HAND GRIP L UL	9.52 ± 7.20	13.31 ± 6.48	0.13
NHPT R UL	0.05 ± 0.10	0.06 ± 0.12	0.42
NHPT L UL	0.08 ± 0.14	0.03 ± 0.06	0.37
Mood features			
HADS Total score	12.30 ± 3.90	13.35 ± 6.57	0.44
HADS Anxiety score	7.00 ± 2.88	7.41 ± 4.48	0.78
HADS Depression score	5.30 ± 1.84	6.00 ± 2.73	0.20

Note: Values are given as means ± standard deviations and absolute frequencies.
Abbreviations: ALSFRS-R, amyotrophic lateral sclerosis functional rating scale revised; F, females; HADS, Hospital Anxiety and Depression Scale; L, left; M, males; MRC, Medical Research Council Scale; NHPT, Nine-Hole Peg Test; R, right; UL, upper limb.

TABLE 4 | Intragroup differences between baseline and post-treatment values, and differences in post-treatment values between the ALS control and AAT groups.

	Group	Baseline	Post-treatment	p*	p**
Motor UL features					
HAND GRIP R UL	AAT	11.75 ± 7.25	12.51 ± 6.74	**0.04**	**0.02**
	Control	9.93 ± 6.88	10.78 ± 7.22	0.25	
HAND GRIP L UL	AAT	13.31 ± 6.48	14.14 ± 6.53	**0.03**	**0.0007**
	Control	9.52 ± 7.20	10.85 ± 8.11	0.18	
NHPT R UL	AAT	0.06 ± 0.12	0.08 ± 0.13	0.35	0.10
	Control	0.05 ± 0.10	0.02 ± 0.01	0.87	
NHPT L UL	AAT	0.03 ± 0.06	0.09 ± 0.14	0.30	0.69
	Control	0.08 ± 0.14	0.07 ± 0.14	0.72	
Mood features					
HADS Total score	AAT	13.35 ± 6.57	11.00 ± 5.85	**0.001**	**0.05**
	Control	12.30 ± 3.90	12.38 ± 3.90	1.00	
HADS Anxiety score	AAT	7.41 ± 4.48	5.64 ± 3.69	**0.002**	**0.003**
	Control	7.00 ± 2.88	7.23 ± 2.45	1.00	
HADS Depression score	AAT	6.00 ± 2.73	5.41 ± 2.69	0.08	0.57
	Control	5.30 ± 1.84	5.15 ± 1.67	0.71	

Note: Values are given as means ± standard deviations. Bold values are those with $p < 0.05$.
Abbreviations: HADS, Hospital Anxiety and Depression Scale; L, left; NHPT, Nine-Hole Peg Test; R, right; UL, upper limb.
*Wilcoxon signed rank analysis results.
**ANCOVA analysis results.

improvements in dexterity [36, 37], suggesting that when both are observed, strength recovery typically precedes dexterity enhancement. Future studies are warranted to further elucidate these aspects.

The present study has some limitations. The main constraint was the small number of enrolled patients, mainly due to the inclusion criteria. Related to this, although the number of patients with ALS was sufficient to perform separate analyses, this was not the case for patients with other NMDs. Therefore, the results of the analyses of the entire AAT and control groups should be interpreted with caution, as the inclusion of patients with considerably different conditions may have influenced the findings. A second drawback is that the duration of the intervention was constrained by the length of hospitalization, which may have affected the treatment outcomes. It is not possible to rule out that the observed effects of AAT on muscle strength might be short-term neuroadaptive responses rather than actual disease-modifying effects. Additionally, the generalizability of AAT programs may be limited by some factors, both patient-related (e.g., dog allergies or fear of dogs) and/or context-related (e.g., availability of trained dogs and personnel and associated costs). Finally, an important limitation is the lack of direct evaluation of patient-reported outcomes, which is essential for a valid estimation of minimal clinically important differences.

Despite the aforementioned limitations, this study provides evidence that dog-assisted OT is a robust rehabilitation strategy for patients with ALS and other NMDs, improving both motor and psychological symptoms, and therefore possibly enhancing the quality of life. Further studies involving larger cohorts are warranted to assess the long-term effects of this therapeutic approach across various NMDs as well as to determine the clinical relevance of symptom improvement from the perspectives of patients.

Author Contributions

Elisa Giove: writing – review and editing, conceptualization, writing – original draft, methodology, formal analysis. **Pilar Maria Ferraro:** writing – review and editing, formal analysis, methodology, writing – original draft, conceptualization. **Mirela Lungu:** writing – review and editing, methodology. **Lara Pasquinelli:** writing – review and editing, methodology. **Romina Truffelli:** writing – review and editing, methodology. **Clotilde Trinchero:** writing – review and editing, resources, methodology, conceptualization. **Bruna Rebagliati:** writing – review and editing, resources, supervision. **Claudia Caponnetto:** writing – review and editing, supervision, resources. **Manuela Vignolo:** writing – review and editing, project administration, supervision, conceptualization, resources. **Fabrizio Rao:** writing – review and editing, project administration, supervision, conceptualization, writing – original draft, resources.

Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** mus70012-sup-0001-Supinfo.docx.