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Effects of an optimised approach to home-based respiratory care in individuals with amyotrophic lateral sclerosis: a study protocol for a randomised controlled trial

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ABSTRACT

Introduction This study aims to investigate the effects of an optimal home-based respiratory care protocol in individuals with amyotrophic lateral sclerosis (ALS).

Methods and analysis This is a randomised, blinded controlled trial involving patients diagnosed with ALS, both sexes, age between 18 and 80 years. Patients will be randomly allocated into the conventional respiratory care (CRC) group and the optimised respiratory care home-based (ORC) group. Primary outcomes will be peak cough flow, the number of exacerbations and ALS Functional Rating Scale Revised. Secondary outcomes will include chest wall volumes, maximal respiratory pressures, sniff nasal inspiratory pressure, nasal expiratory pressure and forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV_1) and FEV_1/FVC. The CRC group will receive educational information about respiratory care at the clinic. The ORC group will receive conventional care and home-based care. The clinical status of all individuals will be monitored weekly through telephone calls. A 6-month intervention is planned, the outcomes will be assessed every 3 months and 3 and 6 months follow-up after final evaluation. The primary and secondary results will be described as average or median for continuous variables and absolute and relative frequencies for qualitative variables. Treatment effects or differences between the outcomes (baseline, 3 months and 6 months) of the study groups will be analysed using an analysis of variance. The level of significance will be set as $p \leq 0.05$.

Ethics and dissemination The research ethics committee approved the study. It is expected to evaluate respiratory function in patients with ALS in the short, medium and long terms with home-based care protocol applied. The disease's rapid progression is a limitation for performing a long-term clinical study.

Trial registration number RBR-3z23ts; Pre-results.

Strengths and limitations of this study

► Randomised clinical trial with evaluator blinded to interventions.
► Quantitative and qualitative outcomes.
► Respiratory home-based care.
► Short-term, medium-term and long-term follow-ups.
► The rapid evolution of the disease can prevent long-term monitoring of some participants.

limb, thoracic and abdominal muscles,[1] causing loss of deambulation and functionality, difficulties in deglutition, respiratory muscle dysfunction and death due ventilatory failure.[2] It is one of the most disabling neuromuscular diseases, with considerably rapid and fatal progression.[3]

Studies of ALS epidemiology vary in relation to incidence and prevalence rates due to the geographic and demographic diversity of the global ALS population with variable rates of incidence of 0.3–3.6 cases/100 000 persons/year and prevalence 1.0–11.3 cases/100 000 persons.[4] There are only a few clinical-epidemiological studies about ALS in Brazil.[5] The incidence of 0.4 cases/100 000 persons/year and prevalence of 0.9–1.5 cases/100 000 persons[6] were estimated on data provided by a study performed in São Paulo city.[7]

In ALS, disease onset often occurs in two distinct ways: limb onset ALS or bulbar onset ALS. Limb onset ALS occurs in most patients with asymmetric and painless weakness. The clinical examination usually reveals atrophy, muscle weakness and fasciculations that indicate involvement of the lower motor neuron impairment.[8 9] The presence of hyper-reflexia and mild-to-severe hypertonia, indicating degeneration of the upper motor neuron.[9] On the other hand, bulbar onset ALS occurs

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is characterised by signs and symptoms of degeneration of upper and lower motor neurons. This leads to progressive weakness of bulbar,

in about 20% of patients. The weakness begins in bulbar muscles, dysarthria, dysphagia and tongue fasciculations. When there is limb hyper-reflexia, it suggests that the disease has already spread. Patients with bulbar onset ALS have a worse prognosis than patients with limb onset, with an average survival of 2 years and long-term survival (>10 years) of only 3%.[8 9] About 3%–5% of patients have respiratory onset ALS with signs of orthopnoea or mild dyspnoea, even with no limb or bulbar signs. The prognosis is an average survival of 1.4 years and no long-term survival.[9] It is associated with a rapid disease progression and a higher decline of the forced vital capacity (FVC) and respiratory muscle strength.[10–12]

The progression of the disease decreases the patient's physical function and interferes with activities of daily living (ADL). These activities can be assessed using the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). The ALSFRS-R is a validated scale based on a questionnaire that measures the physical function of performing ADL of patients with ALS, with a more improved assessment of respiratory symptoms, more sensitive to change and has a better ability to predict survival than the original ALSFRS.[13]

The underlying mechanisms of disease progression are related to motor and respiratory functions. Muscle weakness progresses variably and asymmetrically in the upper and lower limbs from the early stages of the disease, and it is characterised by a reduced functional performance that negatively affects the ADL. The progressive loss of respiratory muscle strength is one of the main problems that afflict individuals with ALS.[14]

Respiratory muscle weakness impairs the capacity to expand the rib cage and elastic recoil, which changes lung compliance and reduces total lung capacity, vital capacity and functional residual capacity.[15] The combination of inspiratory muscle weakness and reduced chest wall compliance limits the operating volume required for effective coughing. This operating volume is the volume of air inspired at the end of the inspiratory cough phase, and it is considered the most critical determinant of peak cough flow (PCF), as it affects the length of the expiratory muscle and its contraction efficiency. When glottis dysfunction is present, adequate pressure for generating compressive forces for the expectoration of airway secretions cannot be attained, and the effectiveness of coughing is further reduced.[16–18]

Physiotherapy plays an important role in monitoring signs and symptoms of respiratory impairment, as very low PCF can accelerate the development of respiratory failure and death in ALS. Signs and symptoms of respiratory impairment include cyanosis, tachypnoea, tachycardia, use of auxiliary respiratory muscles, decreased chest movements, dyspnoea on exertion or talking and peripheral blood oxygen saturation (SpO_2) below 90%, which is a clinical emergency.[19]

Currently, no cure or effective medical treatment is available for ALS; nevertheless, multidisciplinary symptomatic treatment can be provided.[3] According to a systematic review,[19] specific respiratory care interventions, such as inspiratory muscle training, recruitment of lung volume by air stacking and manual cough assistance for coughing, may increase the survival of patients with ALS, easing the symptoms of respiratory failure and should be incorporated to the daily routine of these individuals.

Therefore, patients with ALS' management aims to maintain respiratory function, and it involves all aspects of care, including at home. It should be based on a model that integrates interventions with health education for patients and their families to be safe in applying cough assistance techniques and preventing recurrent complications and, therefore, hospitalisations. This study is aimed at investigating the effects of a home-based optimised protocol respiratory care of individuals with ALS.

METHODS AND ANALYSIS
Study design
This study is a controlled, randomised and single-blind clinical trial to be conducted at a single research centre. We will perform both intention-to-treat (ITT) and per-protocol analyses. The research will follow the Standard Protocol Items: Recommendations for Interventional Trials.[20]

Patients
Inclusion criteria
We will include patients with (a) the diagnosis of definite ALS, probable ALS, probable ALS—laboratory supported, possible ALS or suspected ALS according to *El Escorial* revised criteria,[21] both sexes, (b) age between 18 and 80 years, (c) good cognitive level (≥17 score) on the ALS Cognitive Behavioural Screen scale,[22] (d) FVC >50% of predicted, (e) sniff nasal inspiratory pressure (SNIP) >40 cm H_2O, (f) a responsible caregiver who will accept the training and follow the programme, (g) a telephone to contact the assistance team, (h) no history of respiratory physiotherapy for at least a month before the survey and (i) informed consent (IC), in writing or verbally, for participation in the study will be obtained from the participant and may be signed by a witness in case the volunteer cannot write.

Exclusion criteria
Volunteers with (a) cognitive impairment, (b) cardiac, respiratory or musculoskeletal comorbidity, (c) users of invasive mechanical ventilation and (d) patients with tracheostomy will be excluded from the research.

Recruitment procedure
The patients will be recruited in a Neuromuscular Diseases Outpatient Service at the University Hospital Onofre Lopes. All participants will be evaluated at the PneumoCardioVascular Lab. The study has a date for the first registration in August/2021 and the last registration in August/2022.
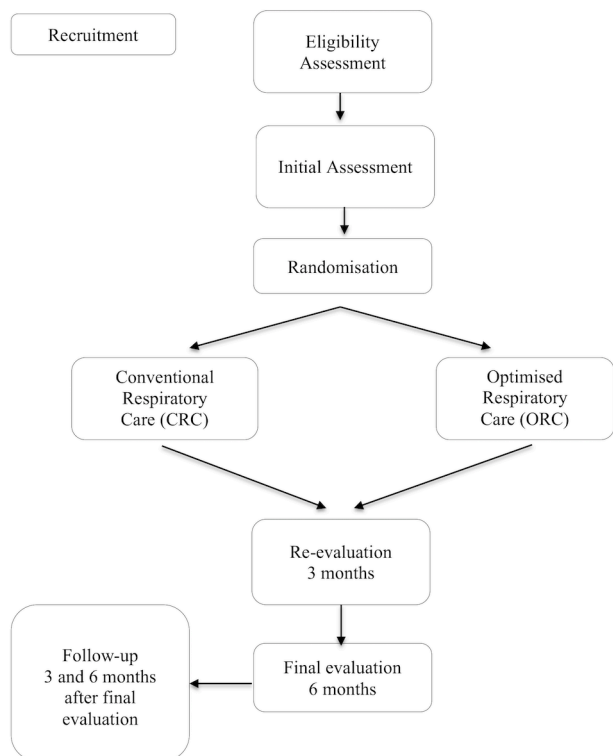
Figure 1 Flowchart of allocation and evaluations of intervention protocols.

Demographic data will include age (years) and gender. Anthropometric data will include height in metres (m) and weight in kilograms (kg). Subsequently, the body mass index, which is the reference measure for obesity control expressed as weight divided by height squared, will be calculated.[23] Vital signs, including systolic blood pressure, heart rate and respiratory rate, will be monitored manually, and peripheral blood oxygen saturation (SpO_2, Omron, HEM 7320).[24]

A trained physiotherapist, blinded to the intervention allocation group, will perform the evaluation, which will include lung function, chest wall volumes, PCF, respiratory muscle strength (maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), SNIP and sniff nasal expiratory pressure (SNEP)) and physical function through ALSFRS-R.[13]

Another researcher will use the randomisation system (randomization.com) to allocate participants into two groups after the assessment: conventional respiratory care (CRC) and optimised respiratory care home-based (ORC). The system will initially generate a random numerical list used to allocate the participants in the order of arrival in the study groups before they will receive intervention by a physiotherapist. The same initial evaluator will re-evaluate participants after 3 and 6 months after the beginning of the interventions. A follow-up will be conducted through telephone calls every 3 months until the first year after the beginning of the interventions to assess any exacerbations that may have been caused by emergency care (figure 1).

During the intervention period, all research participants will be followed-up weekly through phone calls to encourage the maintenance of guidelines and provide guidance on the management algorithm designed to determine the best approaches for specific situations (figure 2).

Randomisation procedure and allocation concealment

The participants will be randomised by an external researcher through a website, 'randomization.com', in four blocks of nine individuals and one block of eight individuals to prevent losses. A list will be generated and used to organise individually sealed and sequentially numbered envelopes. At the beginning of each participant's therapy, the researcher will provide the physiotherapist responsible for the intervention with a coded envelope. This researcher will be the only one with knowledge of each participant's group. After the group allocation, the evaluator will be kept blind during all evaluations and re-evaluations at the PneumoCardioVascular Lab. Participants and caregivers will be instructed not to comment on their treatment. A fourth researcher will be invited to analyse the data at the end of the research.

Intervention groups

The CRC group will receive education on respiratory care during quarterly hospital visits. The educational information will consist of guidelines on positioning in bed and during fluid and food ingestion as well as the stimulus to mobilisation. The caregiver will be trained on aspirating the oral cavity secretions and assisting patients in coughing through air stacking by manual ventilation with a bag and an oronasal mask (Artificial Manual Breathing Unit—AMBU) when needed. The physiotherapist will provide settings to use or improve non-invasive ventilation and the adaptation of masks, if necessary, on quarterly hospital visits.

The ORC group will receive education on respiratory care during quarterly hospital visits (same that CRC group) and weekly home visits by a physiotherapist. During the visit, the physiotherapist will provide settings
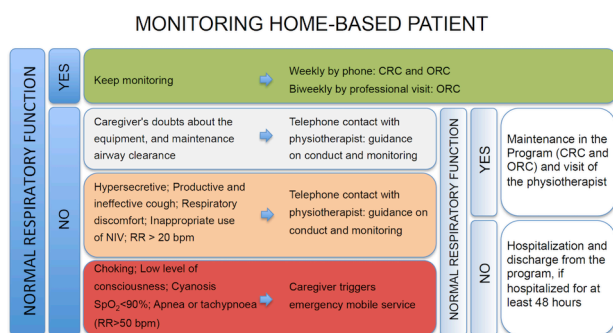

Figure 2 Therapeutic algorithm for respiratory and non-respiratory events in patients with ALS. SpO_2, 95%-100%; RR, 12bpm-20bpm. ALS, amyotrophic lateral sclerosis; CRC, conventional respiratory care; NIV, non-invasive ventilation; ORC, optimised respiratory care; RR, respiratory rate; SpO_2, peripheral oxygen saturation.

to use and improve non-invasive ventilation, bronchial hygiene techniques, aspiration of upper airways and assisted coughing through ventilation by mechanical insufflation-exhaustion (CoughAssist E70 Philips Respironics) and/or air stacking.

A trained physiotherapist who is experienced in treating patients with neuromuscular diseases will perform all interventions. Both groups will receive weekly telephone calls to monitor patients and provide the needed assistance to minimise possible complications and exacerbations. Furthermore, all caregivers will be trained to monitor vital signs (systemic blood pressure, heart rate and respiratory rate) and peripheral oxygen saturation.

Weekly monitoring and prior scheduling for consultation with a neurologist during each quarter may help participants to adhere to the study protocols.

Statistics
Sample size calculation
Due to the difficulty in conducting clinical trials in people with ALS, the sample size was calculated using data from a previous controlled and randomised clinical trial involving a patient who had a subacute stroke who had glottis dysfunction and difficulty in eliminating secretions.[25] We calculated, a priori for the investigation of the primary outcome, a total number estimation 44 patients will be divided into two groups. This number was calculated for the primary outcome (peak cough flow (14.63±9.48)). Using G*Power software V.3.1.9.2 (University of Düsseldorf, Kiel, Germany),[26] an analysis of variance analysis was performed, and a dropout rate of 20% was considered (power=0.8; p=0.05; f=0.25; N (min)=36).

Statistical analysis
The Kolmogorov-Smirnov test will be used to analyse the normality of the sample's data. The patient baseline characteristics and outcome variables (both primaries and secondaries) will be summarised using descriptive measures of central tendency and dispersion for quantitative variables, and absolute and relative frequencies for qualitative variables. Possible correlations will be made using Pearson or Spearman tests depending on the normality of the data. Associations will be performed using the X^2 or Fischer's exact test. Treatment effects or differences between the outcomes (baseline, 3 months and 6 months) of the study groups will be analysed using an ordinary two-way analysis of variance (ANOVA) will be performed, if the sample is parametric. In case the sample has a non-parametric distribution, paired t-tests and an ordinary one-way ANOVA will be used. Intergroup analyses will be performed using the t-test or the Wilcoxon test, depending on the normality of the data. The analysis will be compared as primary outcomes pre and post treatment of PCF, numbers of exacerbations and ALSFRS-R and secondary outcomes pulmonary function, SNIP, SNEP, MIP and MEP.

The disease progression rate (ΔFS) will be calculated using a functional scale by the difference between the total value of the ALSFRS-R (48) and the value of the scale in the initial assessment divided by the time (months) since the initial assessment (ΔFS=48–ALSFRS-R at initial assessment/months).[27] So, the patients will be classified in slow, intermediated or fast progression if the results of disease progression ΔFS ≤0.5, 0.5 ≤ ΔFS ≤1 and ΔFS ≥1, respectively. In case of sufficient data, a subanalysis between groups will be performed.

The analyses will be based on the ITT principle, and they will involve data of all randomised participants with at least one outcome measure. The level of significance will be set as p≤0.05. All participants will be included in the analysis of the original groups following the Consolidated Standards of Reporting Trials (CONSORT) recommendations. The data will be analysed using GraphPad Prism software V.7.0 (GraphPad Software, San Diego, California, USA).

Patient and public involvement
A patient and public involvement panel was not specifically recruited to inform the design, recruitment, conduct or dissemination plan for this study.

Monitoring
The researcher responsible for the interventions and control of the groups will monitor the research. During each session of intervention, participants will be assessed for vital signs and asked about any changes during activities that could result in the termination of the research.

The analyses will be based on the ITT principle, and they will include data on all randomised participants with at least one outcome measure. The significance level will be set at 95% (p<0.05). All participants will be included in the analysis of the original groups following the CONSORT recommendations.

OUTCOMES
Primary outcome
ALSFRS-R
The ALSFRS-R will be administered through interviews with the volunteers at the end of the assessments. It consists of 12 items on a scale of 0–4 with a total score ranging between 0 and 48 points, representing maximum disability and normal functioning, respectively.[13] The ALSFRS-R will be quantified as a total score and with domain-specific subscores to compare the different moments of assessment and analysis of disease progression.[28]

Number of exacerbations
The exacerbation occurs with the impaired ability to cough and eliminate secretions from the airway during upper respiratory tract infections due to respiratory failure and concomitant weakness of the oropharyngeal muscles. The resulting bronchial mucus plug can decrease vital capacity and SpO2. Exacerbations are

hypoventilation, and hypercapnia[29] with SpO_2 below 90%, requiring emergency care.[24]

The episodes of emergency care that patients will encounter due to the worsening of their respiratory conditions will be counted to determine the efficiency of the service.

PCF

PCF and chest wall operating volumes will be assessed non-invasively through kinematics of the chest wall, using optoelectronic plethysmography (BTS Bioengineering, Italy). The system allows a three-dimensional assessment of the chest wall kinematics of a patient placed 90° in the supine position using 52 retro-reflective markers and 6 cameras (3 on the left and 3 on the right of the participant) that have been previously calibrated, following the described protocol.[30] SmartCapture software will be used for data collection and for the three-dimensional model analysis and volumetric calculation for the quantitative analysis of operating volumes and PCF; DiaMov software (customised software designed and developed at the Politecnico di Milano, Italy) will be used.

Secondary outcome
Pulmonary function

The absolute and predicted FVC, forced expiratory volume in the 1st second (FEV_1) and FEV_1/FVC will be measured with the patient seated using a Koko DigiDoser spirometer (nSpire Health, Longmont, USA) calibrated with a 3 L syringe. For execution, the American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations will be adopted.[31] Analysis of the obtained values, based on the values proposed for assessing the normality of spirometric tests in healthy Brazilian adults, will be performed.[32]

SNIP

SNIP will be measured using a rigid material nasal plug, and one nostril will be occluded during the manoeuvre through the contralateral nostril. The plug will be connected to the NEPEB-LabCare/UFMG digital mano-vacuometer (Minas Gerais, Brazil) through a polyethylene catheter (internal diameter of approximately 1 mm and length of 72 cm), and it will be comfortably and safely positioned in one of the nostrils to prevent it from falling during manoeuvres. The volunteer will be instructed to perform 12 manoeuvres of maximum inspiration through the contralateral nostril from the functional residual capacity while sitting and keeping the mouth closed.[33] Verbal encouragement for strong and quick inspiration without hesitation will be provided at the end of observed exhalations preceded by breaths at the level of tidal volume. The following criteria will be used to choose the correctly developed manoeuvres: manoeuvres performed quickly and strongly, a total duration of SNIP of less than 500 ms, pressure peak sustained for less than 50 ms and a smooth, descending respiratory curve without a biphasic peak. SNIP will be performed in the sitting position. The highest value obtained for the manoeuvres that meet the acceptance and reproducibility criteria will be used as a reference and for data analysis. The obtained values will be analysed based on the values proposed for healthy Brazilian adults.[34]

SNEP

The evaluator will measure nasal expiratory pressure through an oronasal mask worn by the patient to prevent air leakage from the sides; the mask will also be connected to the digital manometer vacuum NEPEB-LabCare/UFMG (Minas Gerais, Brazil) through a polyethylene catheter of dimensions previously described. The volunteer will be instructed to perform 10–20 maximum expiration manoeuvres, starting from the functional residual capacity. Verbal encouragement will be given at the end of inspiration, preceded by breaths at the tidal volume level, so that air will be released quickly and forcefully through the nose while the mouth is closed. The nasal expiratory pressure will be measured with the patient in a sitting position. The verbal command will be, 'loose strong', and the eligibility criteria for the manoeuvres will be the same as those used for the SNIP manoeuvres. The highest value that will meet the criteria will be used for data analysis and as a reference. The nasal expiratory pressure assessment technique was developed in our laboratory, based on previous clinical studies, and its methodological characteristics will be published soon.[35]

MIP and MEP

The strength of the respiratory muscles will be measured using a digital manometer (NEPEB-LabCare/UFMG, Brazil), following the recommendations of ATS/ERS (2002), with the volunteer in a sitting position. A disposable cylindrical mouthpiece with a 2 mm orifice will be used to minimise the pressure generated by the orofacial muscles during MEP and prevent glottis closure at the MIP. A nose clip will be used for both tests. Prediction equations will be used to analyse the data obtained.[36] For MIP, the volunteer will start from the residual volume; the volunteer will be instructed to breathe at the functional residual capacity level and release as much air from the lungs as possible. Following this, a positive signal will be provided, and the evaluator will request maximum inspiration while simultaneously introducing the mouthpiece. For MEP, the manoeuvre will start from the total lung capacity. With the inverse command, the participant will be instructed to fill the lungs with air, and at the positive signal, the evaluator will attach the mouthpiece and request maximum expiration against airway occlusion. To prevent air leakage and the use of the orofacial muscles, the evaluator will press the volunteer's cheeks.

For each test, a minimum of three manoeuvres and a maximum of five will be performed, of which three will

Table 1 Study schedule

	Study period						
	Enrolment	Allocation	Post-allocation				Close-out
Time point (months)	$-t_1$	0	1–3	3–6	6–9	9–12	t_x
Enrolment							
Eligibility screen	X						
Informed consent	X						
(Phone contact)			X	X	X	X	
Allocation/randomisation		X					
Interventions							
(Conventional respiratory care)			X	X			
(Optimised respiratory care)			X	X			
Assessments							
(Peak cough flow)	X		X	X			X
(Forced vital capacity)	X		X	X			X
(Maximal respiratory pressure)	X		X	X			X
(Nasal respiratory pressures)	X		X	X			X
(Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised)	X		X	X	X	X	X

have to be acceptable (lasting at least 1.5 s) and at least two reproducible (the values of the two major manoeuvres cannot differ by more than 10%, and the value of the third-largest cannot differ by more than 20% from the largest value). Considering the learning effect, the last manoeuvre cannot have the highest value; if it happens, the exam will continue until a lower value is obtained. A minute's rest will be allowed between tests. The highest value obtained will be used for data analysis and as a reference.

The study schedule is shown in table 1.

ETHICS AND DISSEMINATION
Ethics approval and consent to participate
The project was approved by the Research Ethics Committee of the University Hospital Onofre Lopes of Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil (CAAE: 11731019.5.0000.5292) and registered in the Brazilian Registry of Clinical Research—ReBEC with the number RBR-3z23ts on 7 August 2019. Updated: 12 March 2021. Patients and their caregivers will be invited to participate voluntarily and all information about randomised group and intervention will be given. After that, they will be required to sign IC term (online supplemental file).

Consent for publication and confidentiality
All information collected from the participants of the study will be kept confidential and stored in the laboratory's database, during and after the trial. They will only be accessed by the researchers to ensure anonymity and

respect for human dignity and fulfil all the bioethics requirements of Resolution 466/2012 of the National Health Council and the Helsinki Declaration for research with humans.

Results of this study will be reported in full through peer-reviewed journals and presented at scientific conferences. Significant protocol modifications will be communicated to the participants, trial register and journals. A model of the informed consent form will be provided, if requested.

Availability of data and materials
The study protocol and data sets generated and/or analysed of all identified included participants during the current study will be available from the corresponding author on reasonable request to achieve the approved proposal aims.

DISCUSSION
Individuals with ALS have respiratory complications that worsen rapidly, and this can culminate in death. These patients should be provided with regular daily respiratory care and assistance by caregivers and family members as well as professional monitoring to reduce exacerbations.

The challenges associated with public health assistance for patients as well as the lack of knowledge among health professionals and the community favours the worsening of ALS and consequently increased hospitalisations and public spending.

We hope that the study can demonstrate the importance of home-based physiotherapy with specialised assistance,

which will provide patients and their families the convenience and safety. We believe that a well-implemented therapeutic programme will reduce the morbidity and mortality rates of patients with ALS.

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