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HOMECARE PALLIATIVE CARE IN PATIENTS AFFECTED BY NEURODEGENERATIVE MOTOR NEURON DISEASES

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INDEX

1. INTRODUCTION

Researchers define Neurodegenerative Motor Neuron Disease (NMND) as the set of pathologies whose pathogenesis comprises a progressive loss of motor neurons in specific brain areas.

The set of pathologies, whose causes are not yet fully known, is highly heterogeneous. The most valid hypothesis is that they originate from several concomitant factors: genetic, hereditary, environmental. [1]

They manifest themselves in different ways concerning the area of the brain affected and the type and amount of neuronal loss. Nonetheless, they may show common elements:

- The onset of the disease often does not manifest symptoms that appear only when the neuronal damage is already quite severe.
- They feature an irreversible progression.
- There do not exist drugs that could slow the progression of the disease but only drugs that improve symptoms

The most common neurodegenerative diseases comprise Parkinson's disease, Alzheimer's disease and other Dementias. Amyotrophic Lateral Sclerosis (ALS) is rarer with respect to those diseases, but there exist rare forms where it overlaps with dementias and PK.

The patients suffering from ALS spend most of their life at home after diagnosis: on average, they survive 3 to 4.

Home Palliative Care (established in Italy with periodic counselling during Home Integrated Aiding (also called ADI), and then assisted by Home Palliative Care Unit (UCP-DOM) represents indispensable actors in the hospital-territory healthcare path of a patient suffering from NMND (especially in the case of ALS), not only in the advanced and terminal stages, but already in the early stages of the disease. In this way, in close collaboration with the specialist centres, the follow-up of these patients can be guaranteed at home, reducing the frequency and/or duration of admissions to specialist centres and ensuring a high standard of care.

Maddalena Grassi Foundation deals with integrated home care (ADI) and Home Palliative Care (UCP-Dom), promoting proportionate care and suffering relief to patients who face their end of life at home, next to their beloved families.

Since 2019 the Foundation has launched a specific project regarding the management of the patients who have ALS, a pathology for which home management is often complex

both for the multitude of professional figures that the patient needs, and for the complexity of the clinical picture and its progression.

Amyotrophic Lateral Sclerosis (ALS) is the reference pathology of the chapter *Motorneuron Disease* which also includes Spinal Muscular Atrophy (SMA), Primary Lateral Sclerosis (PLS), Post-Polio Syndrome, Paraneoplastic Syndromes, and other rare forms of disease. In Italy, specialists register more than 3600 at any moment. The prevalence in Lombardy is approximately 600 cases while the incidence is about 150-200 new cases yearly. The disease may present spinal, bulbar or rarely respiratory onset. A 10% of familial forms are recognized. The peak incidence is around the age of 60 in sporadic forms but may be earlier in familial forms. The average duration of the disease is about 3-5 years, but there exist more rapidly evolving forms -usually bulbar- with survival rate of less than three years from diagnosis and slow-evolving forms with survival pace of more than ten years (about 10%).
The evolution of the disease is characterized by progressive motor deficit up to tetraplegia and complete impairment of phonatory, swallowing and respiratory functions. A considerable number of patients, approximately 15%, present a specific form of fronto-temporal dementia, whilst about 50% of patients exhibit fewer specific alterations in their behaviour. Technologies for enteral nutrition and ventilation are progressively changing disease survival estimates compared to previous decades: patients with Percutaneous Endoscopic Gastrostomy (PEG) and invasive ventilation can currently survive over 15 years. A 12 months elapse between onset of symptoms and diagnosis on average is reported. The negative prognostic factors are: onset at age over 65 years, rapid progression to outpatient controls (evaluated with the Amyotrophic Lateral Sclerosis – Functional Rating Scale, ALS-FRS), a low Body Mass Index, and dyspnoea as a symptom of onset.

Researchers include ALS in the list of rare diseases with exemption from health expenditure (code RF0100) reported in Annex 7 of the Prime Ministerial Decree of January 12th, 2017. [2]
In the classical forms the Home Health Assistance (in Italy called Assistenza Domiciliare Integrata, henceforth abbreviated: ADI) for physiotherapy is usually activated when the patient has insufficient autonomy to attend physiotherapy at the reference centre. The ADI team can also include the nurse for the management of nutritional and respiratory devices,

the psychologist for support to the patient and his entourage, the social and health worker for personal care, the speech therapist for the re-education of swallowing and phonation. The order and timing of activation of the various professional profiles vary concerning to the initial symptoms of onset and the disease rate growth.

A critical issue is the decision to move from the ADI service to that of Palliative Care. Most patients with an estimated prognosis of more than one year still have symptoms and problems deserving of access to palliative care. If there are no criteria for taking charge in Home Palliative Care Units (from now: UCP-Dom) (according to the criteria of sub-annexes E and F of the Lombardy DGR n ° 4610/2018), the patient should still be able to access the specialist consult of hospital or local palliative care. The home care assistants arrange periodic follow-ups at the specialistic centre of reference until the advanced stages of the disease: every actor involved in patients' health assistance must be able to collaborate to manage the clinical evolution according to the highest healthcare standards.

The number of ALS patients assisted by the Maddalena Grassi Foundation (FMG) has recently increased. In January 2019, it comprised 34 patients. During 2019, there were 12 new activations and 10 discharges, counting 46 patients treated during the year. The average duration of care is about two years, with cases of assistance lasting over seven years. The professional figure most frequently involved in the assistance is the physiotherapist, followed by nurse, auxiliary, palliative doctor (in about 15% of ADI vouchers), psychologist, speech therapist, specialist doctor (anesthesiologist for replacement of the tracheostomy cannula and surgeon for replacement of the PEG probe), occupational therapist.

1.1 ALS: definition and introduction

ALS is a progressive neurodegenerative disease caused by the degeneration of cortical motor neurons (first or central motor neuron), brain stem and spinal cord (second or peripheral motor neuron) causing cell death and consequently atrophy and paralysis of the affected muscles. The same clinical condition is also called "Charcot" or "Lou Gehrig" disease. Jean Martin Charcot first described it at the end of the 19th century as a purely neurodegenerative disease; today we know that the disease is a multisystemic neurodegenerative disorder with clinical, genetic and neuropathological heterogeneities.

Not all cells are affected by the event simultaneously, but they become so over time. In these time intervals, the functions performed by the neurons that degenerate are vicariate by the remaining neurons, at least in part in the peripheral neurons.
The leading cause of death is respiratory failure generated by the involvement of the neurons of the respiratory muscles.

Since the 90s of the last century, there has been a growing interest in understanding the disease's clinical and scientific aspects. The advancement in the understanding of the role of glutamate neurotransmitters has stimulated new interest in research: physicians studied the heterogeneity of presentation and manifestation of the disease, and it has also been understood how survival in ALS depends on numerous factors, including clinical presentation (phenotype), speed of progression, the early manifestation of respiratory problems and patient nutritional status.
Life expectancy in ALS, in fact, seems to depend on advances in understanding its pathogenesis that can lead to the development of diagnostic methods that can detect the disease at increasingly early stages. There is a crucial need to formulate therapies not only to slow disease progression, but also to intercept and improve symptoms induced by the onset of respiratory failure and malnutrition. Indeed, very important is also the creation and development of registers of the population affected by ALS, a fundamental contribution to allow the study of the disease and its development in different populations and phenotypes. These efforts will certainly allow the improvement in understanding of the progress of ALS and the consequent development of guidelines to improve patient care.

Numerous factors complicate epidemiological studies in ALS, such as the determination of a precise date of onset of the disease and the potentially long interval between the onset of the first signs of disease and the direct manifestation of the disease: this interval is due to the well-known neuronal redundancy.

The disease has an incidence of 1.6/2.7 cases per 100,000 yearly, with a prevalence of 5/7 cases per 100,000. [3]
Some endemic outbreaks have been identified in the Western Pacific, where an ALS, Dementia and Parkinson's disease association is also found.
Males are more affected than women with a ratio of 1.5:1.

Initial symptoms usually occur between 50 and 70 years, with cases of juvenile ALS (so defined if the onset occurs before the age of 25).
ALS is in 90/95% of cases a disease with sporadic presentation and is defined SALS; however, there is a 5-10% hereditary familial form called FALS.
Some of the mutations responsible have been identified in familial ALS: for the most part we speak of autosomal dominant inheritance, but recessive forms have also been described.
Point mutations have been identified in the SOD1 gene (superoxide dismutase 1 Cu-Zn dependent with antioxidant action on Chr 21 in 20% of reported cases of FALS and in 2% of SALS.
In 5% of familial forms and 1% of sporadic forms, mutations in the TARDBP gene (TDP-43) have also been described, while alterations in the FUS gene have been identified in 4% of familial and 1% of sporadic forms.
Despite the different genes identified, there are no substantial clinical or neuropathological differences between SALS and FALS. Extensive interfamily and intrafamilial variability has been documented regarding age of onset, symptoms of onset and duration of the disease.
The pathogenesis of the sporadic forms is currently unknown and no certain correlation between risk factors and disease development has been documented.

At this moment, there is no definitive diagnostic test or specific biomarker for ALS, and the diagnosis is therefore based on clinical criteria, except for familiar forms and in a few sporadic forms where the diagnosis takes place through the identification of the genetic mutations affecting SOD-1, TDP-43 and FUS. Therefore, the diagnostic criteria coincide with the formulation by a physician of the diagnostic suspicion.
As a result, so far, the clinical criteria used to diagnose ALS are:

1) worsening paresis of central and peripheral type, without sensitivity disorders
2) strength deficit that affects voluntary muscles:
1. distal upper limbs (e.g. difficulty in handling objects)
2. distal lower limbs (i.e., difficulty walking)
3. laryngeal (i.e., difficulty with phonation)
4. lingual (i.e., difficulty phoning, swallowing or articulating)
5. more rarely respiratory
3) often associated with easy fatigue, cramps, muscle fasciculations

4) it is important to remember that the sensory pathways are NOT affected, so any symptom or sensory deficit must pose a strong diagnostic doubt about ALS diagnosis or receive an alternative explanation

At the clinical level, the involvement of the first (UMN) or the second motor neuron (LMN) can be defined by analyzing signs and symptoms, and four phenotypes can therefore be defined:

a) **Spinal Phenotype**: mainly involves the limbs, with a contemporary involvement of both the UMN and the LMN, with symptoms mainly in the limbs

b) **Bulbar Phenotype**: in which the symptoms are mainly related to the phonatory /swallowing / respiratory area, with dysphagia, dysarthria, coordination disorders and early respiratory fatigue.

c) A less frequent Phenotype with **prevalent UMN involvement**

d) A progressive muscle atrophy, with an essential **involvement of the LMN**.

The main characteristic trait of ALS is the contemporary involvement of UMN and LMN. Patients may have a bulbar onset (in 25% of cases) or spinal onset (70% of cases), or with a rarer form involving trunk and/or respiratory muscles (5% of cases).
More specifically, the involvement of the UMN determines spasticity in the limbs, progressive decrease in strength, and increase in osteotendinous reflexes, while the involvement of the LMN involves fasciculations, atrophy and weakness.

The UMN-Bulbar Phenotype determines at the clinical level mainly spastic dysarthria, which is characterized by a slower, more laborious, and distorted speech articulation, with a quality of phonation tending to the nasal.

The LMN-Bulbar Phenotype instead can be identified by loss of tongue strength and fasciculations, accompanied by a flaccid dysarthria, which in turn involves in a nasal vocalization, due to the weakening of the palatal component of phonation, and a weakening of the coughing act.

The recent identification of cytoplasmic accumulations of TDP-43 in glial and neuronal cells in 98% of diagnosed cases of sporadic ALS has been correlated with the onset of

Frontotemporal Dementia (FTD): about 20/50% of patients with ALS, after careful diagnostic investigations, receives a diagnosis of FTD.
The distinctive feature of FTD is the onset of deficits of executive functions, involving both language and personality: patients progressively manifest difficulties of judgment, impulsivity, and a general deterioration in the ability to pursue the usual daily routine, contributing to the difficulty in patient management.

To further support the hypothesis of correlation between ALS and FTD, structural abnormalities and frontotemporal atrophy have been identified by MRI investigations beside bilateral atrophy of the motor and premotor cortex. Patients diagnosed with FTD, and ALS concomitantly, also have a higher rate of frontotemporal area atrophy than patients diagnosed with ALS alone.
Further investigations by PET identified how frontotemporal atrophy appears to be associated with neuronal loss and cortical gliosis.
In addition to TDP-43 aggregates, FUS and ubiquitin-positive deposits were also identified in TDP-43 negative FTD patients, further confirming how important and concrete is the link between ALS and FTD.

1.2 Diagnosis and diagnostic tests

The internationally recognized diagnostic criteria are the criteria of "El Escorial" which provide for the simultaneous involvement of the I and II motor neuron with the exclusion of all differential causes that can give an overlapping clinical manifestation.
Depending on the different characteristics, different types of ALS diagnosis can be distinguished:

1. *Defined ALS*: Involvement of the I and II motor neuron documented in the bulbar region and in at least two spinal regions - involvement of the I and II motor neuron in 3 spinal regions
2. *ALS clinically probable*: two sites between the bulbar and the spinal ones but the involvement of the I motor neuron is rostral at II
3. *Clinically probable ALS with laboratory confirmation*:
    - Involvement of the I and II motor neuron from a clinical point of view in 1 region.

- Involvement only of the I motor neuron in one region and evident involvement of the II motor neuron in the EMG in at least two regions.

4. *ALS possible*: involvement limited to only one site (I and II motor neuron), in two or more sites there is involvement only of the motor neuron or the II is affected but rostral compared to the I in at least two regions.

To reach the diagnosis, at present, we rely, in addition to the clinic, on the instrumental elements: among these certainly very important is electromyography, which is helpful in confirming the neuronal motor involvement.

The ElectroMyoGraphy (EMG) identifies fasciculations, positive waves (sign of active denervation), fibrillations, polyphasic and long-lasting abnormal potentials and potentials of motor units of greater amplitude and duration, difficulty in achieving interference activities. Special electromyographic techniques are available that give information on the amount of muscle fibers involved: single fiber EMG, macro-EMG, EMG decomposition and amplitude analysis, quantitative analysis of motor unit potentials, estimation of the number of motor units, may be performed but are not necessary for diagnosis.

As regard to the speed conduction, it is possible to report a conduction speed and latency substantially in the norm or slightly reduced, in addition to the detection of a slowdown in the central motor conduction, found in 30% of cases and reduced enrolment of the potentials of motor units, expression of the damage at the level of the central motor neuron. Initially the conduction of the signal, in the initial stages of ALS, can be preserved; in the more advanced phases the reductions in the amplitude of the motor action potentials can be found (index of denervation), while the sensory action potentials remain unchanged.

MRI can also greatly help in the diagnostic phase, especially to rule out other diseases.

One of the most disturbing and intense symptoms of ALS is certainly dyspnoea, given by respiratory failure which results from the degeneration of the respiratory motor neurons (belonging to the phrenic nerve) and the resulting loss of force of the respiratory muscles. Initially respiratory failure manifests itself in the form of nocturnal hypoxia, associated with symptoms such as lethargy, difficulty in concentrating, morning migraines and an unrestful sleep.

Diaphragmatic weakness can be diagnosed with spirometry, through which a progressive reduction in vital capacity (CV) is identified during the disease; more accurate than the CV in predicting the strength of the inspiratory muscles are the maximum inspiratory and expiratory pressure (MIP or PiMax and MEP) and the Sniff Nasal Inspiratory-Force Test (SNT).

Non-Invasive Ventilation (NIV) greatly improves patients' quality of life and survival.

In patients with a bulbar impairment or important sialorrhea, the adoption of NIV should be carefully evaluated, which they may not tolerate: in this case, maximum attention should be paid to the control of secretions.

When NIV is not sufficient because it is poorly tolerated or insufficient due to muscle weakness, invasive ventilation via tracheostomy is an option.

Another important factor to keep in mind is certainly malnutrition, a fundamental aspect of prognosis. The development of malnutrition in ALS is multifactorial, and also includes malnutrition resulting from dysphagia or hypermetabolism: about 50/60% of ALS patients have a condition of hypermetabolism, but the causes and mechanisms are not yet fully elucidated.

The adoption of PEG (Percutaneous Gastrostomy Tube) allows the supplementation of the diet by mouth or the complete replacement of the eating by mouth through the use of specific diets or preparations that respond to the metabolic demands of patients: for this reason, it is a therapeutic option that should be proposed to patients with rapid weight loss, even in the absence of dysphagia. [1]

1.3 Pathophysiological mechanisms

The pathophysiological mechanisms underlying ALS are still being defined, and appear to be multifactorial, with increasingly important evidence regarding the existence of complex interactions between genetic and molecular pathways.

In Sweden, for example, a case-control study has identified how a low or high maternal age and the existence of a younger sibling are associated with a higher risk of developing ALS.

In addition, increased exposure to typical preschool and school infections also appear to increase the risk of developing ALS. Other various environmental factors have been related to ALS, for example intense muscle activity, such as that of US Army soldiers or Italian footballers, in which it was identified that a career longer than 5 years, especially if played in the role of midfielder, has been associated with an increased risk of developing ALS, and the same has been also observed among footballers of the English amateur series.

Cigarette smoking is also a factor that, among others, increases the risk of developing ALS.

Some neurotoxins, among which the most impactful is the β-methyl-amino-L-alanine, have been correlated with the development of a form of ALS endemic to the island of Guam. This neurotoxic amino acid

It has certainly been found in high concentrations in patients (belonging to the Chamorro tribe) suffering from ALS-Parkinson's with a history of consumption of the meat of a particular bat. This animal, in fact, feeds on Cycas, a tropical plant present in the archipelago, which has high concentrations of the neurotoxic amino acid.

Mutated SOD1 appears to be responsible for a conformational mutation which determines the formation of cytoplasmic aggregates that inhibit the proteasome’s normal function, dysregulate the axonal transport and vital functions of the cell, leading it to death.

Glutamate-induced excitotoxicity is another of the main mechanisms involved in the pathogenesis of ALS.

Glutamate is the main excitatory neurotransmitter of the CNS and binds to NMDA and AMPA receptors on postsynaptic membranes. An excessive activation of the postsynaptic receptors induced by glutamate determines the activation of the Ca++ channels, which in turn determines the production of free radicals that leads to neurodegeneration through cellular damage and the overproduction of proinflammatory mediators.

Among the other mechanisms identified in the pathogenesis of ALS we find the presence of structural abnormalities of the mitochondria, malfunctions of the Na-K pump, autophagy and dysregulation of the axonal transport system.

As previously mentioned, TDP43 has also been recognized as the main component of cytoplasmic ubiquitinated protein aggregates, not present in the nucleus as in normal neurons, but in the cytoplasm.

TARDBP mutations that lead to FALS, in fact, seem to be involved in the dysregulation of RNA processing.

FUS, located on chromosome 16, is also associated with familial forms of ALS, although its mechanism is still the subject of studies and investigations. [4]

1.4 Therapeutic approaches

Currently there is no drug that can block or slow down the neurodegenerative process. Only one drug that can prolong the life of patients by a few months is officially recognized as an ALS treatment, called Riluzole, which has the function of counteracting glutamate by reducing its excitotoxicity.

From AIFA note n. 1224 of 28/6/2017, the medicine Edavarone was also recognized among the drugs that can be dispensed at the total expense of the NHS. The functioning of Edavarone is based on the ability of the drug to counteract oxidative stress.

However, there are a series of symptomatic and rehabilitative treatments aimed at reducing as much as possible the pains deriving from muscle spasticity, through motor rehabilitation and physio kinesitherapy (FKT) or, in the more advanced stages when indicated, through the use of muscle relaxants such as baclofen, dantrolene, tizanidine and diazepam. [5]

1.5 Aiding aspects

The PDTA of the Lombardy Region regarding the health care of patients suffering from ALS proposes that the best path that allows to follow with constancy and meticulousness the patients suffering from ALS provides outpatient visits every 1/3 months:

1) To have a control of the clinical situation
2) To give the patient the opportunity to report problems arising step by step
3) To organize visits with other specialists involved in care in a timely manner

A critical aspect is certainly represented by the fact that the pathology in question cannot be considered of neurological relevance alone, but must be addressed in its complexity, with the participation of a multi-professional team to address the various critical issues that arise during the disease.

The specialists who can be involved in shaping a multidisciplinary approach to ALS are:

- physiatrist
- gastroenterologist
- pulmonologist
- geneticist
- otolaryngologist
- resuscitator
- psychologist
- nutritionist dietician
- physiotherapist
- speech therapist
- occupational therapist
- nurse
- social and spiritual worker
- ethics consultant

and for the connection with the territory:

- general practitioner
- doctor, nurse, social worker of the ASL district
- agencies agreed for the provision of integrated home care (ADI)
- doctors and staff of the RSA with the possibility of managing the care of patients with high care complexity
- hospice and palliative care network

- patient organizations

-volunteering (Third Sector)

- companies for electromedical equipment and services

- 118 emergency/urgency [1]

2. STATE OF THE ART RELATED TO GENETIC STRUCTURE

At the genetic aspect, the investigation is indicated only in cases with a family presentation.

Among the particularly significant mutations involved are:

1) SOD1, mapped on chromosome 21q: coding for the enzyme superoxide dismutase 1 Cu/Zn-dependent able to act as an antioxidant agent: its deficiency therefore entails greater freedom on the part of oxidizing agents to create neuronal damage through the accumulation of free radicals; it is responsible for about 20% of familial forms

2) TARDBP, located on chromosome 1p36, encoding the TDP-43 protein

3) FUS, responsible for about 4% of familial forms

4) C9ORF72 mapped on chromosome 9, responsible for causing both ALS and frontotemporal dementia characterized by intraneuronal deposits of the TDP-43 protein, important when genetic DNA information is transcribed into proteins.

5) NF-H, present on chromosome 22, and TAU, on chromosome 17: these mutations are also involved in the forms in which ALS is associated with FrontoTemporal Dementia and Parkinson's.

6) Other forms, much lower in frequency, concern the ALS or SEXT genes (chr9q34), ALS2 (chr 2q33) and DCTN (chr2q)

Before proceeding with a genetic test, however, it is necessary to deepen the family implications associated with the test: subjects at risk could have access to presymptomatic diagnosis only if belonging to families where a mutation in a gene involved in the pathogenesis of ALS has been found; at the moment access to the test for minors and subjects at risk of suicide is excluded.

It cannot be requested by family members or third parties, and the test must be delivered, by the geneticist or neurologist, only to the person concerned or his legal guardian.

Further elements for easy the diagnosis, not essential for the diagnosis but that can help in the understanding of the clinical picture are the MRI, which will basically be normal and will therefore allow to make differential or exclusionary diagnosis, will be an increase in blood CPK (creatine phosphokinase), AST (aspartate transaminase- SGOT), LDH (lactate

dehydrogenase) especially when there is a rapid onset of muscle atrophy, because they are all indicators of muscle damage.

Differential diagnosis should be made with:

- Post-polio syndrome
- Cervical spinal cord injuries
- Motor multifocal neuropathy with or without conduction blocks
- Endocrinopathies such as hyperparathyroidism or hyperthyroidism
- Lead poisoning
- Infections
- Inflammatory diseases
- Paraneoplastic syndromes
- Cranial or spinal canal skeletal abnormalities
- Myopathies (such as body myopathy included)
- Progressive bulbar paralysis (with sensorineural deafness)

Regarding the criteria of predictability of disease, in recent years there have been numerous studies related to biomarkers that may be specific to ALS: among the most studied, certainly the Serum C Reactive Protein (CRP) is taking on a leading role.

Lunetta et al try to determine the role of CRP in ALS progression: CRP is an acute-phase protein regulated by proinflammatory response, especially by IL-6.
C-reactive protein is a biomarker of the inflammatory response with a significant prognostic value for several types of tumours, cardiovascular diseases and rheumatic diseases.
Recently Miller et al find a novel immune regulator called NP001, that may be implicate in ALS. Despite negative results of the trial, they showed that patients treated with NP001 whose baseline CRP levels were above the median for the entire randomized population had a slower progression of ALS than did patients with the same elevated baseline CRP levels who received placebo.
Keizman et al found how clinical disability in a small group of ALS patients is related to some sensitive inflammatory biomarkers including CRP. [6]
In Lunetta et al study, serum levels of CRP were evaluated at enrolment and correlated

with the clinical demographics of patients with ALS, such as age at diagnosis, sex, duration of disease at time of evaluation, site of onset, ALSFRS.R total score, body mass index, smoking status and survival. To standardize the threshold, they decided to choose the median value (0,20mg/dL) obtained in NEMO cohort to subdivide patients with normal CRP levels (< or = 0,20mg/dL) and elevated CRP levels (> 0,20 mg/dL).
The phase 2 trial of NP001 was a randomized, double-blind, placebo-controlled clinical trial of patients with probable or definite ALS according to El Escorial criteria.
Patients were allocated in 1:1:1 manner to receive 1mg/kg of NP001, 2mg/kg of NP001 and placebo; patients received a total of 20 infusions for 6 cycles during a 25week double-blind treatment period.
In their analysis, CRP was not correlated with age at diagnosis, sex, disease duration or site of onset of ALS. Serum CRP levels were correlated with the severity of functional impairment, as measured in ALSFRS-R total score. They also found an important negative correlation between the slope of the ALSFRS-R score and the slope of serum CRP levels, emphasizing the significance of the CRP as a useful, feasible and potentially prognostic factor in patients with ALS.

An important correlation between CRP levels and patient survival was found: patients with ALS and elevated CRP levels at first evaluation had a significantly shorter survival than those with normal serum CRP levels.

The importance of CRP levels is validated by some studies that found how CRP levels are increased in cerebrospinal fluid of patient with ALS.

CRP was involved in both acute and chronic inflammation: it stimulates the release of proinflammatory cytokines, mainly IL-6, into the bloodstream. The liver responds to this release by producing acute-phase reactants such as CRP. CRP is also an in vivo activator of complement: the complement pathway has been postulated to contribute to motor neuron disease. Activation of inflammatory and complement is not specific of ALS but in cerebrospinal fluid, the phosphorylated neurofilament heavy chain to CRP ratio showed significant differences in ALS compared with both disease controls and healthy control groups, suggesting that inclusion of general inflammatory responses allows more specificity in identifying ALS.
High CRP levels increase permeability of the blood-brain barrier and elicit microglial activation in the brain: animal studies showed that systemic inflammation contributes to the neurodegenerative process through microglial activation.

Moreover, CRP can be produced locally in the brain and its production is sharply upregulated in areas damaged by neuro-degenerative processes as in Alzheimer disease. Lunetta et al also showed that the increment of serum CRP levels is correlated to neurological impairment and survival in patient with ALS in the early phase of the disease and without an active inflammatory process support the hypothesis that the increment of CRP levels in the peripheral blood may be the mirror of the upregulation of the production of CRP in the central nervous system. [7]

Benatar et al try to propose serum neurofilaments as a prognostic and biomarkers for ALS. serum neurofilaments is divided between light (NfL) and phosphorylated heavy (pNfH). Both, finding in cerebrospinal liquid (CSF) and blood, have been proposed as potential ALS biomarkers with diagnostic value, utility in predicting prognosis and as possible pharmacodynamic biomarkers. In their study they found that higher serum NfL was associated with older age, higher ΔFRS, female sex, the presence of C9ORF72 repeat expansion, and bulbar symptom onset, but not with baseline ALSFRS-R, while higher CSF pNfH levels were associated with an higher ΔFRS, without reaching any statistical significance.
Adding baseline NfL to the model they produced shows that this biomarker adds prognostic value that is not already explained by known clinical predictors. When both NfL and pNfH were jointly considered, the results showed that, together, these biomarkers added significantly more prognostic values independent of clinical predictors and this result is primarily driven by NfL.
Then they saw that the presence of C9ORF72 repeat expansion, higher ΔFRS at baseline, an higher baseline serum NfL levels were each associated with worse prognosis but baseline pNfH levels were not.
In conclusion, from this study Benatar et al found that serum NfL is prognostic of future ALSFRS-R decline and survival duration, providing information that is not captured by readily available clinical predictors. While absolute values can vary between patients, serum NfL levels remain largely stable in each patient over time. This may portend clinical utility as pharmacodynamic biomarkers if there are detectable changes in levels following exposure to an experimental therapeutic. [8]

Starting from the identification of the role of neurofilaments, Malaspina et al analyzed the activity of humoral response: while, after an initial increase of Nf concentrations, they

remain largely stable, antibodies didn't act like NfL. Clinical heterogeneity in ALS may be linked to concerted innate and adaptive immunological responses, including the reduction of circulatory T regulatory cells (Treg): loss of Treg function in thought to lead to diminished self-immune tolerance and to raise the levels of endogenous antibodies (Abs) and immune complexes (ICs) to self-proteins, including Nf. A state of enhanced autoimmunity to self-proteins (like NfL, NfM and NfH) but also to Dipeptide Repeats (DPR, the product of translation of C9ORF72 gene), may be caused by a changing self-tolerance environment in ALS.
So Nf and DPR- specific humoral responses could be investigated as potential disease progression biomarker and tested for the clinical stratification of ALS. [9]

2.1 Staging

There is currently no validate disease-stage biomarkers for ALS, so until a laboratory-based biomarker is developed, clinical staging is an alternative.
The ALS Functional Rating Scale (ALSFRS) is a validated rating instrument for monitoring the progression of disability in patients with amyotrophic lateral sclerosis (ALS). One weakness of the ALSFRS as originally designed was that it granted disproportionate weighting to limb and bulbar, as compared to respiratory, dysfunction. We have now validated a revised version of the ALSFRS, which incorporates additional assessments of dyspnoea, orthopnoea, and the need for ventilatory support. The Revised ALSFRS (ALSFRS-R) retains the properties of the original scale and shows strong internal consistency and construct validity. ALSFRS-R scores correlate significantly with quality of life as measured by the Sickness Impact Profile, indicating that the quality of function is a strong determinant of quality of life in ALS. [10]

Clinical disease staging allows a simple description of the extent of disease progression. Staging systems have been used in cancer to guide patient management for years and are designed so as to be intuitively obvious in having higher numbers representing later or more advance disease.
Trying to propose a universal method of clinical stage is important because:
- it is simple to administer and understand
- patient with different disease stages have different health care and needs
- it facilitates health and economics analysis
- staging has uses in research

- staging can facilitate clinical trial design and analysis [10]

In ALS, two recent staging systems have been proposed, King's clinical stage and Milano-Torino staging (MiToS).

The King's system is like cancer staging in mapping clinical spread with disease progression, it is more focused on anatomical disease spread and significant involvement of respiratory muscles; is able to differentiate early to mid-disease stage.

MiToS is aimed more towards the distinction of functional capabilities during the spread of the disease; it is able to differentiate late stages in detail.

While King's uses five stage (from 1 to 5), MiToS uses six stages, from 0 (normal function) o 5 (death). The King's system is not based on ALSFRS-R scores but can be estimated from them with 92% concordance.

There are also other systems to evaluate stage and evaluation of the disease: for example, Lombardy Region since 1992/1994 try to define the stage of ALS correlating the clinical stage with the disability, in order to define how patient is able/unable to work and to take care himself and how important have to be the social and economic support: it is called Lomb Scale and it is based on 4 grade of disability, from moderate to complete deficit, based on 4 set of activities, as nutrition, breath, communication and motricity.

There is also a scale that investigate the dysphagia, developed from Diamanti et al, based on Bergamaschi studies. [11]

3. HOMECARE CLINICAL MANAGEMENT

Imparting a diagnosis of ALS requires skills because it would be devastating in person who receive the diagnosis and in his caregivers; this explain why is important to have skill in that. The risk is to destroy the physician-patient relationship.
From the moment in which diagnosis is made, it starts a new path that include the also irremediability of a neurodegenerative illness and his consequence: this is why is so important to start a multidisciplinary care way, in order to be able to adjust and improve symptoms and everyday life accident related to the illness.
The specialist involved in this multidisciplinary clinic team involved: neurologist, respiratory physician and therapist, gastroenterologist, rehabilitiation medicine physician, social consuellor, occupational therapist, speech therapist, specialized nurse, physical therapist, dietitian, psycologist, dentist and palliative care physician.
Neudert et al report that in UK and Germany half of patients affected by ALS decided to die at home, but the anticipation of patient's imminent deaths may increase caregiver distress and anxiety, this explain why start with palliative care also when it seems to be early may help lots of patients and their families. [12]
There are lots of symptoms that may occur in a ALS patient, and lots of them may be treated at home with specific treatment.

- **scialorrhoea** is as common as disabling symptoms in ALS. It may worsen the respiratory performance and intensify anxiety and depression feelings in patient. It might be investigated and intercept as soon as possible in order to control the impact also in emotive tone; amytriptiline is often used, but there are no formal studies proving its efficacy. Oral doses of 10mg three times a day are often sufficient; in alternative, it can be used oral or transdermal hyoscine or sublingual atropine drops; AIFA has recently confirmed the existence of correlation between the use of butylbromide and the regression of sialorrhea or rasping in palliative care [13]

- **bronchial secretions** are another problem to be solved considering homecare assistance of ALS patient. Mucus accumulation is a negative prognostic factor in patient with ALS with Non-Invasive ventilation (NIV), being source of infection and symptom of the progression to respiratory insufficiency. In this case it might be two different types of patients: the one who is able to cough and in this case is mandatory use a mucolytics (like guaifenesin or N-acetylcisteine) in order to

facilitate the fluidification and elimination of the fluids; in case of patient isn't able to cough, the need becomes to reduce as possible the quantity of fluids and secretion that might be accumulated in airways. This purpose might be obtained using anticholinergic bronchodilatator or even furosemide; mechanical cough-assisting devices have been effective in patient with ALS

- **Emotional lability** is a concrete symptom in ALS patients; it isn't correlate with cognitive impairment. The most common used agents are tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs)
- **Spasticity** and **cramps** are other common symptoms in ALS patient, and this is the reason why physical therapy is the mainstay treatment for this kind of problems. Other physical intervents like hydrotherapy, heat, cold, ultrasound, electrical stimulation and chemodenervation have been used although no controlled studies in ALS exist.
  Pharmacologically, gabapentin, tizanidine, tetrazepam and diazepam have been used to treat this kind of symptoms.
- Also **depression** and **anxiety**, as a result of physical deterioration, occur frequently in patients with ALS. Empirically tricyclic antidepressants and SSRIs may be effective, but the choice may be guided by the coexistence of other symptoms, and often it might be used a combination of two or more drugs to treat the complex combination of symptoms.
- **Insomnia** is another common symptom, as a result of depression and anxiety, and it is more common in the last month of life in patients with ALS. Amitriptyline and zolpidem are the most used medications, with a good expected results.
- Due to immobilization, **venous thrombosis** may be a problem to keep in mind, with an annual incidence of 2,7%. It is important so to manage the risk factors of Deep Venous Thrombosis (DVT) using anticoagulants in case of DVT (GCPP) and with physiotherapy, limb elevation and compression stockings in order to prevent the event. There is insufficient evidence to recommend prophylactic medical treatment with anticoagulants.

Other important problems involved in ALS patients are respiratory management and nutrition.

Respiratory insufficiency is the main cause of death in ALS patients, because of diaphragmatic weakness combined with aspiration and infection (ab ingestis polmonitis).

To control the residual respiratory performance, physicians usually used two tests: erect forced vital capacity (defined as the total amount of air exhaled during the FEV test) and vital capacity (the maximum amount of air a person can inhale after a maximum exhalation); these should be performed regularly. Sniff nasal pressure (SNP) may be more accurate in patients with weak lips but neither forced vital capacity nor SNP is a sensitive predictor of respiratory insufficiency.
Easiest way to screen patients oximetry may be the percutaneous nocturnal oximetry, and it can be used also to determine the need for non-invasive positive-pressure ventilation (NIPPV); also cough effectiveness can be a great indicator and it can be assessed by measuring peak cough flow.
NIPPV increases survival and improves patient's quality of life, it is one of the preferred therapy to alleviate respiratory symptoms; it is used to be start at night to alleviate nocturnal hypoventilation. NIPPV improves quality life in patint with bulbar onset, but it is less tolerated by patient with bulbar palsy, due to increment of secretions.
Invasive ventilation can prolong survival in ALS, also for many years. It is costly and can have significant emotional and social impacts in patients and their families, so it might be adequate introduce this possibility earlier in ALS in order to face every aspect of this important decision.
In what patients they didn't decide to proceed with Invasive Ventilation (IV) but in their respiratory insufficiency wasn't enough the NIPPV, the focus might be put on symptoms management: in this way, parenteral morphine, a benzodiazepine and an antiemetic are used and Palliative Care homecare assistance would be the best way for the last months of life.

Nutritional aspect is another key in ALS management. Patients with ALS have an increased resting energy expenditure that might add to a basal dysphagia: this situation can severely influence the nutritional asset. Initial management have to put attention in dietary counselling, modification of food and fluid consistency, prescription of high-protein and high-caloric supplements, education in patients and carers in feeding and swallowing

techniques such as supraglottic swallowing and postural changes.
When these techniques aren't enough, tube feeding became a need, and three procedures can be done: percutaneous endoscopic gastrostomy (PEG, percutaneous radiologic gastrostomy (PRG) and nasogastric tube (NGT) feeding.
PEG is the most frequently procedure for enteral nutrition: it is easy to do (although a mild sedation is necessary) and it is easy to manage after its installation. It is important because it improves nutrition but there is no convincing evidence that attest the reduction of the risk of aspiration in airways.
The timing of PEG would be decided by the patient and his carers: in ALS patients, PEG and Tracheostomy have usually been installed together. It is a key moments because PEG e Tracheo would change the course of the ill.
PRG is a newer alternative to PEG: it doesn't require sedation, minimizing the operatory risk for installation, but it is not widely available.
NGT can be performed in all patients, but have lots of negative sides, like an increasing in oropharyngeal secretions and discomfort or ulceration; that's why it can be considered only in acute emergency situation.

The aim of Palliative Care is to maximize the quality of life of patients and their families by relieving symptoms. Providing emotional, psychological and spiritual support as needed, removing obstacles to a peaceful death and supporting the family in bereavement.

It is important and early support by Palliative Care also to take decision about the course and evolution of the ill and its consequence: Advance Declarations of Treatment (ADT) or "Living Will" (also called in Italy DAT, Disposizioni Anticipate di Trattamento, L.219/2017) is one of the most important stage in order to put the patient at the centre of the clinical management and allowed him to decided how to work and proceed in case of severe worsening of his clinical conditions that may require the decision between an intensive approach (that consider PEG/PRG and Tracheo with years of attendance estimated alive) or a palliative approach (by the treatment of the symptoms without considering the cause, with attendance of months or weeks before the death).
Another important role of Palliative Care is to coordinate the clinical management between every professional figures that orbit around the patient, especially from that moment when the clinical conditions don't allowed an access to neurological centre or to make exams due to worsening of residual performance. [14]

4. THE ALS PROJECT

Maddalena Grassi Foundation is a home healthcare supplier involved in nursing management and palliative care healthcare working in Milan districts.
Its services are turned to aim every patient that, in case of an incurable ill in its terminal phase, want to end their life at home with their parents.
Since 2019, the Foundation has started a project in which the subject of the study is the ALS patient's management at home, because management in ALS is difficult due both to lots of professional figures turning around the patient and his family and due to the complexity and persistent worsening of clinical condition.
The disease course in ALS is ideally composed by an initial phase in which the patient is followed by acute-cure centre (hospital or neurologic centre) and a following phase in which patient is managed at home by home-healthcare services and with planned accesses at hospital or neurologic centre (for example for PEG or trachea substitution).
Some problems may occur during the disease course like lack of the presence of General Medicine Physician (also called in Italy MMG) or delay in answers by neurological centre, and this is the reason why it might be created a specific path characterised by a "low-intensity cure and high-intensity rehabilitation and support" in order to give an adjustable reaction in case of change in healthy conditions of the patient.

Assisting an ALS patient might include a different concept of Palliative Care, not only like an end-of-life management: if a ALS patient decided not to proceed with tracheostomy and/or PEG, he would start a palliative care assistance correct in the strictest sense of the word; but if a ALS patient decided to continue proceeding with tracheostomy and PEG, this would be possible in order to protect patient and his survival. So Palliative Care in neurologic patients has a slightly different connotation between in oncologic patients.

Starting from the diagnosis, ALS patient would have been followed firstly by the neurological centre where the diagnosis was made. Then, when the invalid condition is made with every benefit that law consider, home healthcare assistance could start: this is the preferable by patients, although lots of difficulties and obstacles in organisation.
In most frequently case, the home assistance starts with a physiotherapy project in order to maintain the residual force and mobility: it is organised on a PAI (in Italian called Piano Assistenziale Individualizzato or Personal Assistance Plan) that regulate the coordination of medical and physical therapy and interventions and how long they would remain in

course.
Periodically, PAI would be renovated or remodulated in order to follow the needs of the patient: this is the Case Manager work. His work, together with Care Manager (specific for every single patient), is to create a personal and targeted clinical path in order to give to patient the professional figures that he needs, in a correct intensity during the duration of the PAI.
The key role of Palliative Care is to create an integration between home healthcare services and periodic medical examination made at neurologic centre.
In order to perform this work as great as possible, Maddalena Grassi Foundation enrolled a specific ALS Case Manager, dedicated only to ALS patients, in order to optimize resources and improve skills and knowledge about this illness and its management.

5. METHODS:

The study involves:

1. Creation and following an Excel Database to collect personal data, social, clinical and assistance information of every single ALS patient followed by Maddalena Grassi Foundation both in nursing management and in Palliative Care assistance.

2. Enrolling patient in the study starting from informed consent, an oral and written explication of the project and its aims and goals.
   Inclusive criteria are ALS diagnosis, an home healthcare service activation, a clinical analysis at least for one year from the enrolment. Eventually, new patients can enter in the project later, but they would be considered in the study only if they reach one-year analysis.
   Monthly evaluation by the dedicated ALS Case Manager, in which data are caught to develop the database and to check that home assistance is congruent to the needs of patient

3. Trimestral ALSFRS-R and Lombardian legal-disability scale (LOMB Scale, for the first year, followed by DYALS scale for dysphagia) administration to check congruence between the clinical development of illness and the scales

4. Data Analysis made by a specific physician involved in Palliative Care home assistance.
   The analysis involved both quantitative (starting from the database) and qualitative (based on specific questionnaire with open or closed request) data for evaluate specific targets.

5. Assessment and satisfaction questionnaire administration addresses to patients and their caregivers; in the same way, a similar questionnaire would be administrated to the professional figures of MG Foundation that are involved in ALS patient home assistance.

The study would be adjuvate by Neurologic IRCCS Mondino Foundation

6. DATABASE

The creation of the database has been mandatory to organize the research activity: it is based on personal data like age, months from diagnosis, phenotype, neurological centre, decision about PEG or Tracheo, professional healthcare specialist involved in assistance and how frequently are established visits from healthy operators.

Monthly, ALS Case Manager meet the patient to analyse clinical condition and what and how it changes from the previously month to modify clinical assessment and accesses' frequency if needed (changing also PAI that regulates frequency accesses).

Every three months the ALSFRS-R and LOMB scale will be administer in order to put data in databases and proceed with analysis. From the results, it will be necessary modify clinical interventions and its frequency, and this means that PAI needs to be change.

7. RESULTS

From the start of the project in February 2020, ASL patients followed by Maddalena Grassi Foundation were 37: the study was proposed to everyone affected by ALS, but somebody decided not to participate (also due to pandemic conditions induced by COVID), so the project started with 28 patients. During the first year, enrolling process continued but some families decided not to continue being part of the project, so at the end of 2020 (November 2020) the sample includes 32 patients (including 7 deaths).
At the end of 2021, patients affected by ALS followed between 2020 and 2021 by Maddalena Grassi Foundation were 49.
We observe that patients followed by Maddalena Grassi Foundation between 2020 and 2021 for more than 3 consecutive trimestral evaluation are 24.

About Phenotype, the bulbar one was the more frequent with a 79% of cases, against 17% of spinal patients and one patient with suspected ASM diagnosis.

The diagnosis time average is about 6.5 years ago (82 months), starting from 1 year, arriving to about 20 years of illness.

At the time-control, PEG is used by 75% of the sample, while 17% continue to feed by mouth. 8% decided not to proceed with PEG if the clinical conditions might worsen.

Looking at the respiratory path, 58% has a tracheostomy, while 42% don't have
About patient with respiratory support, 58% of patients need Invasive ventilation (IV), while 33% prefer to use the Non-Invasive Ventilation (NIV) and 9% don't have any respiratory support.
In this sample, 6 patients decided to refuse tracheostomy if needed; of those, 2 express the refuse also for PEG.

Urinary catheter is used by 67% of patients followed by Foundation, against 33% that didn't need the catheter.

Communication is verbal in 25% of patients, non-verbal in 75%; in patients who used technology, 8% talk by smartphone, and 33% using ocular pointer; 8% communicate in non-verbal way. In 25% of patients, communication is absent.

Relating to clinical conditions, we observed that 79% of patients are quadriplegic, while 13% are paraplegic; in 8% of patients, there is a locked in syndrome. 8% of the remaining patients are already able to walk.
We observed that in 25% of cases, sacral lesions can appear; in 8% of case, due to respiratory mask, nasal wounds appeared; in 4% of cases feet or heel need medications due to immobility.

Every three months, ALSFSR-R and LOMB scale have been administrated to all the patients from the ALS Case Manager.

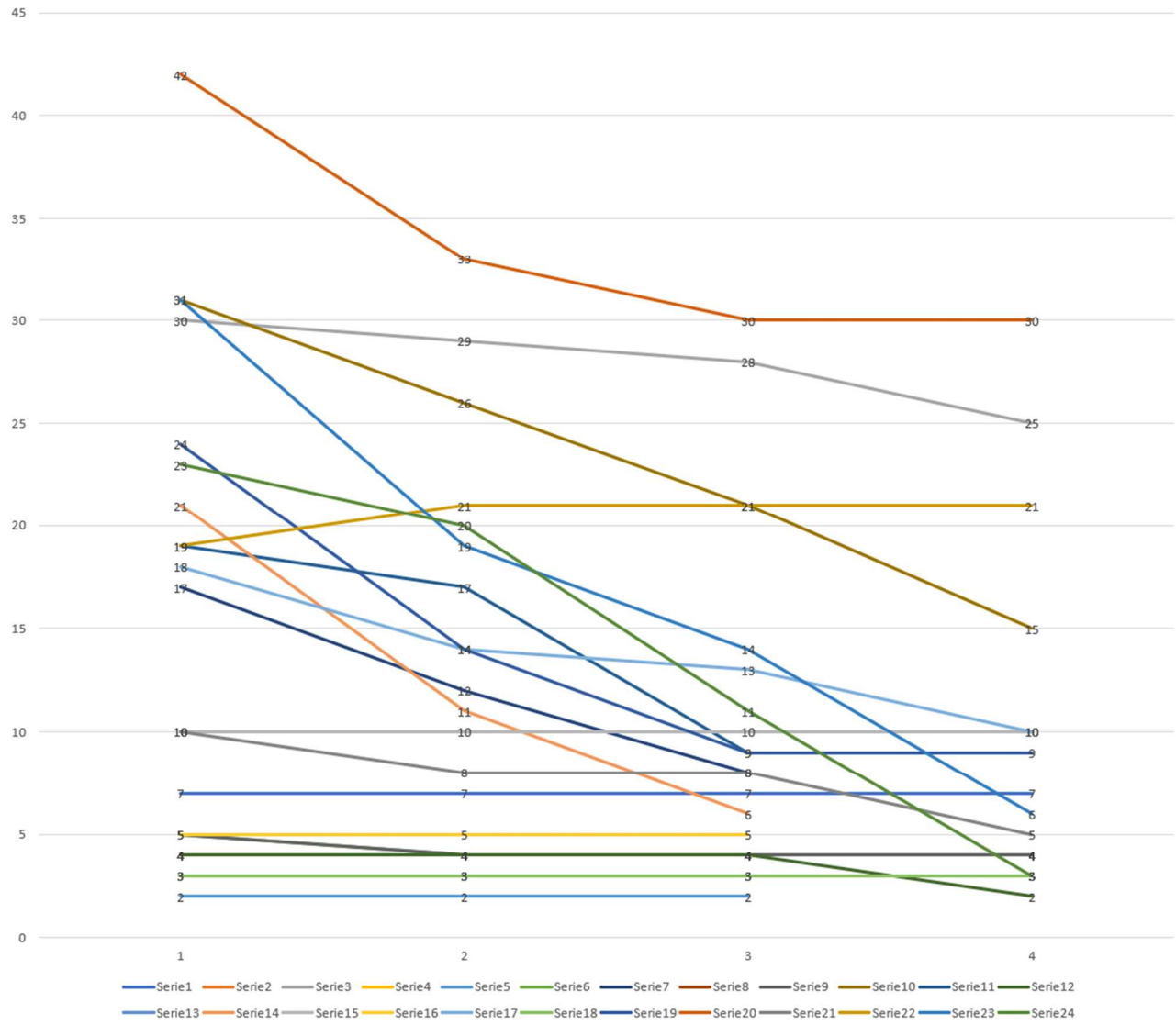


Figure 1 ALSFRS Points of every patient involved in ALS Project

LOMB Scale wasn't considered at the end of the study because of the uniformity of the results that give compared to different clinical stages and performance in patients that belong to the same group: approximately 90% of the patients is included in "complete deficit" stage.
Also, DYALS scale wasn't considered at the end of the study because it was possible to propose it to only 3 patients, not giving us meaningful results.

About social data: in 58% of cases, the familiar setting is based on 2 people, and in 21% of cases only one person (including colf or in-home nurse);
In which familiar situation where the caregiver is only one person, in 8% of situations, the

caregiver is the direct relative, while in 4% of cases there's an hour-paid colf and in 17% of cases there is a cohabitant colf.
When the cohabitants are two, often the relative is helped by an hour-paid colf (33%) or a cohabitant colf (38%).

75% of the patients enrolled in the project were followed by nursing management (ADI) and 25% were followed by the Palliative Care Unit; during the follow up, 6 patients in ADI changed in Palliative Care service: 5 of them died at their home.
In 67% of patients followed by Foundation, there was at least one visit of medical examination from palliative care physician.
Unplanned Hospitalisation is registered only in 3 cases, other 3 patients went to hospital for PEG installation.
In 83% patients, their PAI considers from 3 to 6 professional figures involved in home clinical assistance, with an average Assistential Complex Index (ICA) of 0,7.
We observed that 17% of patients were followed by 2 healthcare workers, 33% by at least 3 healthcare workers, 29% by 4 healthcare workers, 13% by 5 healthcare workers and 8% of patients by 6 healthcare workers.
ICA is obtained by the ratio between days in which one of the professional healthcare figures come at a patient's home and the days in a month (N day with at least 1 professional access/ day in a month): 7 patients received more than 7 accesses in a week.
The average number of professional healthcare figures involved in the assistance is 3.

The professional home healthcare figures are:

- Nurse (70%)
- Physiotherapist (96%)
- Auxiliary nurse (33%)
- there's also the possibility, if needed, to start a path with psychologist, speech therapist, and, of course, palliative care physician.
- Palliative Care Physician (62%)

Neurological centres are often the actors that make the warning of ALS patient that need a homecare assistance to prevent major complications due to the ALS: in particular, 58% of our patients are followed by NeMO (NeuroMuscolar Omnicentre), followed by IRCCS

Maugeri (13%) and Don Gnocchi Foundation (13%), then Auxologico Istitute (8%) and IRCCS Mondino (4%) and Neurologic Institute Besta (4%).

During the project (Feb2020-Dec2021), 27 patients died:

- 8 of those died during the palliative care assistance (6 of those during the palliative sedation).
- other 8 died during the nursing assistance due to a worsening of the clinical conditions related to the ALS.
- 3 patients died during an hospitalisation (hospice or hospital)
- The 8-remaining died for an unpredictable acute event.
-

It is important talk about Shared Planning of Treatments (In Italy called PCC or Pianificazione Condivisa delle Cure): patient is at the center of assistance and it is mandatory that he could decide how to face the problems due to the ALS: not everybody want to proceed with PEG and/or Tracheo when respiratory insufficiency and dysphagia occur, so it might improve the quality life talking with the patient in order to hear his preferences about how to face the worsening of clinical conditions due to the illness.
In our study, we saw that only 25% of patients decide how to proceed when their clinical conditions will became difficult to understand.

During the project, a questionnaire oriented to patients and their caregiver (both if relatives and extra-familiar assistants) is made to understand what's the families' point of view about the specific ALS Case Manager, and how to improve the Foundation's home assistance.
Lots of aspects of the study were been investigated, as the connection between centre and family about clinical information, or if the specific Case Manager would improve the quality of assistance, and the results show how 33% of the people involved in assistance (both patients and their families and colfs/maids) considered the appreciation about the assistance as extremely good, in 61% we registered a good appreciation, in 15% a little appreciation and in 2% of cases any improvement since the introduction of specific case manager in the management of the clinical assistance.
In the open questions, patients and their familiars give some advice in what they would prefer to improve in the homecare assistance.

DOMANDA		MOLTISSIMO	MOLTO	POCO	PER NIENTE		
1) In generale, rispetto al "Progetto SLA", le sue aspettative sono state soddisfatte?	PAZIENTE	22%	67%	11%		100%	
	PARENTE	25%	50%	25%		100%	
	ASSISTENTE NON FAMIGLIARE	67%	33%			100%	
	Media	38%	50%	18%	0%		CAMPIONE: 28 RISPOSTE (100%)
2) Parliamo dell'introduzione della figura del Case Manager Infermieristico dedicato ad una patologia come la SLA: quanto pensa questa scelta possa migliorare l'assistenza e la presa in carico del paziente?	PAZIENTE	45%	45%	10%		100%	
	PARENTE	25%	50%	25%		100%	
	ASSISTENTE NON FAMIGLIARE	33%	67%			100%	
	Media	34%	54%	18%	0%		CAMPIONE: 28RISPOSTE (100%)
3) Parliamo delle modalità per mantenere e facilitare i contatti con l'Equipe (Whatsapp, telefono, mail): quanto pensa che queste tecnologie possano facilitare e migliorare il livello di comunicazione?	PAZIENTE	45%	33%	22%		100%	
	PARENTE	44%	44%	12%		100%	
	ASSISTENTE NON FAMIGLIARE	33%	67%			100%	
	Media	41%	48%	17%	0%		CAMPIONE: 28 RISPOSTE (100%)
4) Secondo l'esperienza fatta ad oggi durante il "Progetto SLA", quanto ritiene che la comunicazione con il centro specialistico/MMG sia migliorata?	PAZIENTE	11%	67%	22%		100%	
	PARENTE		69%	19%	12%	100%	
	ASSISTENTE NON FAMIGLIARE	33%	67%			100%	
	Media	22%	68%	21%	12%		CAMPIONE: 28 RISPOSTE (100%)
7) A proposito delle scale funzionali utilizzate (ALSFRS-R, scala Lomb) quanto la loro somministrazione è stata semplice?	PAZIENTE		100%			100%	
	PARENTE	9%	82%	9%		100%	
	ASSISTENTE NON FAMIGLIARE		67%	33%		100%	
	Media	9%	83%	21%	0%		CAMPIONE: 21 RISPOSTE (100%)
8) Parlando dell'assistenza domiciliare fornita da Fondazione Maddalena Grassi, quanto si è sentito supportato nella ricerca di risposte a problematiche di tipo sociali/amministrative?	PAZIENTE	22%	78%			100%	
	PARENTE	32%	50%	12%	6%	100%	
	ASSISTENTE NON FAMIGLIARE	67%	33%			100%	
	Media	40%	54%	12%	6%		CAMPIONE: 28 RISPOSTE (100%)
9) Quanto è soddisfatto dell'addestramento rivolto al caregiver da parte degli operatori di Fondazione Maddalena Grassi?	PAZIENTE	22%	67%	11%		100%	
	PARENTE	19%	62%	19%		100%	
	ASSISTENTE NON FAMIGLIARE	33%	67%			100%	
	Media	25%	65%	15%	0%		CAMPIONE: 28 RISPOSTE (100%)
10) Ritiene che la risposta alle sue esigenze assistenziali da parte di Fondazione Maddalena Grassi sia stata tempestiva ed	PAZIENTE	22%	78%			100%	
	PARENTE	32%	62%	6%		100%	
	ASSISTENTE NON FAMIGLIARE	67%	33%			100%	
	Media	40%	58%	6%	0%		CAMPIONE: 28 RISPOSTE (100%)
11) Quanto ritiene che l'assistenza fornita sia d'aiuto a creare un clima più positivo e	PAZIENTE	22%	78%			100%	
	PARENTE	32%	62%	6%		100%	
	ASSISTENTE NON FAMIGLIARE	100%				100%	
	Media	51%	70%	6%	0%		CAMPIONE: 28 RISPOSTE (100%)
RISULTATI COMPLESSIVI (media)		33%	61%	15%	2%		

Figure 2 Results of the questionary created for Patients and their families

Another questionnaire was made to understand the role of the professional figures involved in home healthcare assistance, their background and their role in healthy assistance; lots of professional areas were investigated, such as how to improve health care skills in ALS patient management (for example, ventilator management or cough machine).

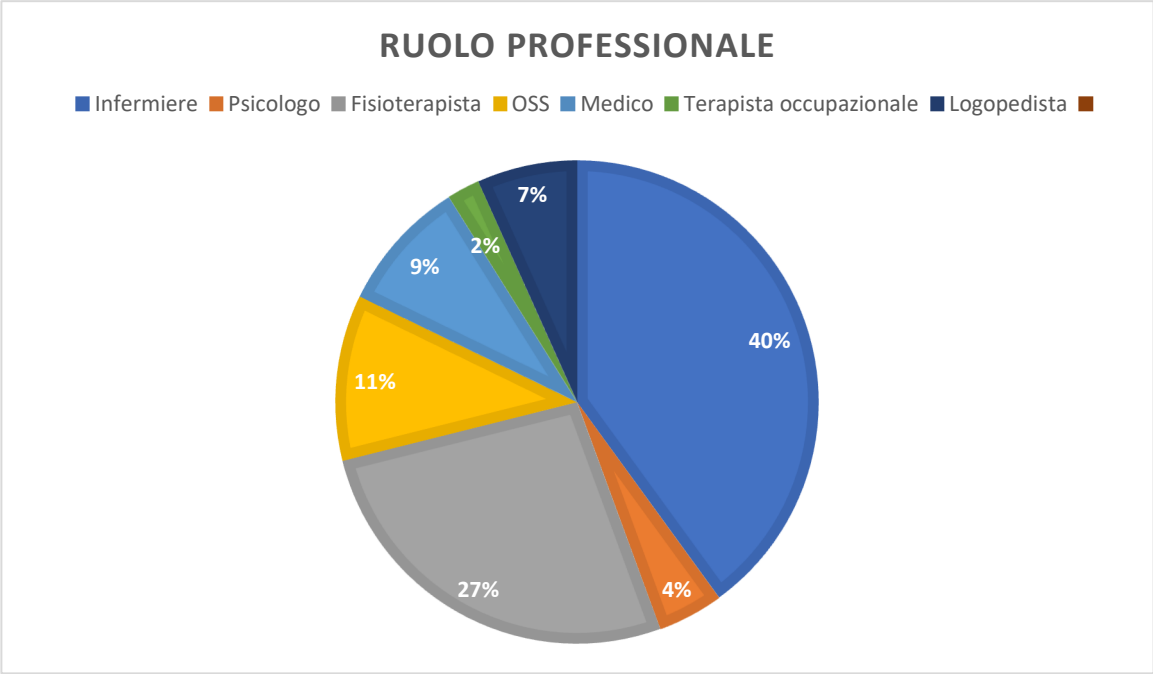


Figure 3 Numeric analysis of the role of professional figures involved in ALS Project

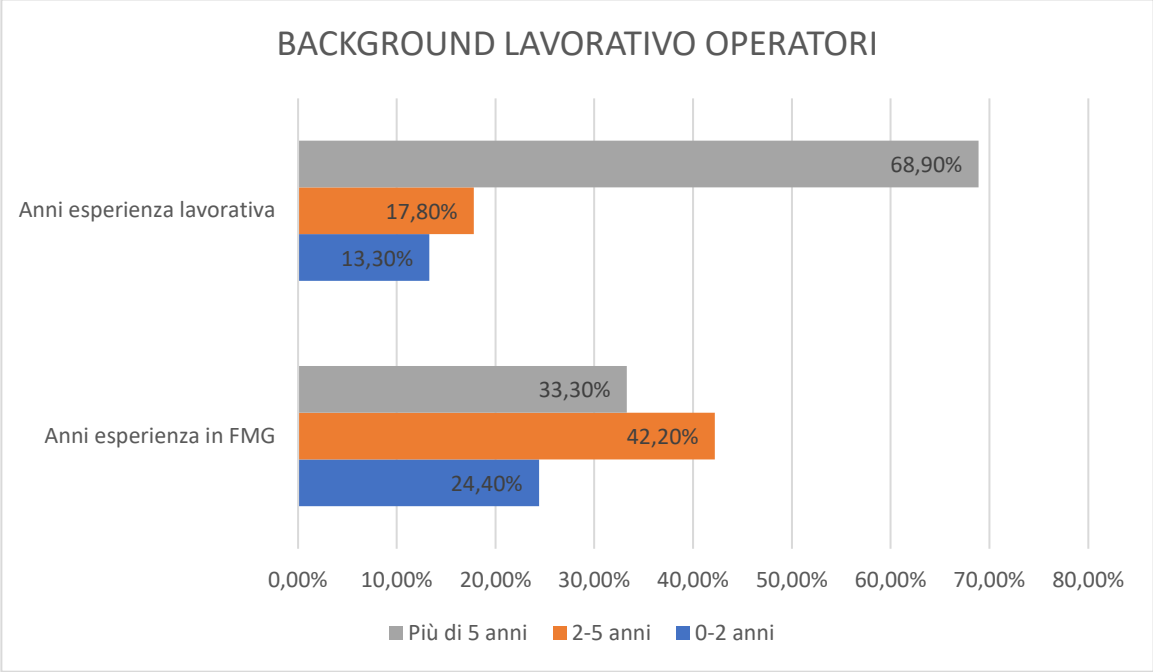


Figure 4 Analysis of the working background of the workers involved in ALS Project

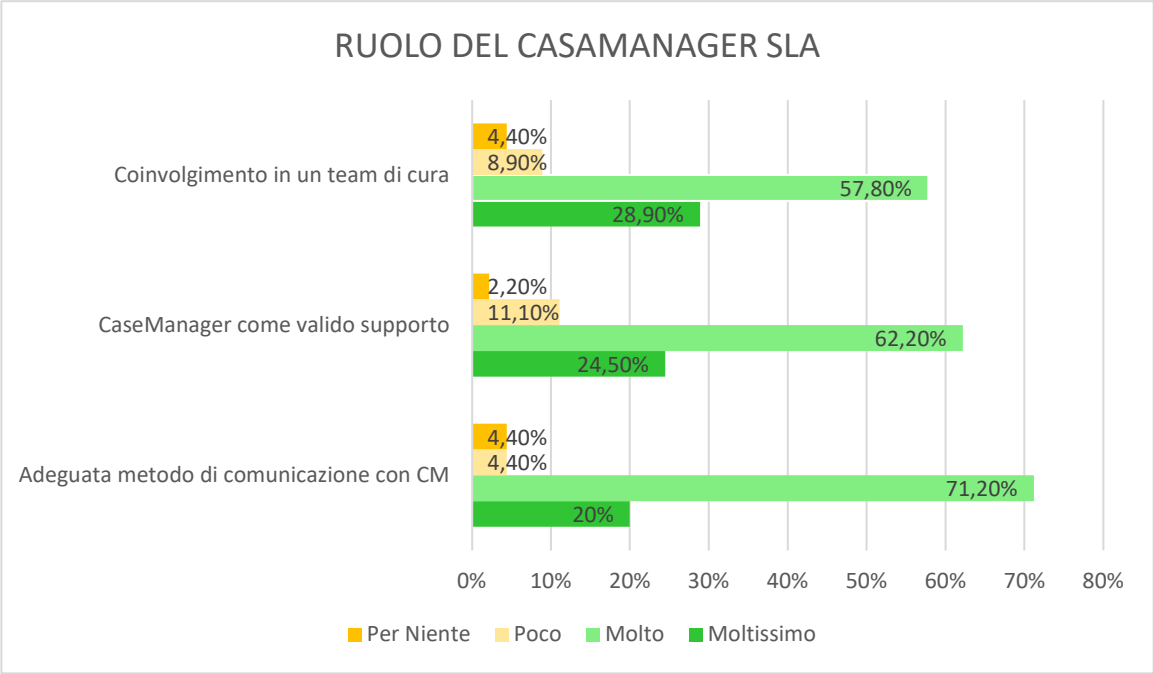


Figure 5 Approval Rating of the figure of ALS CaseManager

ATTIVITÀ CHE SI VORREBBE APPROFONDIRE	NUMERO OPERATORI	% OPERATORI
Utilizzo del ventilatore	17	37,7%
Broncoaspirazione	5	11,1%
Utilizzo del comunicatore	3	6,6%
Fisioterapia respiratoria	3	6,6%
Medicazione e gestione tracheostomia	3	6,6%
Utilizzo macchina della tosse	2	4,4%
Interazione con vissuti psicologici del paziente	2	4,4%
Esecuzione dell'igiene nel paziente in ventilazione invasiva	1	2,2%
Esecuzione dell'igiene nel paziente portatore di PEG	1	2,2%
Interazione con la situazione familiare	1	2,2%

Nessuno	7	15,5%

Figure 6 Answer of the workers about how to improve their own skills in the aiding of ALS patient

Starting from the data contained in the Database, we were able to create different groups in our population, for example for progression or for type of handicap in the deambulation.

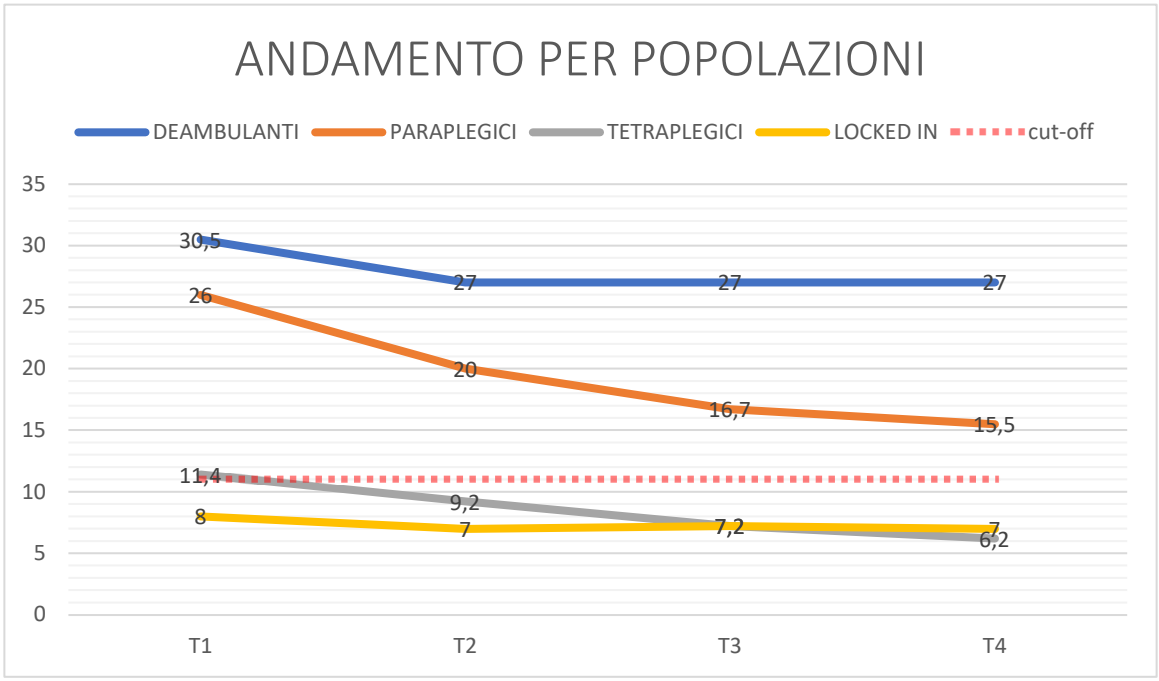


Figure 7 Results of different ALS populations based on residual abilities

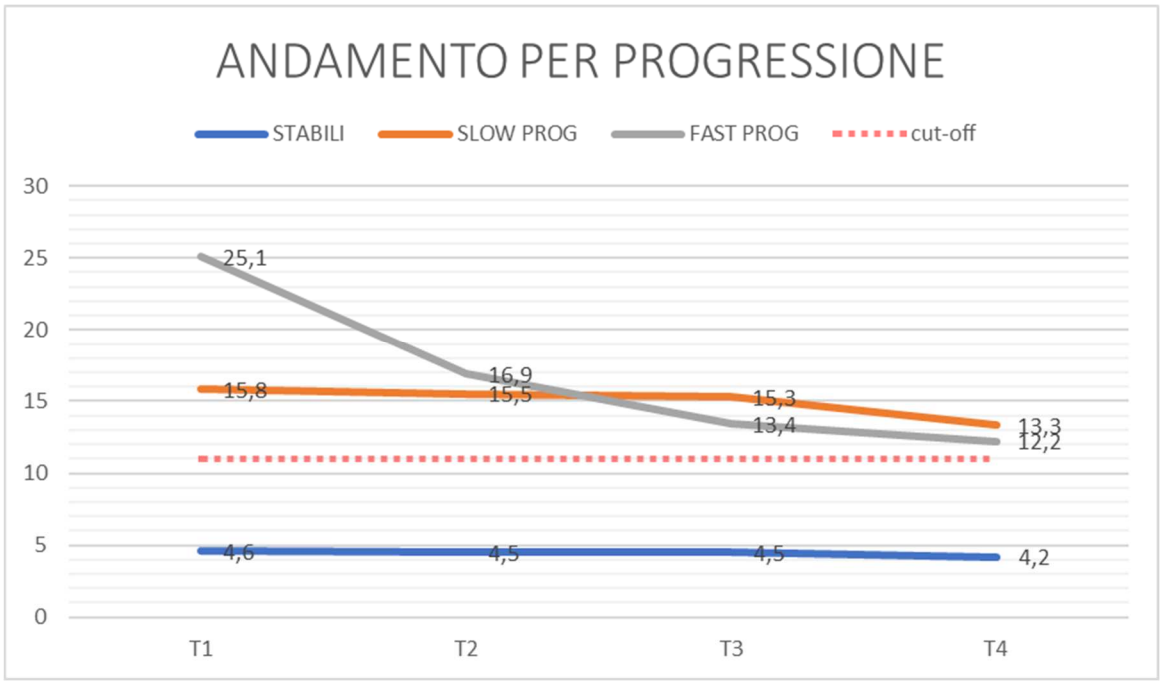


Figure 8 Results of different ALS populations based on speed in progression

We identify the value ALS=11 as a cut off to divide the needs in the population of the Project and we study if it can be used as a validated cut off also in the statistic way.

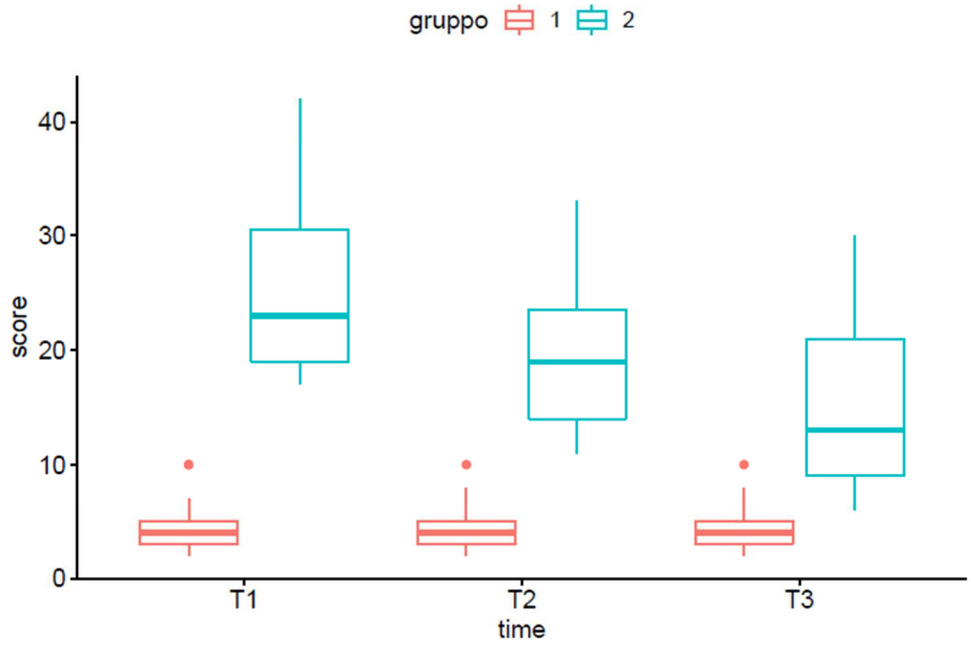
A) Group 1: patients with score T1 <11; Group 2: patients with score T1≥11

- Patients in which we analyse 3 time points (T1-T2-T3, sample: 24 patients)

PRIMI 3 TIME-POINTS, escludendo T4

Gruppi:

- gruppo 1: pazienti con score al T1 < 11
- gruppo 2: pazienti con score al T1 >= 11



	Effect	DFn	DFd	F	p	p<.05	ges
1	gruppo	1.00	22.00	51.05	3.65E-07	*	0.68
2	time	2.00	44.00	31.00	3.97E-09	*	0.13
3	gruppo:time	2.00	44.00	27.12	2.11E-08	*	0.11

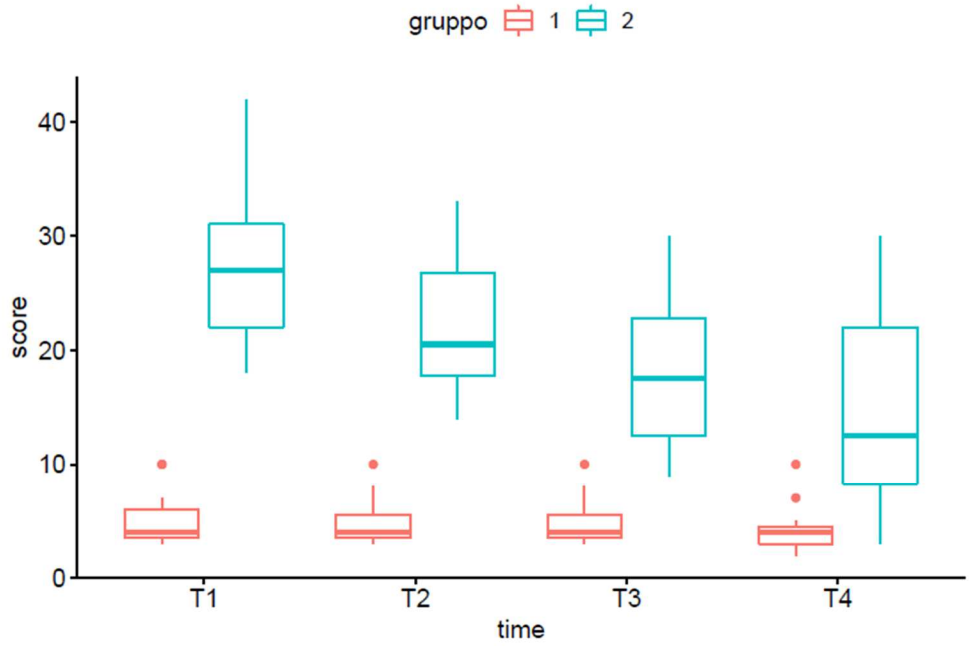
Figure 9 Analysis of trend in patient with T1/T2 and T3 > or < 11

- Patients with four evaluations (T1-T2-T3-T4) excluding patients without T4 (sample: 19 patients)

TUTTI i TIME-POINTS, escludendo i pazienti con T4 mancante

Gruppi:

- gruppo 1: pazienti con score al T1 < 11
- gruppo 2: pazienti con score al T1 >= 11



	Effect	DFn	DFd	F	p	p<.05	ges
1	gruppo	1.00	17.00	45.47	3.44E-06	*	0.69
2	time	3.00	51.00	20.89	5.78E-09	*	0.17
3	gruppo:time	3.00	51.00	16.44	1.33E-07	*	0.14

Figure 10 Analysis of trend in patient with T1/T2/T3 and T4 > or < 11

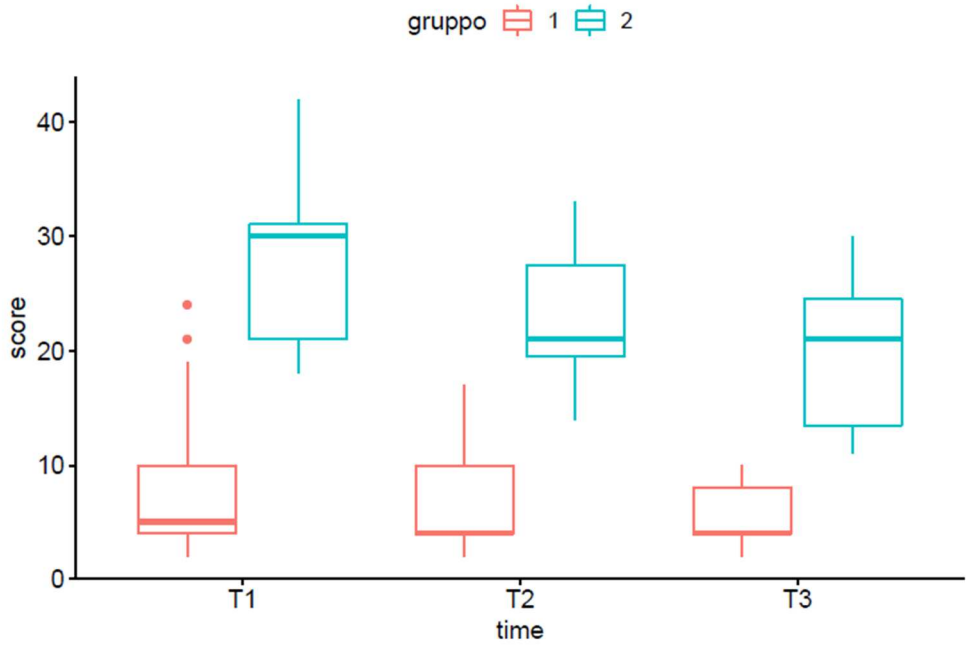
B) Group 1: patients with ALS<11 in at least one evaluation; Group 2: patients with ALS ≥11 in every evaluation

- Patients in which we analyse 3 time points (T1-T2-T3, sample: 24 patients)

PRIMI 3 TIME-POINTS, escludendo T4

Gruppi:

- gruppo 1: pazienti con score ad almeno un time-point < 11
- gruppo 2: pazienti con score >= 11 in tutti i time-points



	Effect	DFn	DFd	F	p	p<.05	ges
1	gruppo	1.00	22.00	48.73	5.25E-07	*	0.65
2	time	2.00	44.00	16.88	3.63E-06	*	0.12
3	gruppo:time	2.00	44.00	3.25	4.80E-02	*	0.03

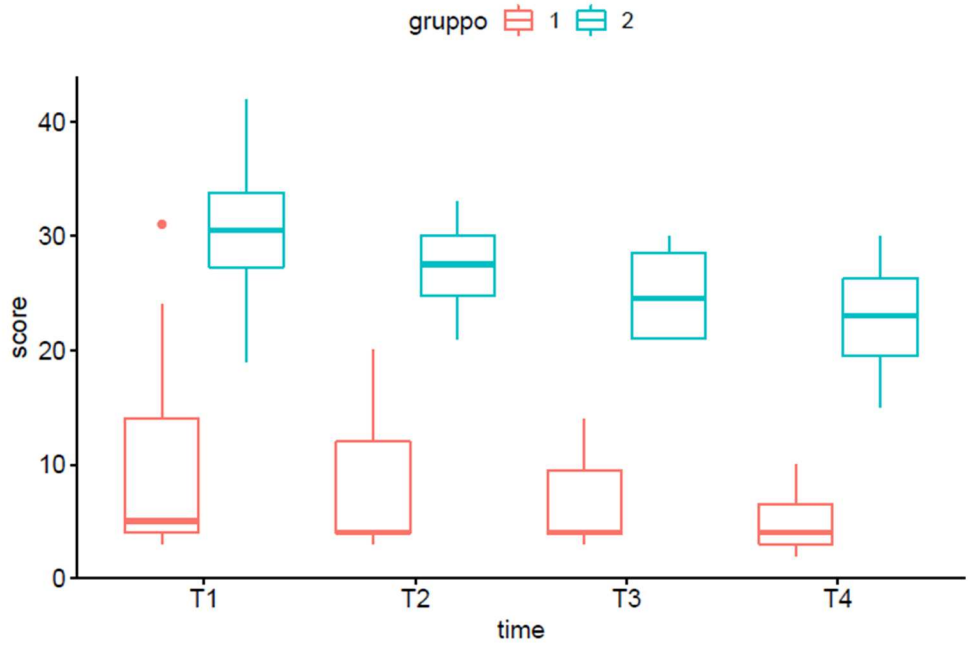
Figure 11 Analysis of trend in patient with at least one of the three evaluations > or < 11

- Patients with four evaluations (T1-T2-T3-T4) excluding patients without T4 (sample: 19 patients)

TUTTI i TIME-POINTS, escludendo i pazienti con T4 mancante

Gruppi:

- gruppo 1: pazienti con score ad almeno un time-point < 11
- gruppo 2: pazienti con score >= 11 in tutti i time-points



	Effect	DFn	DFd	F	p	p<.05	ges
1	gruppo	1.00	17.00	41.62	5.97E-06	*	0.64
2	time	3.00	51.00	7.04	4.75E-04	*	0.10
3	gruppo:time	3.00	51.00	0.30	8.23E-01		0.01

Figure 12 Analysis of trend in patient with at least one of the four evaluations > or < 11

8. DISCUSSION

Maddalena Grassi Foundation decided to start the “ALS Project” during the 2020 with the purpose to improve homecare assistance of their patients affect by ALS.
Starting from 2020, ALS patients followed by Maddalena Grassi Foundation were 49, with different levels of assistance.
The enrolment in ALS Project started from February 2020 and ended in February 2021.
The purpose of the study is to identify a sample of ALS population, followed for at least 9 consecutive months, in order to understand needs and issues that may occur in a healthy homecare assistance, and improve the quality of that: working on this way, a specific Case Manager dedicated to ALS patients became the coordinator of the assistance with a monthly access to the house of every single patient to control that needs and issues are well controlled and to collect data about the study (like ALSFRS-R, Lomb scale, education of the caregiver).

The domiciliary health assistance is an important key of the Italian National Health Service; it allowed to assist patients that:

- don’t need a long-lasting hospitalisation but want to stay at their own home, not renouncing to a home medical assistance.
  It is important also because this kind of assistance allow to reduce waste of money during a hospitalisation
- don’t want to spend their residual time, when the predicted prognosis is about few months, in an hospital or a rehabilitative residence, far away from their home and families.

The profile of the healthcare service may have two levels: ADI (or nursing and rehabilitative home care) and UCP-Dom (palliative homecare assistance).
The differences between the two types of service are that one is turn to patients with at least a good residual clinical performance but that need a nursing assessment (PEG and/or Tracheostomy need frequently control and substitution by the nursing) or rehabilitation path (such as physiotherapy in case of paraplegic or tetraplegic to avoid pressure ulcers), while the latter is turn to patient in an advanced or complex stage.

ALS patients especially begin a domiciliary assistance due to a **physiotherapic path**: people that are losing their ability in movement and coordination, in fact, may have lots of benefits by making physiotherapy; this is one of the most important (and appreciated) figure in this domiciliary assistance. Physiotherapist may focus his attention also to the sensorial and cognitive alterations during the evolution of the ill.
Physiotherapist so can be important in the first stages of ill to improve the patient's abilities but also in the advanced stages of the ill to maintain the residual performance.
in the first stages, physiotherapy has the objective on preventive function, to reinforce and maintaining the motor and breathing abilities. In the advanced stages, during the worsening of the ill, the gradual spastic paralysis and immobilism that would occur (often related with pressure ulcer) can be alleviate by mobilisation. Despite the absence of a specific therapy and the rapid worsening of the ill, a targeted program created specifically for every patient may improve the quality of their life.
Focusing the work of the physiotherapist with ALS patients, it is turned to improving the force and coordination of the muscles that mainly going into a weakness in their function, losing also elasticity and enrolment in the motor schemes. It is specifically important working toward to muscles involved in deglutition, breathing, phonation, prehension and writing. Important is also the muscles involved in the maintaining of the upright state, seated state, about the control of the trunk and involved also in the changing in position of the body in the space (specifically in the bed or in the sofa).
The right use and the right moment of introduction of orthosis or medical aid is another important stage of medical assistance of ALS patients. The improvement of the mobility is important also for the caregivers and caretakers of these patients, because can alleviate their own sense of powerlessness facing the ALS.
Despite the weak of bibliographic materials about the importance of the physiotherapy in ALS patients, we can clearly see how the quality life may be improved after the introduction of this kind of support: in some patients we also see an improvement of the abilities so important that also the ALSFRS points increase in the consecutive evaluations (Patient 22): obviously it isn't referred to an improvement of the ill, but it is a clear signal about how important is an earlier introduction of a specific support of abilities in a degenerative ill like ALS.
It is important, on the other side, not to exaggerate with the exercise and training: the progression of the ill turn inevitably to a faster muscular depletion and burn-out, and it is

important to adequate the training sessions with the physiotherapist with the ill stage, and modify the frequency of the sessions.
Other type of exercises made with physiotherapist includes respiratory training, for example abdominal thrust, important for the excretion of oral and bronchial secretions. In advanced phases, physiotherapist might be important to explain to the family and caregivers how cough-machine or in-exsufflation machine work and when it is important to use.

Another important professional role in ALS domiciliary assistance is **nurse**.
Nurse is involved in lots of important procedures, includes management of tracheostomy or evaluation of PEG.
In the early phase of ill, nursing activities are turned to maintain autonomy and motricity: it is important teach to patients the right way in movement in order to avoid and reduce the fall risk; it is important also manage the initial dysphagia by modifying diet and consistency of the foods.
During the evolution of the ill, became another key element the maintenance of the integrity of the skin to prevent ulcers: in this way it is important avoid maintaining the same position for a long period during the day, and it is important also the right hygiene of the person; this is one reason why a nurse can help the family and caregivers of the patient to identify the right moment of the adoption for example of urinary catheter.
It is important the figure of the nurse to monitoring the evolution of the progression of the illness and its consequence, to reduce the consequences of the deterioration of the performance: this is the reason why the ALS Case Manager chose by Maddalena Grassi Foundation is a nurse specialized in ALS.

Also, the **logopaedist** can be an important figure for ALS patients to face one of the greatest fears of the ALS: the loss of communication. Logopaedist work to maintain the better way of communication as possible by vocal and breathing training, respiratory exercises, and, in advanced phase, by using alternative way of communication (for example Etran tablet or eye communicator),

Other figures that may be included in ADI dedicated to ALS patient is the **OSS**: maintain a good hygienic conditions in patients that may be difficult to move, and wash is important for the dignity of the patient but also to avoid skin complications such as painful ulcers.

Often the washing process can be made together by OSS and the caregiver (relatives or caretaker of the patients) with the target to train the families to take care of a difficult patient like ALS ones. OSS has the role to maintain appropriate hygienic conditions by education of the families and caregivers, but also, through the coordinated work of physiotherapist, nurse and OSS, to educate the caregivers to adopt the right manner for Mobilisation of the patient.

When the clinical condition of the patient may turn to a progressive massive deterioration and/or the life attendance became predictably less than 12/24 months, UCP-Dom (Palliative Care Unit) could be activated with the adding of the regular medical supervision, turn to better assist the patient and his family in the contest of the progression of the ill and to decide if proceed in a domiciliary assistance or to proceed with a hospitalisation in a Hospice. If the patient and his family decide to continue at their own home, UCP-Dom can be activated.
During the UCP-Dom assistance, the finality of the clinical management tends to maintain an adequate psychological balance and to reduce symptoms such as pain, fatigue, dysphagia, or breath insufficiency by a medical support, avoiding the recourse to emergency services like ER or hospitalisation in an acute hospital; physiotherapy and rehabilitation services can proceed if patient's clinical condition allowed it. It is important to reduce the activity that could worsen the clinical condition and intensify the assistance in what could help the patient (for example hygiene assistance or nurse supervision).

From the beginning of the Project, there were at least 49 patients that decided to accept the project in which a deeper analysis of clinical conditions of these patients were allowed, to improve their quality of life and the quality of life of their relatives.
We found that, in our population, 51% of patients were male while 49% were women.
We divide patients into categories of ill: we found that we have Bulbar phenotype in 38 patients (78% of our population), a Spinal phenotype in 9 patients (18%) and a flail leg case (2%); we also have an uncertain diagnosis between ALS and SMA (2%).

The distribution between ADI and UCP-Dom is shifted to the ADI (40 patient with an 82%) than that UCP-Dom (9 patient for a 18% of patients): the reason why we have that difference between the two levels of healthy assistance is that ALS may have a long period of development, especially if the patient decides to proceed with trachea and/or

PEG, and his clinical need at home can be fulfil by a nursing-centred assistance; on the same way, a concrete palliative care assistance at home is needed only in the advanced clinical situation, or in case of a deeper worsening of clinical conditions.

During the lock-down with the pandemic in full swing due to COVID, some of our patients decided to suspend the visits of their healthcare personnel (11 patients, 22% of the sample): this is a decision made in most cases from families where their relative was fundamentally stationary and this is the reason why they weren't considered available for data received by the Project.

Focusing our attention in having a reliable data to analyse, we considered in our study only patients with at least 3 consecutive ALSFRS-R evaluations in the last year (from February 2020 to February 2021), excluding patients lost during the follow up but including those who died during the year.

VARIATION (Time Interval: 3 months)	**T1-T2 (Sample 24 patients)**	**T2-T3 (Sample 24 patients)**	**T3-T4 (Sample 19 patients)**
Unvaried	10 (41,6%)	14 (58,3%)	12 (63,1%)
Variation 1-2 points	5 (20,8%)	2 (8,3%)	1 (5,3%)
Variation 3-5 points	4 (16,7%)	6 (25%)	3 (15,8%)
Variation 6-10 points	3 (12,5%)	2 (8,3%)	3 (15,8%)
Variation 11-22 points	1 (4,2%)	/	/
Improved	1 (4,2%)	/	/
Average Variation	2,63 pts	1,91 pts	1,38 pts

Figure 13 Numeric ad percentual Variation in consecutive ALSFRS results

ALS	I val	II val	III val	IV val		LOMB	I val	II val	III val	IV val		RICOVERI		ICA
PZ1	7	7	7	7		PZ1	Deficit completo	Deficit completo	Deficit completo	Deficit completo		1		0,8
PZ2	4	4	4	4		PZ2	Deficit completo	Deficit completo	Deficit completo	Deficit completo				0,7
PZ3	30	29	28	25		PZ3	Deficit grave	Deficit medio-grave	Deficit grave	Deficit grave		1		0,8
PZ4	3	3	3	3		PZ4	Deficit completo	Deficit completo	Deficit completo	Deficit completo		1		0,8
PZ5	2	2	2			PZ5	Deficit completo	Deficit completo	Deficit completo					1,0
PZ6	5	4	4	4		PZ6	Deficit completo	Deficit completo	Deficit completo	Deficit completo				0,9
PZ7	17	12	8			PZ7	Deficit completo	Deficit completo	Deficit completo					0,4
PZ8	4	4	4	4		PZ8	Deficit completo	Deficit completo	Deficit completo	Deficit completo				0,8
PZ9	5	4	4	4		PZ9	Deficit completo	Deficit completo	Deficit completo	Deficit completo				0,5
PZ10	31	26	21	15		PZ10	Deficit medio-grave	Deficit completo	Deficit completo	Deficit completo				0,3
PZ11	19	17	9			PZ11	Deficit completo	Deficit completo	Deficit completo			1		0,7
PZ12	4	4	4	2		PZ12	Deficit completo	Deficit completo	Deficit completo	Deficit completo				0,8
PZ13	3	3	3	3		PZ13	Deficit completo	Deficit completo	Deficit completo	Deficit completo				0,9
PZ14	21	11	6			PZ14	Deficit grave	Deficit completo	Deficit completo					0,8
PZ15	10	10	10	10		PZ15	Deficit completo	Deficit completo	Deficit completo	Deficit completo		1		0,5
PZ16	5	5	5			PZ16	Deficit completo	Deficit completo	Deficit completo					0,8
PZ17	18	14	13	10		PZ17	Deficit completo	Deficit completo	Deficit completo	Deficit completo				0,7
PZ18	3	3	3	3		PZ18	Deficit completo	Deficit completo	Deficit completo	Deficit completo				0,9
PZ19	24	14	9	9		PZ19	Deficit completo	Deficit completo	Deficit completo	Deficit completo				1,0
PZ20	42	33	30	30		PZ20	Deficit medio-grave	Deficit moderato	Deficit grave	Deficit grave				0,3
PZ21	10	8	8	5		PZ21	Deficit completo	Deficit completo	Deficit grave	Deficit grave				0,7
PZ22	19	21	21	21		PZ22	Deficit completo	Deficit medio-grave	Deficit medio-grave	Deficit medio-grave				0,7
PZ23	31	19	14	6		PZ23	Deficit medio-grave	Deficit medio-grave	Deficit completo	Deficit completo		1		0,4
PZ24	23	20	11	3		PZ24	Deficit grave	Deficit grave	Deficit completo	Deficit completo				0,7

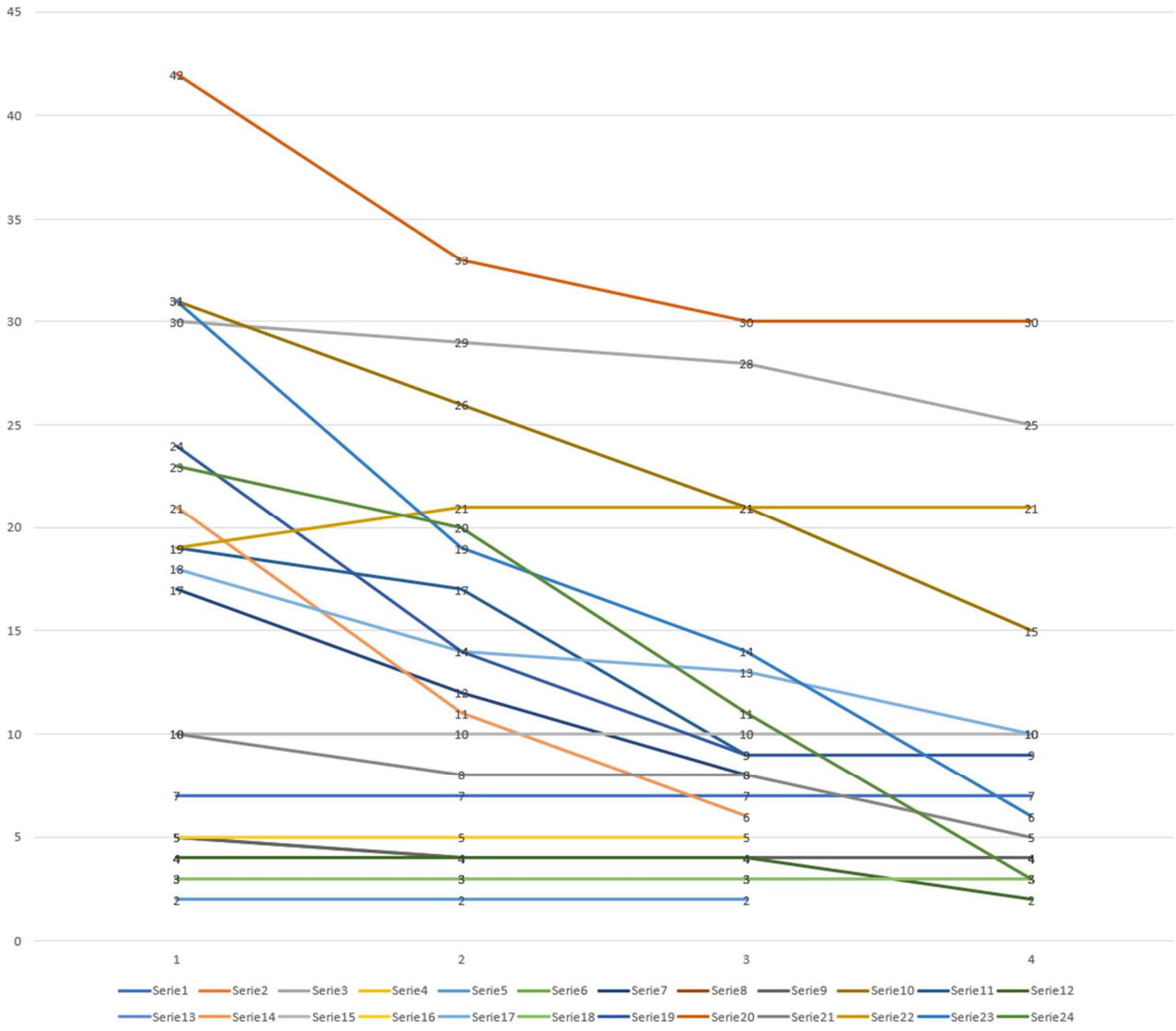
Figure 14 Merging of the ALS points and LOMB evaluations in every patient involved in ALS Project

Thanks to ALSFRS-R, it is possible to understand how fast clinical conditions change and in what specific area. In particular, we observed that the average decrease of ALS evaluation is about 2 points every three months, but we can also clearly see that the majority part of the sample maintains fundamentally a stable clinical situation or a little loss of points between one evaluation and the following.

In the population, we observe that the average age is 67 (with results including between 38 and 86) and is it fully coherent with the bibliographic data that identify the average age in ALS between 50 and 70 years.

Distribution in sex is about 13 male patients (54%) versus 11 female patients (46%).
We analyse the average months since the diagnosis in every single patient and we find a result of 83 months (about 7 years and 3 months): this is slightly upper than the data reported in the literature, but it cannot be explained because some ALS cases can be so quick in their progression that they need an hospitalisation (an home assistance can be not enough).
19 patients, the 79% of the sample, is assisted by Maddalena Grassi Foundation in ADI, while 5 patients (21%) are followed in UCP-Dom setting.

We analyse patients using at least 3 consecutive ALSFRS-R (4 when possible) and Lomb scale like we reported in Figure 1:



It is important to note that despite most patients didn't have a critical clinical condition, the consultation of the palliative care physician has been made in 50% of patients and 42% of patients received a regular periodic evaluation made by palliative care physician with an average access/week of 0,83.
ALS is a progressive neurodegenerative pathology, and the definition explain how palliative care an important role since the diagnosis has: no curative treatment is already present, and the purpose of the clinical assistance, since the diagnosis, is to control the onset of the symptoms, trying to limit them and making a rehabilitative path to reinforce and maintain the residual performance (especially respiration, speech and deglutition and motricity).

Another important observation that the database allowed is that the most frequently healthy figure involved in home assistance in an ALS patient is the Physiotherapist with an average number of accesses to patient's home of 3/week, and he is enrolled in 83% of patients involved in ALS Project; the second healthy figure involved most frequently is the Nurse, with an average frequency access to patient's home of 2,25/week, enrolled in 70% of patients. Then there are the OSS (33% of patients, 1,5/week) and Phycologist (23% of patients, 1/week).
Specialist physician is also involved in home assistance (23% of patients): they are mainly pneumologist, anaesthetist or otolaryngologist, involved in the management of tracheostomy and PEG and in their recurring substitution.

Lomb scale demonstrate to be not enough detailed to describe the clinical situation of the patients: we observe patients with ALS 31 and ALS 5 with the same classification (complete deficit), while ALSFRS-R allow to detail the clinical situation and, thanks to the different areas investigated, to understand what the needs are of every specific patient.
On the other way, Lomb scale is connected with the ICA, that means the frequency of accesses during a week by the health personnel: patients with a medium-severe deficit is associated with a ICA < 0,5, that it means a low-intensity assistance, while patients with a deficit from severe to complete has a ICA > 0,5 (medium ICA 0,8), that it means a high-intensity assistance with lots of healthy professional figures enrolled in the home assistance.

We decide to analyse patient in two ways:

a) Patients with every T1<11 vs Patients with every T1>11
b) Patients with at least one evaluation <11

In every analysis we made, we consider only three evaluations, or we excluded patients without T4, in order to analyse how important is the fourth evaluation and to analyse the correlation between clinical conditions and progression of the ALS scores.

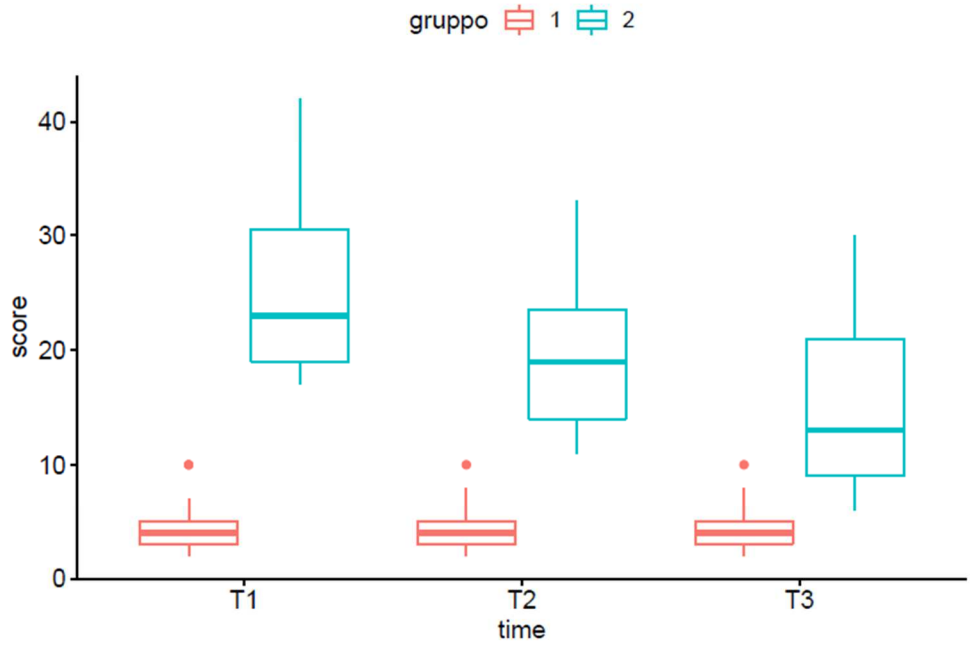
a) In the first analysis, we identify that in both analysis patients with T1<11 have a different speed in the evolution of the ill: results of ALSFRS-R for patients with T1<11 remain more stationary compared to patients with T1>11 in which we can observe a more variability between T1, T2 and T3 (and T4).
   More variability in a patient with weakness as ALS means that a more frequent revaluation by CareManager is necessary to control and manage every problem that may occur such as dysphagia or respiratory insufficiency at their initial phases: it is important educate family and caregivers in identify and then in the management and correction of the problems in order to minimize the impact of the problems on the quality of life.
   Patients with ALS<11 has a more stable clinical situation, although an advance stage of ill: the medicalisation of the patient is high, with lots of access of healthy professional figures such as Nurse for management of tracheostomy/respiratory or PEG, and Physiotherapist to avoid cutaneous ulcers and maintain the mobility of the articulations.
   Palliative Care physician is important in this phase, in order to analyse the progression of the illness and to identify the right moment in which Palliative Care assistance is necessary to face to the progression of the illness and to the PCC (Pianificazione Condivisa delle Cure or Shared Planning of Treatments) and decide how to take care of the patients.

- **Group 1: patients with score T1 <11; Group 2: patients with score T1≥11**
- Patients in which we analyse 3 time points (T1-T2-T3, sample: 24 patients), Figure 9:

PRIMI 3 TIME-POINTS, escludendo T4

Gruppi:

- gruppo 1: pazienti con score al T1 < 11
- gruppo 2: pazienti con score al T1 >= 11



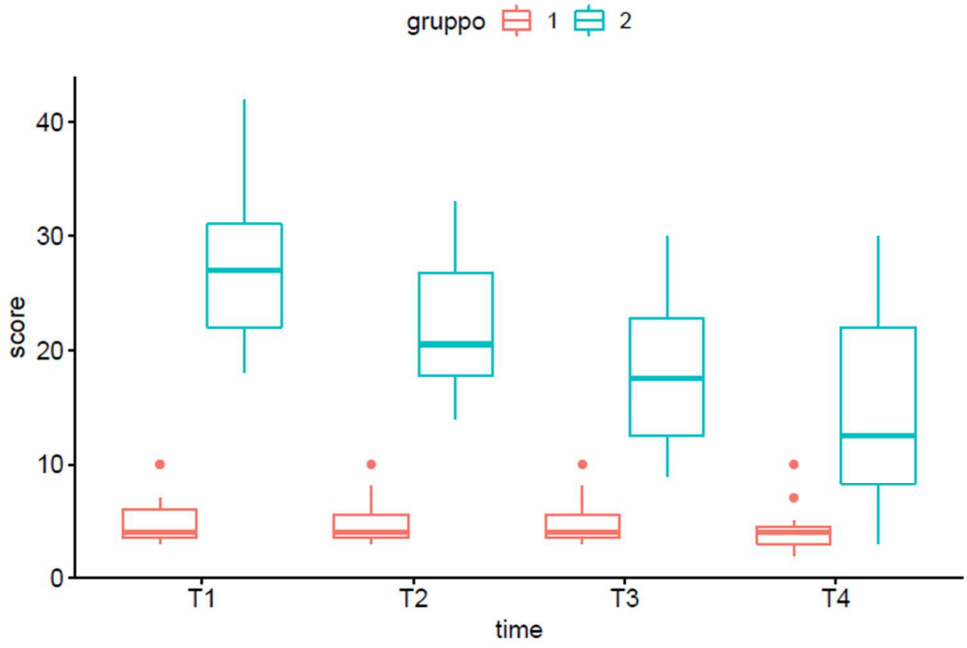
	Effect	DFn	DFd	F	p	p<.05	ges
1	gruppo	1.00	22.00	51.05	3.65E-07	*	0.68
2	time	2.00	44.00	31.00	3.97E-09	*	0.13
3	gruppo:time	2.00	44.00	27.12	2.11E-08	*	0.11

- Patients with four evaluations (T1-T2-T3-T4) excluding patients without T4 (sample: 19 patients), Figure 10:

TUTTI i TIME-POINTS, escludendo i pazienti con T4 mancante

Gruppi:

- gruppo 1: pazienti con score al T1 < 11
- gruppo 2: pazienti con score al T1 >= 11



	Effect	DFn	DFd	F	p	p<.05	ges
1	gruppo	1.00	17.00	45.47	3.44E-06	*	0.69
2	time	3.00	51.00	20.89	5.78E-09	*	0.17
3	gruppo:time	3.00	51.00	16.44	1.33E-07	*	0.14

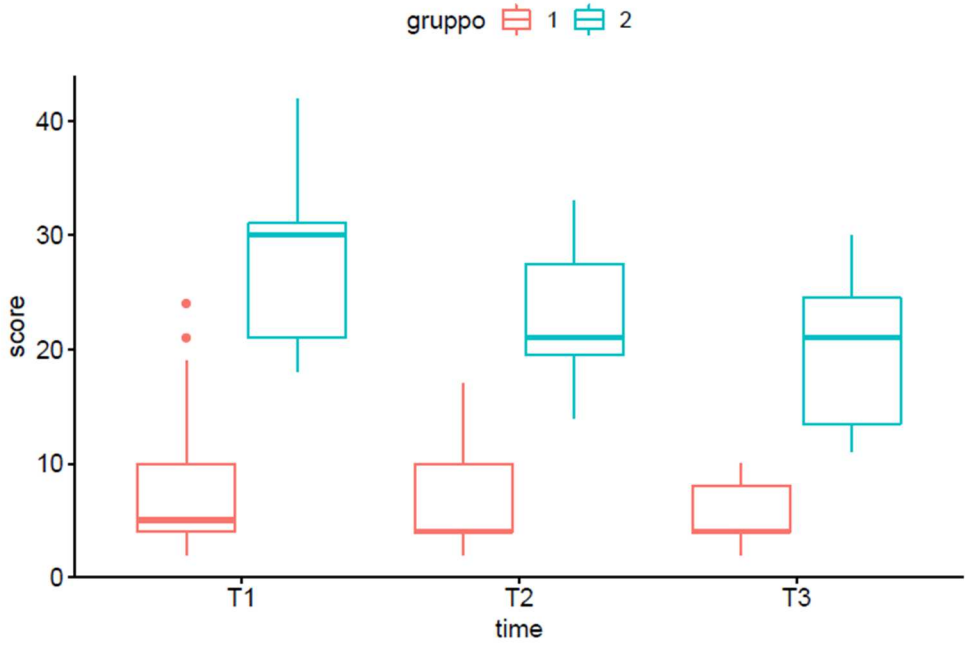
b) In the second analysis, we divide patients in two groups: one in which patients have every ALS>11 and second group with every ALS<11: as we made in the previous analysis, we analysed every patient with 3 evaluations, and every patient with 4 evaluations, excluding patients without the fourth evaluation (5 patients).
The conclusion is similar to the evaluation a) but with lighter evidence: P-value is higher than 0,05 (0,8) due probably to the dimension of the sample.

- **Group 1: patients with ALS<11 in at least one evaluation; Group 2: patients with ALS ≥11 in every evaluation**
- Patients in which we analyse 3 time points (T1-T2-T3, sample: 24 patients), Figure 11:

PRIMI 3 TIME-POINTS, escludendo T4

Gruppi:

- gruppo 1: pazienti con score ad almeno un time-point < 11
- gruppo 2: pazienti con score >= 11 in tutti i time-points



	Effect	DFn	DFd	F	p	p<.05	ges
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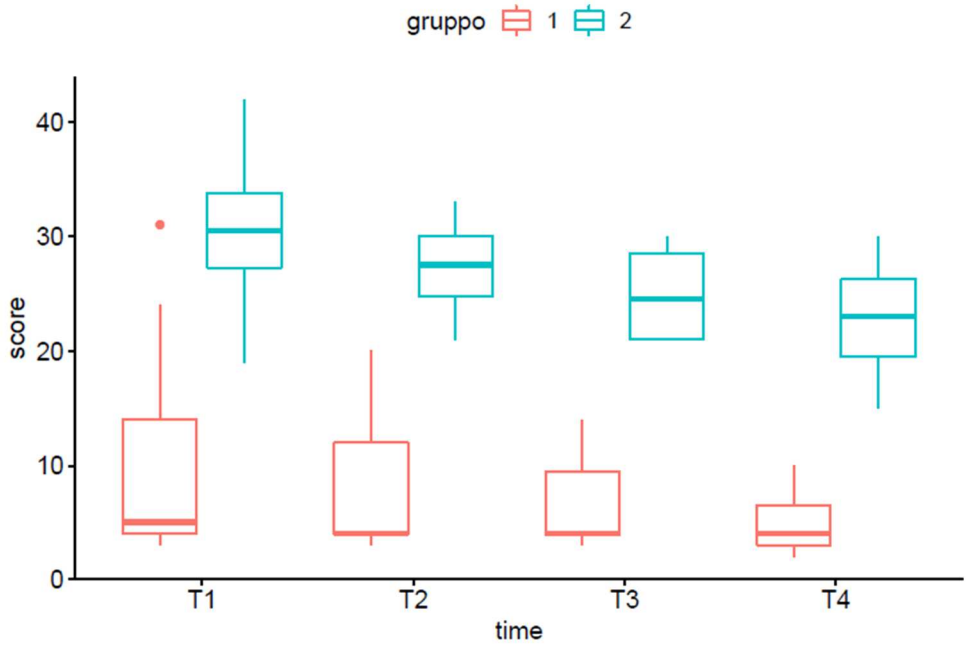
2	time	2.00	44.00	16.88	3.63E-06	*	0.12
3	gruppo:time	2.00	44.00	3.25	4.80E-02	*	0.03

- Patients with four evaluations (T1-T2-T3-T4) excluding patients without T4 (sample: 19 patients), Figure 11

TUTTI i TIME-POINTS, escludendo i pazienti con T4 mancante

Gruppi:

- gruppo 1: pazienti con score ad almeno un time-point < 11
- gruppo 2: pazienti con score >= 11 in tutti i time-points

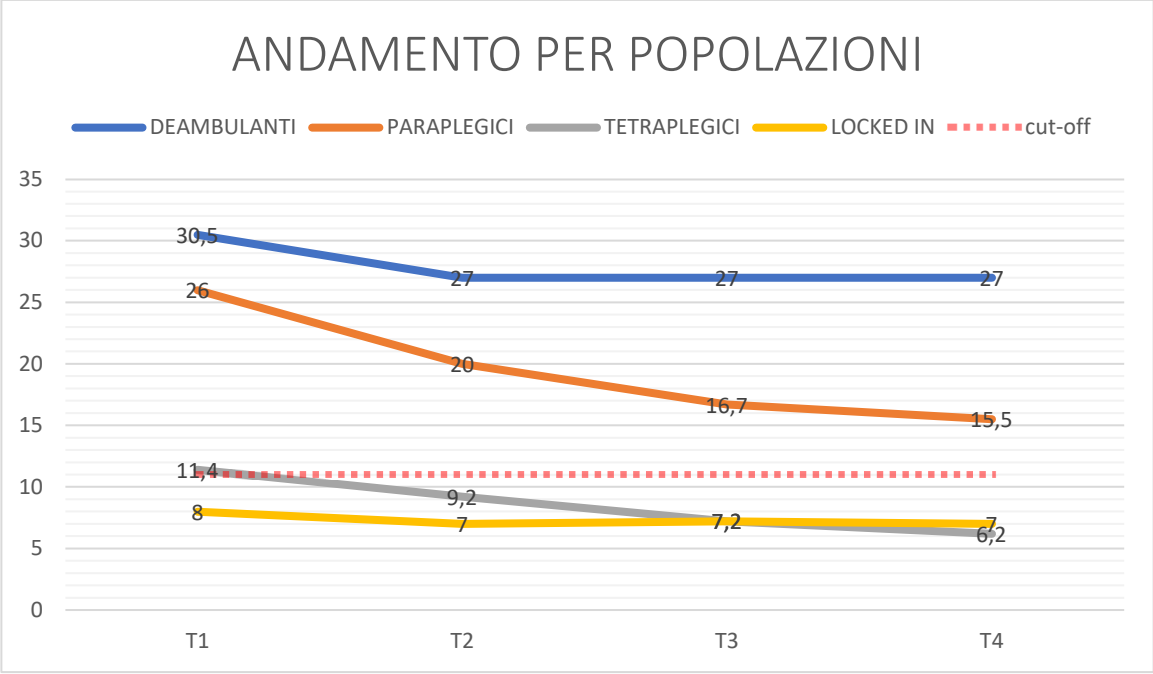


	Effect	DFn	DFd	F	p	p<.05	ges
1	gruppo	1.00	17.00	41.62	5.97E-06	*	0.64
2	time	3.00	51.00	7.04	4.75E-04	*	0.10
3	gruppo:time	3.00	51.00	0.30	8.23E-01		0.01

ALS=11 as cut-off is founded by the analysis made on the population, in which we divide patients based on the residual autonomy.

We classify in, as shown in Figure 7:

- Quadriplegic
- Paraplegic
- Deambulant
- Locked In Syndrome

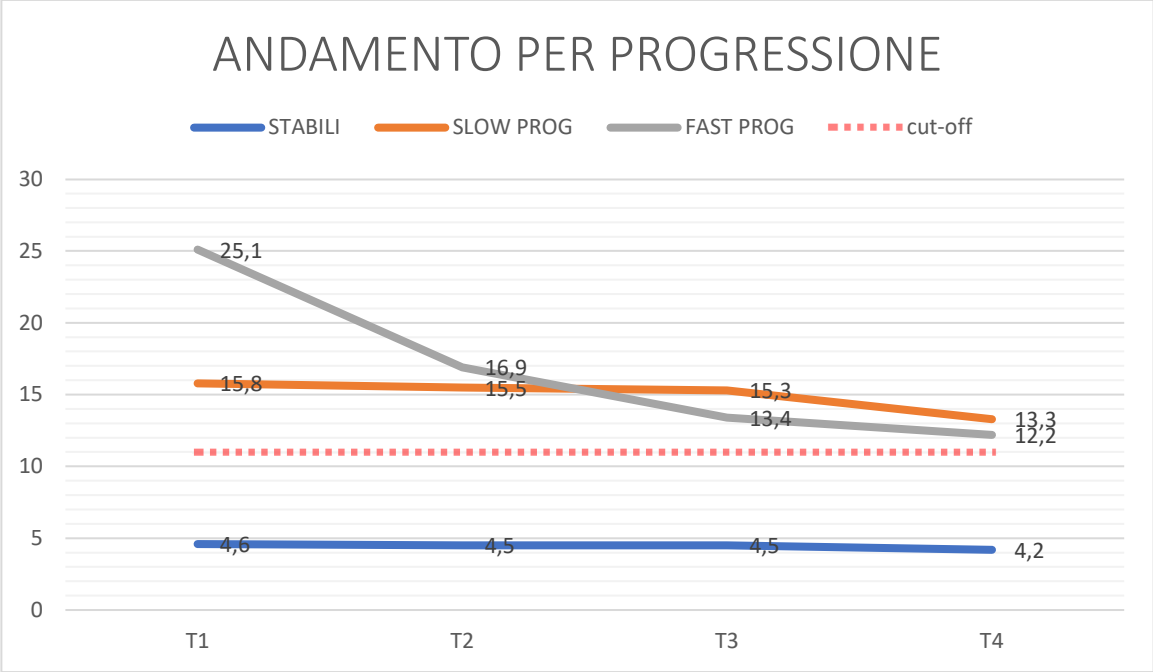


As we can see, the difference in ALSFRS-R evaluation in patient that belong to different group for autonomy, there's an important difference in evaluation: walking patients or paraplegic patients maintain a higher evaluation than quadriplegic and locked in, due to a different stage of ill that worse also performance in other areas such as dysphagia o breathing.

Starting from the bibliography information about velocity of progression in ALS, we found in Huber and Jing Jing Yeo a confirm in what we think about the correlation between clinical progression and ALSFRS-R evaluation. [15]

We identify three conditions, as shown in Figure 8:

- *Fast Progressor*, as a patient with at least one variation in ALS point >3 (patients: 9)
- *Slow Progressor*, as a patient with at least one variation in ALS point 1< n ≤ 3 (patients: 4)
- *Stationary*, as a patient with at most a variation of 1 point in the 3 consecutive ALSFRS-R evaluations (n ≤ 1, patients: 11)



From this table is easy understand how ALS=11 is a possibly sensible cut-off that can divide patients for rate of progression and could help in advance needs and problems that would appear with the worsening of the ill. Secondary, this is not only a cut-off related to prognosis, but may also be used as an indicator of an acute event on chronic condition and as a marker of modified needs.

DOMANDA		MOLTISSIMO	MOLTO	POCO	PER NIENTE		
1) In generale, rispetto al "Progetto SLA", le sue aspettative sono state soddisfatte?	PAZIENTE	22%	67%	11%		100%	
	PARENTE	25%	50%	25%		100%	
	ASSISTENTE NON FAMIGLIARE	67%	33%			100%	
	Media	38%	50%	18%	0%		CAMPIONE: 28 RISPOSTE (100%)
2) Parliamo dell'introduzione della figura del Case Manager Infermieristico dedicato ad una patologia come la SLA: quanto pensa questa scelta possa migliorare l'assistenza e la presa in carico del paziente?	PAZIENTE	45%	45%	10%		100%	
	PARENTE	25%	50%	25%		100%	
	ASSISTENTE NON FAMIGLIARE	33%	67%			100%	
	Media	34%	54%	18%	0%		CAMPIONE: 28RISPOSTE (100%)
3) Parliamo delle modalità per mantenere e facilitare i contatti con l'Equipe (Whatsapp, telefono, mail): quanto pensa che queste tecnologie possano facilitare e migliorare il livello di comunicazione?	PAZIENTE	45%	33%	22%		100%	
	PARENTE	44%	44%	12%		100%	
	ASSISTENTE NON FAMIGLIARE	33%	67%			100%	
	Media	41%	48%	17%	0%		CAMPIONE: 28 RISPOSTE (100%)
4) Secondo l'esperienza fatta ad oggi durante il "Progetto SLA", quanto ritiene che la comunicazione con il centro specialistico/MMG sia migliorata?	PAZIENTE	11%	67%	22%		100%	
	PARENTE		69%	19%	12%	100%	
	ASSISTENTE NON FAMIGLIARE	33%	67%			100%	
	Media	22%	68%	21%	12%		CAMPIONE: 28 RISPOSTE (100%)
7) A proposito delle scale funzionali utilizzate (ALSFRS-R, scala Lomb) quanto la loro somministrazione è stata semplice?	PAZIENTE		100%			100%	
	PARENTE	9%	82%	9%		100%	
	ASSISTENTE NON FAMIGLIARE		67%	33%		100%	
	Media	9%	83%	21%	0%		CAMPIONE: 21 RISPOSTE (100%)
8) Parlando dell'assistenza domiciliare fornita da Fondazione Maddalena Grassi, quanto si è sentito supportato nella ricerca di risposte a problematiche di tipo sociali/amministrative?	PAZIENTE	22%	78%			100%	
	PARENTE	32%	50%	12%	6%	100%	
	ASSISTENTE NON FAMIGLIARE	67%	33%			100%	
	Media	40%	54%	12%	6%		CAMPIONE: 28 RISPOSTE (100%)
9) Quanto è soddisfatto dell'addestramento rivolto al caregiver da parte degli operatori di Fondazione Maddalena Grassi?	PAZIENTE	22%	67%	11%		100%	
	PARENTE	19%	62%	19%		100%	
	ASSISTENTE NON FAMIGLIARE	33%	67%			100%	
	Media	25%	65%	15%	0%		CAMPIONE: 28 RISPOSTE (100%)
10) Ritiene che la risposta alle sue esigenze assistenziali da parte di Fondazione Maddalena Grassi sia stata tempestiva ed	PAZIENTE	22%	78%			100%	
	PARENTE	32%	62%	6%		100%	
	ASSISTENTE NON FAMIGLIARE	67%	33%			100%	
	Media	40%	58%	6%	0%		CAMPIONE: 28 RISPOSTE (100%)
11) Quanto ritiene che l'assistenza fornita sia d'aiuto a creare un clima più positivo e	PAZIENTE	22%	78%			100%	
	PARENTE	32%	62%	6%		100%	
	ASSISTENTE NON FAMIGLIARE	100%				100%	
	Media	51%	70%	6%	0%		CAMPIONE: 28 RISPOSTE (100%)
RISULTATI COMPLESSIVI (media)		33%	61%	15%	2%		

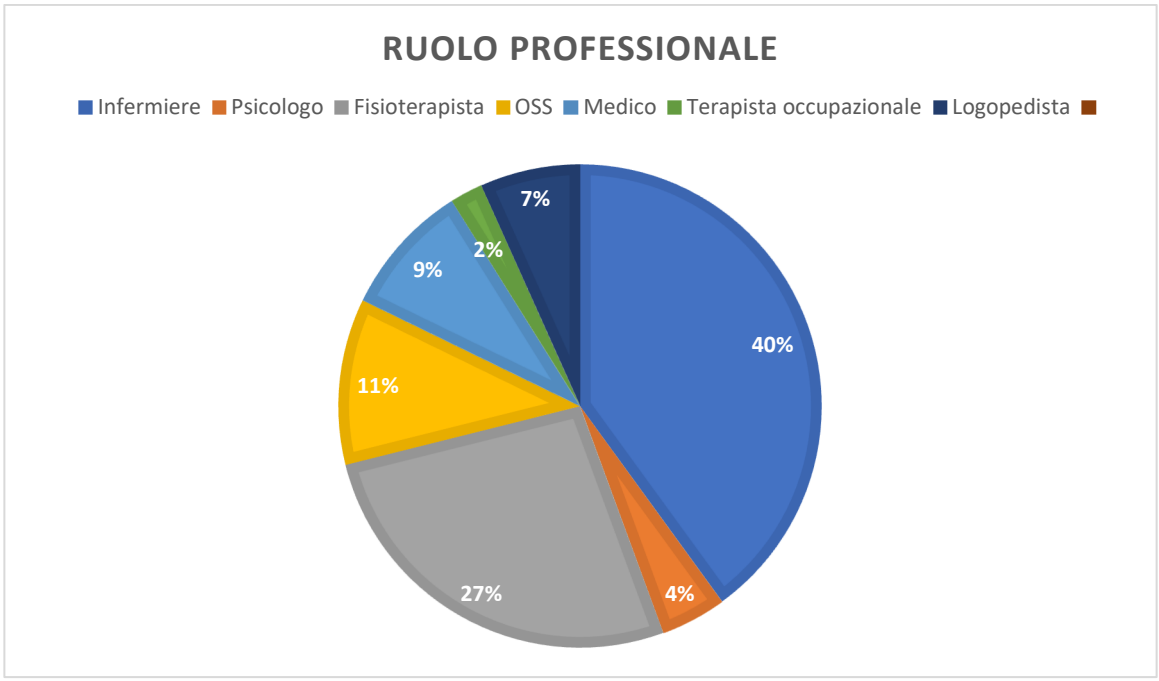
Considering the satisfaction questionnaire turned to the families (patient, caregiver and non-familiar assistant, Figure 2) enrolled in ALS Project, we can observe a positive reaction about the assistance offered by this assistential model including the introduction of ALS Case Manager, with positive results in almost 88% of cases. The average results, at the end of analysis, is that “Very Good” is choose by 33% of people and “Good” by 61% of people enrolled in interrogation.

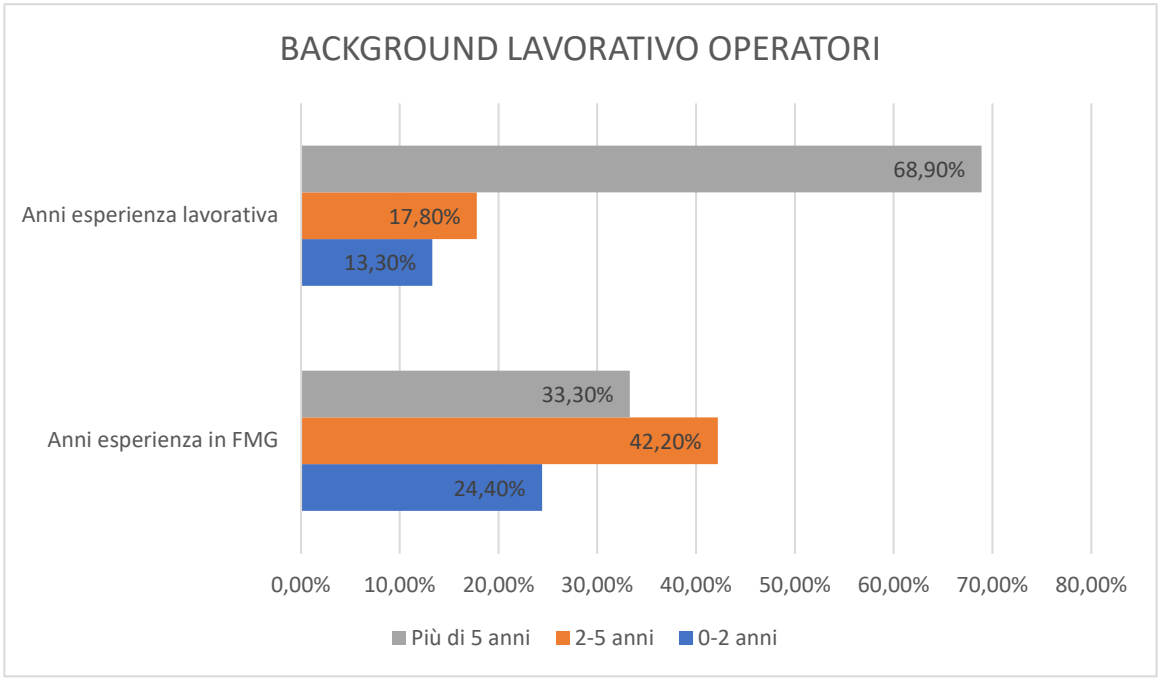
In the open-questions, the requests made by families are turned to the improvement of the coordination between the different health operators and in the will from some families to be trained and educated in advanced medications or in management of cough-machine to be more independent also when the health operators aren’t at patient’s home.

In particular, the ALS Case Manager demonstrated to be a great support both to families and to Equipe, being a connection between the specialistic centre and the families but also between the specialist physicians and the Equipe to face the ordinary or extraordinary problems that an home assistance of a difficult patient like ALS-affected could be.

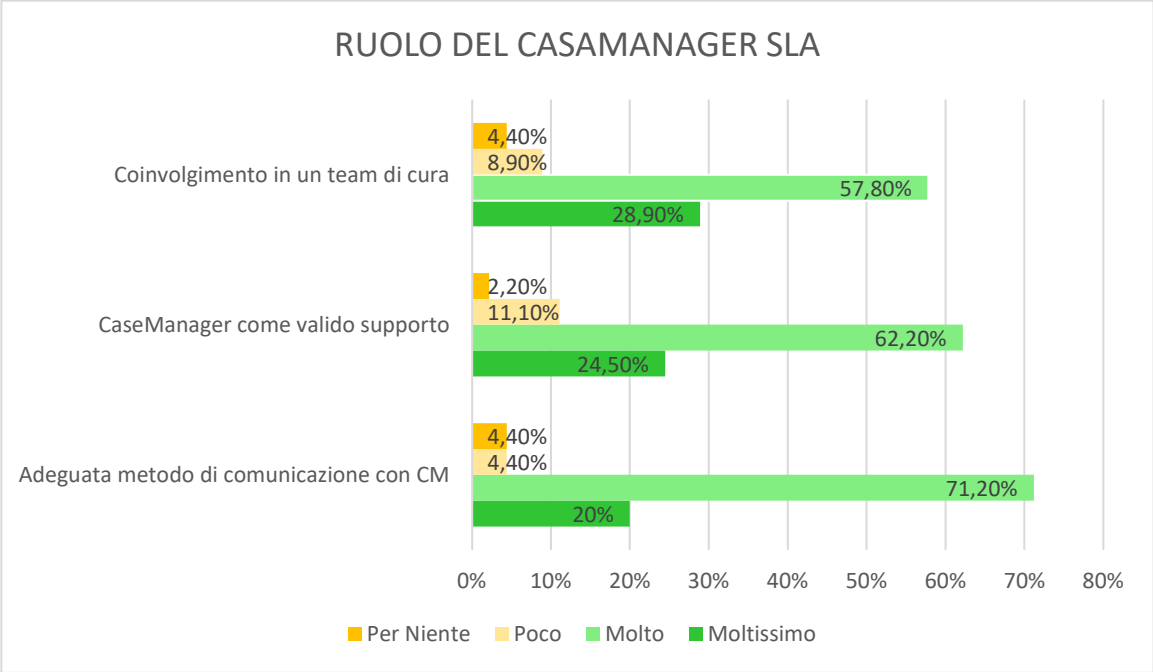
Sars-Cov-2 hasn't a heavy impact in our assistance: 88% of patients and their families decided to continue home assistance without interruption.

We want to involve the health operators that participate in ALS Project to understand how they feel the role of ALS Case Manager and to understand their feelings about their work and skills.
We start from analyse their professional background and their experience with Maddalena Grassi Foundation (Figures 3, 4, 5)





Then we interview them about the feeling about the introduction of specific ALS Case Manager, finding enthusiastic results that demonstrate how ALS Case Manager was considered a good implementation in the organisation of our home health care model.



As we could see, positive feelings are the predominant about the Project and lots of operators ask to organize specific training courses about ALS and the clinical implications connected to a home assistance, with the objective to improve their own professional abilities and efficiency (Figure 6).

ATTIVITÀ CHE SI VORREBBE APPROFONDIRE	NUMERO OPERATORI	% OPERATORI
Utilizzo del ventilatore	17	37,7%
Broncoaspirazione	5	11,1%
Utilizzo del comunicatore	3	6,6%
Fisioterapia respiratoria	3	6,6%
Medicazione e gestione tracheostomia	3	6,6%
Utilizzo macchina della tosse	2	4,4%
Interazione con vissuti psicologici del paziente	2	4,4%

Esecuzione dell'igiene nel paziente in ventilazione invasiva	1	2,2%
Esecuzione dell'igiene nel paziente portatore di PEG	1	2,2%
Interazione con la situazione familiare	1	2,2%
Nessuno	7	15,5%

We also registered some advice to improve our health care model: some operators ask for a more frequent periodic meetings in which deepen knowledge about the clinical history and evolution of patients; somebody ask for an earlier introduction of ALS Case Manager in patients who recently receive a diagnosis of ALS in order to educate since the first stages family and patients about the ill and its evolutions; somebody ask for a combined accesses at patient's home with ALS Case Manager in order to improve the exchange of knowledge.
Starting from these enthusiastic reports from patients and their families but also from the operators involved in clinical management of ALS patients, it could be an important improvement recognize the ALS Case Manager as an administrative official figure include in the voucher for home health care assistance, with a specific role.

Thanks to the data collected during these two years of study, we are able to elaborate two abstracts about this specific theme, that were proposed and accepted by the XXV World International Congress of Neurology 2021 and by the XXVIII Italian Congress of Palliative Care 2021.

9. FUTURE IMPLICATIONS

The Project allowed to understand how to improve the homecare assistance in these patients that have severe limitations to access to specialist centre for periodic controls. The most important discover was understand how important the *ALS Case Manager* is:

- The clinical monitoring made by the ALS Case Manager, together with all the professional health figures that every single patient needed, allowed to reduce the access to ER or hospitalisation: this means also that can reduce the cost in "energy" for the patient: moving a sickly patient could mean use lots of energy that could create a worsening of the clinical situation (for example respiratory insufficiency could appear more frequently during a high stress situation like transport to the hospital).

  This type of assistance may allow also to reduce the cost for hospitalisation where not necessary or where could be solved by the access of a physician or nurse directly at home.
- the ALS Case Manager could divide patients between stable or instable and fit the home assistance in base of the clinical condition and needs: this merge the needs due to clinical situation with the economics aspect, by the optimization of the monetary sources.
- The ALS Case Manager has been an important link between families and patients with the specialistic centre, to manage the assistance and identify how to operate in case of worsening of the symptoms.

  Families appreciate the role of the ALS Case Manager as reference point in the health service that was able to give some help in reply to the doubt or solve and manage clinical or bureaucratic problems.

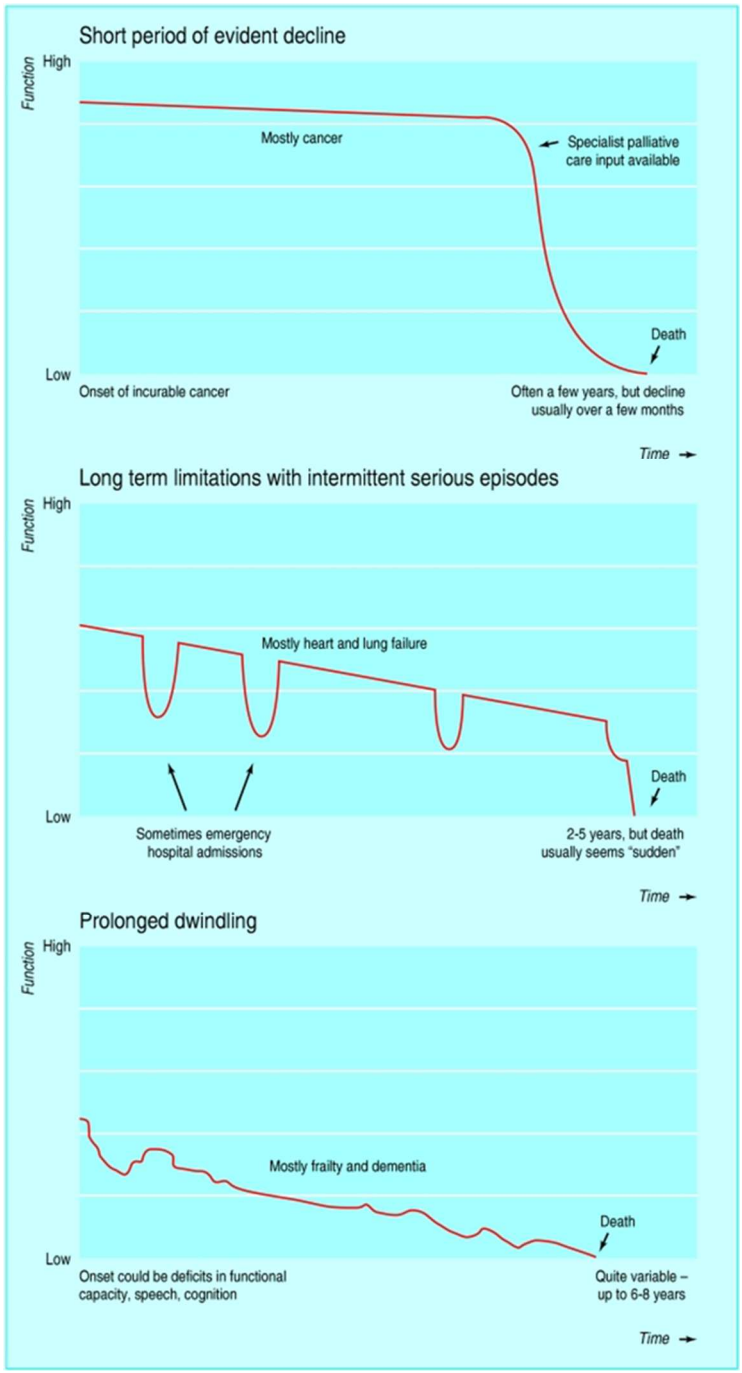


Figure 15 Possibly evolution of a chronic or long-prognosis disease

- As said, another goal of the Project regards the economics implication of this kind of healthy assistential model: following patient at home, we can obtain the reducing of the hospitalisation for predictable main events, and it can be traduced in a reduction of the waste of money. ALS has a trajectory included between a long term illness and a prolonged dwindling illness [16], and an aim may be that Palliative Care could be optimized in order to participate during an emergency in clinical conditions, not only during the terminal stage of the ill: this fact could sensibly improve the quality of the life of the patients.

A limit of the study can be considered the number of patients. In Lombardy, we expected to identify 600 patients, and for example in a city like Rome, ALS patients are more or less 160. More accurate studies need to be developed, and it could be necessary improve the numbers for example by linking different specialistic centres to reach a more numerous groups of patients. This is also the reason why application of DYALS scale didn't give us enough data to be elaborated.

10. ABBREVATION DICTIONARY

ADI: Assistenza Domiciliare Integrata or Home Integrated Aiding
AIFA: Agenzia Italiana del FArmaco
AIFA: Agenzia Italiana del FArmaco
ALS- FRS: Amyotrophic Lateral Sclerosis Functional Rating Scale
ALS: Amyotrophic Lateral Sclerosis
AMPA: α-Ammino-3-idrossi-5-Metil-4-isossazol-Propionic Acid
CNS: Central Nervous System
CRP: C Reactive Protein
CV: Vital Capacity
DPR: DiPeptide Repeats
DVT: Deep Venous Thrombosis
DYALS: DYsphagia Amyotrofic Lateral Sclerosis
EMG: ElectroMyoGraphy
FALS: Familiar Amyotrophic Lateral Sclerosis
FKT: physiokinesitherapy
FMG: Maddalena Grassi Foundation
FTD: FrontoTemporal Dementia
FUS: FUsed in Sarcoma
IC: Immune complex
ICA: Index of Complexity in Assistance
IV: Invasive Ventilation
LMN: Lower Motor Neuron
MIP or PiMax: maximum inspiratory pressure
MiTos: Milano- Torino Staging
MRI: Magnetic Resonance Imaging
NEMO: NEuro Muscular Omnicentre
NfL: Light Phosphorylated Neurofilaments
NGT: NasoGastric Tube
NIPPV: Non-Invasive Positive-Pressure Ventilation
NIV: Non-Invasive Ventilation
NMND: Neurodegenerative Motor Neuron Disease

PAI: Piano Assistenziale Individualizzato or Personal Assistance Plan

PEG: Percutaneous Endoscopic Gastrostomy

PLS: Primary Lateral Sclerosis

pNfH: Heavy Phosforylated Neurofilaments

PRG: Percutaneous Radiologic Gastrostomy

SALS: Sporadic Amyotrophic Lateral Sclerosis

SMA: Spinal Muscular Atrophy

SNP: Sniff Nasal Pressure

SOD1: SuperOxide Dismutase 1

SSRI: selective serotonin reuptake inhibitors

TARDBP: TAR DNA Binding Protein

TReg: T regulatory cells

UCP-DOM: Palliative Care Unit or Unità di Cure Palliative Domiciliari

UMN: Upper Motor Neuron

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