Staging amyotrophic lateral sclerosis: A new focus on progression

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Abstract:

Amyotrophic lateral sclerosis (ALS) is a heterogenous motoneuronal neurodegenerative condition with a panel of phenotypes exhibiting different clinical patterns. Two compounds are currently available for the treatment of ALS but the majority of trials have failed to show a positive effect on prognosis. One of the explanations which could be put forward involves the way efficacy is evaluated: clinicians agree that the ALSFRS-revised scale used in all trials does not fit with highlighting a positive effect. So, the development and validation of new tools allowing a reliable assessment of ALS has become a key issue in clinical research. Over the last three years, two functional scales (the King's College and MiToS staging systems) have been proposed. These scales rely on two different approaches to ALS: an anatomical and prognostic concept, and loss of autonomy. Both scales propose five stages.

We will discuss below the contribution of these two scales to clinical evaluation and the questions which remain to be resolved in the future.

Key words:

Amyotrophic lateral sclerosis; Progression; Staging; MiToS; King's College.

Introduction

Amyotrophic lateral sclerosis (ALS) is an always fatal neurodegenerative condition characterized by motor neuron death in bulbar and spinal territories leading to death from respiratory failure after a median course of 36 months from symptom onset.

Amyotrophic Lateral Sclerosis: a heterogenous condition

There is currently a worldwide consensus to consider ALS as a highly heterogenous entity with at least 10 clinical phenotypes from bulbar ALS to flail leg syndromes, involving predominant upper motor neuron (UMN) or lower motor neuron (LMN) features, variable patterns of disease progression, and spread marked by contiguous or non-continuous extension [1]. Age of onset, site of onset, prominence of UMN or LMN signs, disease spread, and kinetic patterns of the motor neuron death process as well as disease duration all display heterogeneity [2].

One of the main challenges for clinicians and researchers is to reliably assess disease progression, keeping in mind the extreme heterogeneity of the disorder.

Numerous functional scales have been proposed in ALS, especially for trials [3]. Until now, the scale the most commonly used, both in trials and clinical practice, has been the revised ALS Functional Rating Scale (ALSFRS-r). This is a multidimensional scale made up of 12 items, each graded from 4 (normal) to 0 (none), exploring the bulbar domain, upper limb and lower limb motility, and the respiratory domain. This scale grades from 48 to 0. The ALSFRS-r presents several limitations due its multidimensional analysis, to the absence of correlation between the score and prognosis, to the lack of comparability between two patients with the same score, to the non-linear progression of the scale's slope, and to a floor-effect, meaning that patients systematically die before reaching a score of 0 [4]. Some teams have attempted to improve the scale's value by using the slope of its time course, i.e. the estimated number of points lost between the first symptoms and the date of the examination; classically, the rate of progression is around 0.8-1 point/month. This led to define slow progressors with a slope less than 0.5 point/month and fast progressors when the slope exceeds 1 point/month [5].

In any case, the ALSFRS-r model does not completely fit with the expectations of clinicians and researchers. This led to design new functional rating scales that are more

reliable, more appropriate for clinical trials and that allow measuring positive effects of drugs over a short time period.

During the last five years, two scales appeared to measure the functional burden or anatomical extension of the motor neuron pathological process: the King's College staging system and the Milan Torino Staging system called MiToS.

Herein we detail these two scales, highlighting their advantages and drawbacks for clinicians in their daily practice.

King's College staging system (KC)

The King's College team built a new staging system for assessing disease progression in ALS patients. The KC scale is based on two domains, neurological regions and additional prognostic criteria. The number of neurological regions (bulbar, cervical, thoracic, lumbar) displaying UMN or LMN signs defines the three first stages: grading an ALS patient stage 1 means that there is one territory with functional signs, stage 2 corresponds to the involvement of a second region and stage 3 means three anatomical regions are functionally affected by the motor neuron degenerative process. Stage 4 implies the presence of prognostic criteria referring to the presence of nutritional failure (stage 4A) or respiratory failure (stage 4B). The last stage, stage 5, corresponds to death (Figure 1).

Over the last five years, many studies have focused on this staging system, its relevance in clinics and its correlation with the functional socio-economical costs of ALS.

First, KC is suitable in clinical practice for several reasons: there is a correlation between the natural course of the disease and that of KC, since the majority of ALS patients progress from one stage to the next during the course of their disease; this was shown by Balendra et al. [6]. In a retrospective study enrolling 725 patients, the authors found that the majority of their patients moved progressively from one stage to the next rather than skipping a stage, and that none of them moved to a less severe stage [6]. This highlighted that progression along the KC scale strongly matches the classically described disease course. Another point emerged from this study: median duration of KC stages decreased from stage 1 to stage 4.

The second major advantage of the KC is the good correlation between the scale and the ALSFRS-r score which allows a confident assessment of the KC stage from the ALSFRS-r score; there is a 92% correlation between the two scales: the earlier the patient's KC stage,

the higher the patient's ALSFRS-r score [6]. Nevertheless, there is some divergence in when proximal upper limb weakness is present since the items evaluating the functional state of the upper limb focus mainly on distal function, and as well, drooling can arise with bulbar weakness; both of these situations lead to under- or over-estimating the KC stage from the ALSFRS-r score. Finally, there are discrepancies for breathing evaluation since KC focuses on the requirement for respiratory support while the ALSFRS-r scale takes into account its use.

KC is currently the staging system used in the major studies. Many studies had shown a good correlation with numerous parameters used in ALS. Unlike the ALSFRS-s scale, there is a good correlation between KC and disease progression.

With the KC, the time spent from onset to reach each stage can be evaluated. Disease progression can be analyzed step by step: time from symptom onset to diagnosis is estimated at 13.5 months, involvement of a second region occurs after 17.7 months duration of the disease, and that of the third region after 23.3 months. Tube feeding becomes necessary after 27.3 months and non-invasive ventilation after 30.3 months [7]. Comparing bulbar to spinal ALS led to notice that the duration from stage 4A to death was significantly longer for bulbar ALS patients (8.4 months vs 45 months, $p=2.5\ 10^{-4}$), the other transition times being similar [8].

The KC scale can also offer the possibility to estimate patients' quality of life as it declines with disease progression. The hospital anxiety and depression scale (HADS) showed worsening anxiety and depression scores as ASL progressed [9].

KC was also correlated with blood levels of the light chain neurofilament (NF-L). As already known, NF-L antibody levels are higher in ALS compared with the general population, with this increase rising with disease progression leading to a correlation between KC stage and blood levels of NF-L antibodies: median values moving from 0.61 to 0.94 from early stages to late stages of ALS ($p<0.005$) [10].

Finally, KC can be used to estimate the real cost of ALS, cost increasing with disease progression; the main difference involves the costs of care linked to the commitment of relatives of ALS patients.

Milan Torino Staging system (MiToS)

MiToS is the second recent scale proposed by Italian ALS centers. The mode of evaluation relies on loss of function: four domains (movement, swallowing, communication and breathing) are screened with this scale stemmed from the ALSFRS-r scale [11]. In the MitoS classification, a function is lost when the item(s) of the ALSFRS-r scale correspondent to this function is or are graded 1; this involves items 6 or 8 for movement, item 3 for swallowing, items 1 and 4 for communication, and item 10 or 12 for respiration (Table 1). If one function is impaired the patient is graded 1, the grade is 2 if two functions are involved, and so forth until grade 5 at death [11].

Unlike what is observed with KC staging, temporality of MiToS staging is not so linear since the majority of the stages involve the last months of the disease [12].

The progression of this scale over a period of 6 months would allow a suitable prediction of the probability of death, tracheostomy or non-invasive ventilation 23h/d, 12 and 18 months later [13].

The MiToS scale is more suitable for the assessment of dependency conversely to the KC more suitable for the anatomic or prognostic aspect of the disease.

Which scale is the most appropriate to assess ALS progression?

This is a key issue of recent studies on the relevance and suitability of these two scales. The KC scale focuses mainly on anatomical involvement and prognosis for stage 4 conversely to MiToS that focuses more on loss of function. So, these two scales do not provide the same information for clinicians.

On the contrary to what is observed with the KC, the risk of death is globally similar from stage 2 to 4 (around 60%) using the MiTos scale. With the KC, the risk of death increases with progression to higher stages, from 20% for stage 2 to 62% for stage 4B [14]. These scales do not appear to be redundant because they do not evaluate the same domains. A comparison of the two staging systems showed that patients graded 1 or 2 for KC match rather well with MiToS stages 0 and 1 and that patients graded KC 4 can be rated from 0 to 4 on the MiToS scale: this was confirmed by a correlation of 0.54 between the two scales [12].

The approaches of the two scales are also divergent concerning the time for tracheostomy. In the KC assessment, 90% of tracheostomies occur during stages 4 with 62% of cases during stage 4B which matches with what would be expected. On the contrary, tracheostomy is

performed with the same percentages over all the stages in the MiToS system (21.5% at stages 0 and 1, 23% during stage 2 and 25% during stage 3, the remaining cases being performed during stage 4) [14].

The reliability of these new scales for the assessment of drug efficacy in clinical trials has been shown in a retrospective analysis of the historical riluzole trials whose first objective was to determine whether the effect of riluzole on survival involved the entire duration of the disease or only some clinical stages [15]. This analysis compared stage duration (stages 2, 3 and 4 of the KC scale) according to riluzole dose (50 mg/d, 100 mg/d, 200 mg/d) or placebo. This study showed a significant increase in the duration of stage 4 for ALS patients treated by 100 mg/d (490 days compared to 404 in the 50 mg/d group and 391 in the placebo group). There was no difference in the duration of the remaining stages. This study might be considered as a proof of concept for the use of KC in future clinical trials.

So, complementary use of the two scales (KC and MiToS) would appear a relevant approach for daily practice, recognizing that the ALSFRS-r score still remains the gold standard. It might be also necessary to improve the reliability of these scales through the integration of a cognitive assessment that is currently lacking. The question of a new stage 4AB should be raised for ALS patients requiring both nutritional and respiratory support.

Compared to the current gold-standard ALSFRS-R scale, these new staging systems, and more specifically KC staging, are more appropriate to assess disease progression. Conversely to previous systems, it becomes possible to evaluate and adapt health costs of ALS by stage. It might be tempting to construct clinical trials according to progression on KC staging considering the duration of a stage in both groups as the primary endpoint. With a study designed in this way it would be possible to enroll more patients over a shorter period. KC also allows a socio-economic evaluation of the costs of the disease: a recent study in the South-Korean ALS population showed that direct costs double from stage 2 to stage 4 and that in this health economic system ALS patients support around 44% of this charge: similar studies should to be conducted in the French ALS population [16].

As already stressed, cognitive impairment can develop at any time during the course of the disease, with an impact on management practices [9]. Recently, a 4-level cognitive staging theory emerged, grading from no impairment to executive disturbances, behavioral impairment and finally to memory disturbances [17]. This cognitive staging relies on

anatomical injury and also neuropathological progression of the cortical spreading of the pathological process [18].

This new mode of assessment of ALS could be used in clinical practice in the future and could appear as a promising tool in trials.

Disclosure of interest

The authors declare that they have no competing interest.

References:

[1] Swinnen B, Robberecht W. The phenotypic variability of amyotrophic lateral sclerosis. Nat Rev Neurol 2014;10:661-670.

[2] Brown RH Jr, Al Chalabi A. Amyotrophic Lateral Sclerosis. N Engl J Med 2017;377:162-172.

[3] Couratier P, Torny F, Lacoste M. Functional rating scales for amyotrophic lateral sclerosis. Rev Neurol 2006 162:502-507.

[4] Gordon P, Cheng B, Salachas F, Pradat PF, Bruneteau G, Corcia P, et al. Progression in ALS in not linear but is curvilinear. J Neurol 2010;257:1713-1717.

[5] Kimura F, Fujimura C, Ishida S, Nakalima H, Furutama D, Uehara H, et al. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. Neurology 2006;66:265-267.

[6] Balendra R, Jones A, Jivraj N, Steen IN, Young CA, Shaw PJ, et al. Use of clinical staging in amyotrophic lateral sclerosis for phase 3 clinical trials. J Neurol Neurosurg Psychiatry 2015;86:45-49.

[7] Roche JC, Rojas-Garcia R, Scott K, Scotton W, Ellis CE, Burman R,et al. A proposed staging system for amyotrophic lateral sclerosis. Brain 2012;135:847-852.

[8] Balendra R, Jones A, Jivraj N, Knights C, Ellis CM, Burman R, et al. Estimating clinical stage of amyotrophic lateral sclerosis from the ALS Functional Rating Scale. Amyotroph Lateral Scler Frontotemporal Degener 2014;15:279-284.

[9] Jones AR, Jivraj N, Balendra R, Murphy C, Kelly J, Thornhill M, et al. Health utility decreases with increasing clinical stage in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2014;15:285-291.

[10] Puentes F, Topping J, Kuhle J, van der Star BJ, Douiri A, Giovannoni G, et al. Immune reactivity to neurofilament proteins in the clinical staging of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2014;85:274–278.

[11] Chiò A, Hammond ER, Mora G, Bonito V, Filippini G. Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2015;86:38-44.

[12] Fang T, Al Khleifat A, Stahl R, Lazo La Torre C, Murphy C, UK-MND LICALS, et al. Comparison of the King's and MiToS staging for ALS. Amyotroph Lateral Scler Frontotemporal Degener 2017;18:227-232.

[13] Tramacere I, Dalla Bella E, Chiò A, Mora G, Filippini G, Lauria G; EPOS Trial Study Group. The MITOS system predicts long-term survival in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2015;86:1180-1185.

[14] Ferraro D, Consonni D, Fini N, Fasano A, Del Giovane C, Emilia Romagna Registry for ALS (ERRALS) Group, et al. Amyotrophic lateral sclerosis: a comparison of two staging systems in a population-based study. Eur J Neurol 2016;1426-1432.

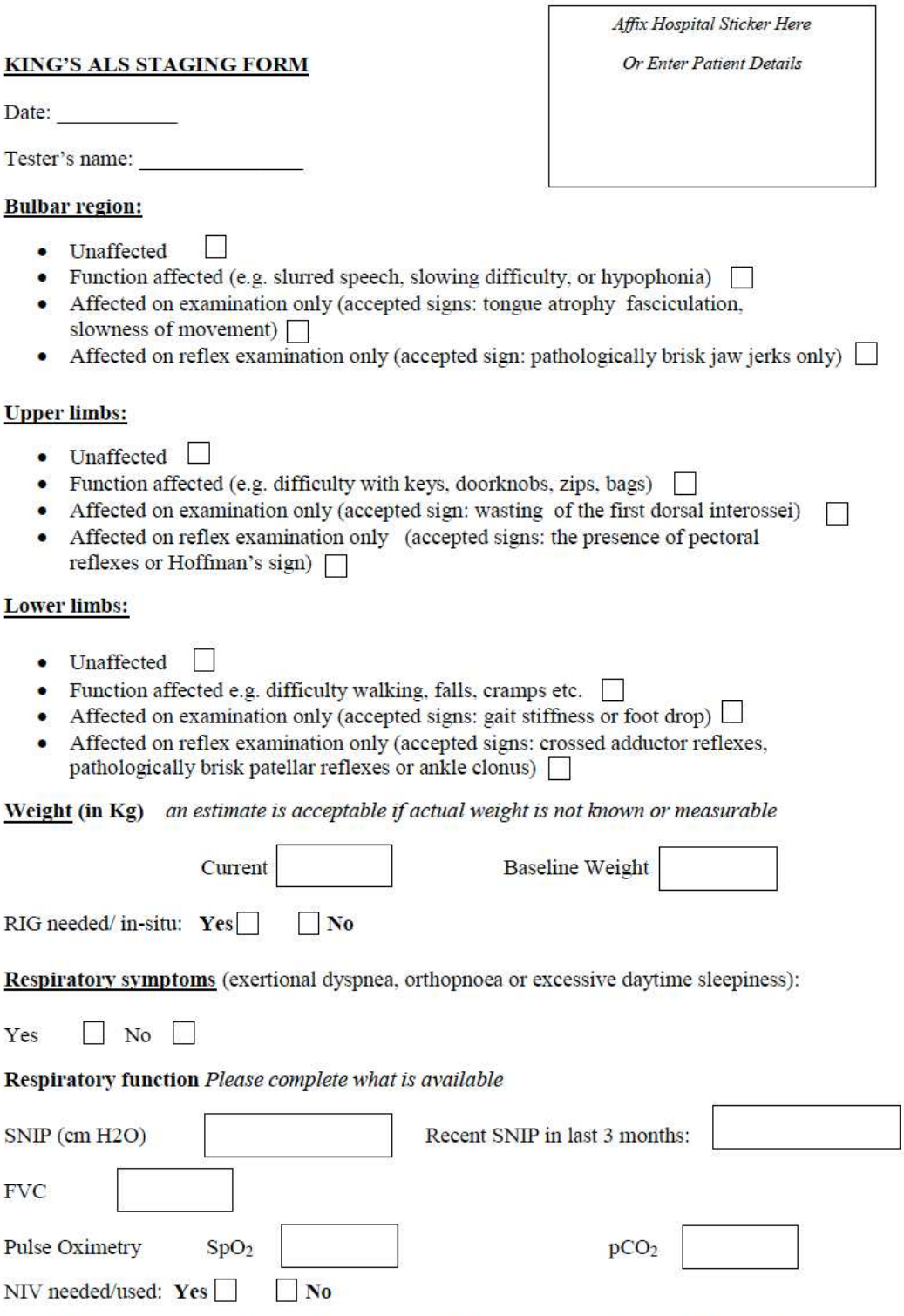
[15] Fang T, Al Khleifat A, Meurgey JH, Jones A, Leigh PN, Bensimon G, et al. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. Lancet Neurol 2018;17:416-422.

[16] Oh J, Won An Jl, Oh S, Ki Oh W, Kim J, Lee J, et al. Socioeconomic costs of amyotrophic lateral sclerosis according to staging system. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2015; 16: 202–208.

[17] Lulé D, Bohm S, Müller HP, Aho-Ozhan H, Keller J, Gorges M, et al. Cognitive phenotypes of sequential staging in amyotrophic lateral sclerosis. Cortex 2018;101:163-171.

[18] Braak H, Brettschneider J, Ludolph, Lee A, Trojanowski J, Tredici K. Amyotrophic lateral sclerosis—a model of corticofugal axonal spread. Nat Rev Neurol 2013;9, 708–714.

Figure 1: King's College Staging form. *Courtesy of Pr Al Chalabi*, King's College, London.



Affix Hospital Sticker Here

Or Enter Patient Details

KING'S ALS STAGING FORM

Date: _____

Tester's name: _____

Bulbar region:

- Unaffected ☐
- Function affected (e.g. slurred speech, slowing difficulty, or hypophonia) ☐
- Affected on examination only (accepted signs: tongue atrophy fasciculation, slowness of movement) ☐
- Affected on reflex examination only (accepted sign: pathologically brisk jaw jerks only) ☐

Upper limbs:

- Unaffected ☐
- Function affected (e.g. difficulty with keys, doorknobs, zips, bags) ☐
- Affected on examination only (accepted sign: wasting of the first dorsal interossei) ☐
- Affected on reflex examination only (accepted signs: the presence of pectoral reflexes or Hoffman's sign) ☐

Lower limbs:

- Unaffected ☐
- Function affected e.g. difficulty walking, falls, cramps etc. ☐
- Affected on examination only (accepted signs: gait stiffness or foot drop) ☐
- Affected on reflex examination only (accepted signs: crossed adductor reflexes, pathologically brisk patellar reflexes or ankle clonus) ☐

Weight (in Kg) *an estimate is acceptable if actual weight is not known or measurable*

Current ☐ Baseline Weight ☐

RIG needed/ in-situ: **Yes** ☐ ☐ **No**

Respiratory symptoms (exertional dyspnea, orthopnoea or excessive daytime sleepiness):

Yes ☐ No ☐

Respiratory function *Please complete what is available*

SNIP (cm H2O) ☐ Recent SNIP in last 3 months: ☐

FVC ☐

Pulse Oximetry SpO_2 ☐ pCO_2 ☐

NIV needed/used: **Yes** ☐ ☐ **No**

NOTE: *If pulse oximetry is the only measure used to test respiratory function AND SpO_2 is ≤94% AND pCO_2 <6kPa then arrange for the patient to have overnight oximetry*

Version 3, Feb 2016

Table1 : MiToS scale

1 Speech	4 Normal speech processes 3 Detectable speech disturbance 2 Intelligible with repeating 1 Speech combined with nonvocal communication 0 Loss of useful speech
2 Salivation	4 Normal 3 Slight but definite excess of saliva in mouth; may have nighttime drooling 2 Moderately excessive saliva; may have minimal drooling 1 Marked excess of saliva with some drooling 0 Marked drooling; requires constant tissue or handkerchief
3 Swallowing	4 Normal eating habits 3 Early eating problems-occasional choking 2 Dietary consistency changes 1 Needs supplemental tube feeding 0 NPO (exclusively parenteral or enteral feeding)
4 Handwriting	4 Normal 3 Slow or sloppy; all words are legible 2 Not all words are legible 1 Able to grip pen but unable to write 0 Unable to grip pen
5a Cutting food and handling utensils (without gastrostomy)	4 Normal 3 Somewhat slow and clumsy, but no help needed 2 Can cut most foods, although clumsy and slow; some help needed 1 Food must be cut by someone, but can still feed slowly 0 Need to be fed
5bCutting food and handling utensils (with gastrostomy)	4 Normal. 3 Clumsy, but able to perform all manipulations independently. 2 Some help needed with closures and fasteners. 1 Provides minimal assistance to caregiver 0 Unable to perform any aspect of task.
6 Dressing and Hygiene	4 Normal function 3 Independent and complete self-care with effort or decreased efficiency 2 Intermittent assistance or substitute methods 1 Needs attendant for self-care 0 Total dependence
7 Turning in bed	4 Normal 3 Somewhat slow and clumsy, but no help needed 2 Can turn alone or adjust sheets, but with great difficulty 1 Can initiate, but not turn or adjust sheets alone 0 Helpless

8 Walking	4 Normal 3 Early ambulation difficulties. Notes some difficulty, but walks without assistance 2 Walks with assistance. Includes AFO, cane, walker, or a caregiver. 1 Non-ambulatory functional movement only 0 No purposeful leg movement
9 Climbing stairs	4 Normal 3 Slow 2 Mild unsteadiness or fatigue 1 Needs assistance 0 Cannot do
10 Dyspnea	4 None 3 Occurs when walking 2 Occurs with one or more of the following: eating, bathing, dressing (ADL 1 Occurs at rest, difficulty breathing when either sitting or lying 0 Significant difficulty, considering using mechanical respiratory support
11 Orthopnea	4 None 3 Some difficulty sleeping at night due to shortness of breath. Does not routinely use2 more than two pillows 2 Needs extra pillow in order to sleep (more than two) 1 Can only sleep sitting up 0Unable to sleep
12 Respiratory insufficiency	4 None 3 Intermittent use of BiPAP 2 Continuous use of BiPAP 1 Continuous use of BiPAP during the night and day 0 Invasive mechanical ventilation by intubation or tracheostomy

Four domains assessed with the MiToS scale:
Communication impaired if: Item 1 and Item 4 graded 1
Movements impaired if: Item 6 or item 8 graded 1
Swallowing impaired if: Item 3 graded 1
Breathing impaired if: Item 10 or Item 12 graded 1