Amyotrophic lateral sclerosis: a comparison of two staging systems in a population-based study

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Background and purpose: To compare two recently developed staging systems for amyotrophic lateral sclerosis (ALS) [King’s College and Milano-Torino staging (MITOS) systems] in an incident, population-based cohort of patients with ALS.

Methods: Since 2009, a prospective registry has been recording all incident cases of ALS in the Emilia Romagna region in Italy. For each patient, detailed clinical information, including the ALS functional rating scale score, is collected at each follow-up.

Results: Our study on 545 incident cases confirmed that King’s College stages occurred at predictable times and were quite evenly spaced out throughout the disease course (occurring at approximately 40%, 60% and 80% of the disease course), whereas MITOS stages were mostly skewed towards later phases of the disease. In the King’s College system there was a decrease in survival and an increase in deaths with escalating stages, whereas in the MITOS system survival curves pertaining to intermediate stages overlapped and the number of deaths was fairly homogenous throughout most stages.

Conclusions: The King’s College staging system had a higher homogeneity (i.e. smaller differences in survival among patients in the same stage) and a higher discriminatory ability (i.e. greater differences in survival among patients in different stages), being more suitable for individualized prognosis and for measuring efficacy of therapeutic interventions.

Introduction
Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive disability and great interindividual variability, making prognosis a challenge. Although several prognostic models, based on clinical/demographic factors at diagnosis, have been created to predict survival, they do not include milestones, which are necessary for staging criteria [1]. A reliable staging system would be of great importance as it could help predict prognosis, would allow personalized counseling and would be useful for conduction of clinical trials and resources allocation.

The most widely used functional scale in ALS [the ALS Functional Rating Scale-Revised (ALSFRS-R)] has relevant intrinsic limitations: it is multidimensional, representing the sum of mean scores of three different domains, and it does not therefore satisfy rigorous measurement standards [2,3].

To address this urgent unmet need, two staging systems have recently been developed [4,5], based on simple clinical milestones that mark the course of the disease.

The first staging system [4], hereafter called ‘King’s College staging system’, considers the number of involved regions for the first three stages and the need...
for gastrostomy and non-invasive ventilation for the subsequent stages (stages 4a and 4b, respectively).

The second staging system [the Milano-Torino staging (MITOS) system] [5] is based on the loss of independent functions in four key domains of the ALSFRS-R. The sum of the lost functions determines the stage. Both systems have only been tested separately in clinical trials/referral-centre populations.

The aim of the present study was therefore to compare the proposed staging systems, in terms of their prognostic performance, in a population-based setting.

**Materials and methods**

**Patients**

Since 2009, a prospective registry [Emilia Romagna Registry for ALS (ERRALS)] [6] has been recording all incident cases of ALS in the Emilia Romagna region in Italy. For each patient, detailed clinical information, including the ALSFRS-R score [7], respiratory function values, body weight, need for procedures (gastrostomy, non-invasive or invasive ventilation), upper and lower motor neuron involvement and death circumstances and date, is collected at each follow-up visit. Data are fed into an online electronic database in a dedicated internet website, accessible only to participating investigators. Regular supervision of the recorded data is performed by the coordinating centre to check data accuracy. Data were complemented by cases from additional sources [6], which led to a total of 15 unobserved cases (registry coverage, 97.25%).

**Protocol approval**

All patients signed an informed consent permitting the treating neurologist to record their data in the registry, which was approved by the ethics committees of the coordinating centre and of the nine Provinces of Emilia Romagna region.

**Staging systems**

The King’s College staging system [4] considers the number of involved regions for the first three stages [but distinguishing time to diagnosis (stage 2a) from involvement of the second region (stage 2b)] and the need for gastrostomy and non-invasive ventilation for stages 4a and 4b, respectively. The stages are well distributed during the disease course, without reversion to earlier stages, with good correlation with ALSFRS-R scores [8]. After having been tested on a prevalent, centre-based cohort, this system has been applied to 725 patients enrolled in two clinical trials (the lithium carbonate in amyotrophic lateral sclerosis trial and the Mito Target trial) [9,10]. Stages were calculated considering the ALSFRS-R scores, and the estimated stage correlated about 92% with the actual clinical stage [11]. Considering that diagnosis may be reached at virtually any point of the disease course, the authors merged stages 2a and 2b into stage 2, which was simply reached with involvement of a second region [11]. In the present study, King’s College stages were calculated considering the loss of at least one point (corresponding to a score of 3 or less) in any item of the ALSFRS-R referring to a certain body region. For example, a patient with a global ALSFRS-R score of 44 due to a score of 2 in items 1 and 3 was considered as stage 1, whereas a patient with a global ALSFRS-R score of 44 due to a score of 3 in items 6, 8, 9 and 10 was considered as stage 2b.

The MITOS system is based on the loss of independent functions in four key domains of the ALSFRS-R. The sum of the lost functions determines the stage of ALS-MITOS, which includes stages from 0 (absence of functional loss in any domain) to 4 (loss of function in four domains). The authors [5] tested the MITOS system using data obtained from two clinical trials [Lithium carbonate in amyotrophic lateral sclerosis (LITALS) and quality of care in ALS study] [12,13] and then in a cohort of 200 patients with ALS randomized in the erythropoietin in amyotrophic lateral sclerosis study [14]. MITOS stages were calculated by considering loss of function, as defined by Chiò et al. [5], in the ALSFRS-R. In both staging systems, stage 5 is represented by death (and not by death or tracheostomy/non-invasive ventilation > 23 h/day). Table 1 summarizes the definition of stages for both staging systems. In our study, retrospective staging was performed before data analysis commenced. The two operations were carried out by different individuals.

**Statistical methods**

A chi-square test was used to explore differences between groups for categorical data, equality of medians and Kruskal–Wallis tests for continuous data.

The median time to each clinical stage was standardized by dividing the time from onset to each clinical milestone by the disease duration and multiplying by 100, using only information from patients who had died.

The equality of medians test was used to explore differences between median times from onset to each stage for each of the staging systems.

Clinical stage was treated as a time-dependent variable, i.e. for each patient we calculated the person time...
at risk during each stage. Kaplan–Meier survival curves followed by log-rank test were used to evaluate survival during each clinical stage of both staging systems.

The performance of a prognostic system has been shown to be related to homogeneity (small differences in survival among patients in the same stage within each system), discriminatory ability (greater differences in survival among patients in different stages within each system) and monotonicity of gradients (the survival of patients in earlier stages is longer than the survival of patients in more advanced stages within the same system) [15].

For comparison of staging systems we used the Cox regression model to calculate the log-likelihood in order to determine homogeneity and the Cochran–Armitage test for trend to measure the discriminatory ability of each staging system. Data were analysed using Stata 11 (StataCorp, TX, USA).

**Results**

**Patient characteristics**

We analysed 545 patients diagnosed with ALS between 1 January 2009 and 31 December 2013 in the Emilia Romagna region of Italy. A total of 272 patients were dead at last observation. Patient characteristics are shown in Table 2.

**Standardized median time to each milestone: comparison of staging systems**

Figure 1a shows standardized median times (SMTs) to stages 2a, 2b, 3, 4a and 4b, where 0 is onset of disease and 100 is death, according to the King’s College classification. Stages 2b, 3, 4a and 4b are reached after an SMT of 42%, 50%, 81% and 79% of the disease course and after an SMT of 42%, 58%, 81% and 73% if patients with dementia are excluded, as in the study by Roche et al. [4]. Therefore, the inclusion of patients with dementia accelerates median time to weakness in a third region.

Figure 1b shows SMT to stages 0, 1, 2, 3 and 4 according to the MITOS staging system. Stages 0–4 are reached after an SMT of 35%, 67%, 79%, 100% and 104% of the disease course, and the exclusion of patients with dementia does not seem to influence SMTs (stages 0–4 are reached at 35%, 65%, 73%, 96% and 108% of the disease course).

In both cases, to calculate SMT, we only used information from patients who had reached the end of the disease course, having died. Table 3 shows median and SMT from onset to each milestone, considering only patients who had died, and comparison of medians between pairs of consecutive stages.

**Number/proportion of deaths throughout stages**

In the King’s College staging system, there is a steady increase in the number and proportion of patients who die throughout stages 2a to 4a/b, when considering the last recorded milestone [stage 2a, 14/65 (22%); stage 2b, 24/67 (36%); stage 3, 53/118 (45%); stage 4a, 33/55 (60%); stage 4b, 148/239 (62%)]. Ninety percent of tracheostomized patients undergo tracheostomy during stage 4 of the King’s College stages (4a, 28%; 4b, 62%). This is due to the fact that King’s College stage 4 explicitly considers ventilatory support; the remaining 10% underwent tracheostomy as an emergency procedure following acute pneumonia, which occurred unexpectedly between two evaluations.

In the MITOS system the number and/or proportions of deaths are fairly homogenous throughout stages 2–4 [stage 0, 58/174 (33%); stage 1, 69/149 (46%); stage 2, 63/92 (68%); stage 3, 39/62 (63%); stage 4, 43/67 (64%)]. The percentage of patients undergoing tracheostomy was evenly spread out throughout stages 0–3 (0, 21.5%; 1, 21.5%; 2, 23%; 3, 25%; 4, 9%).

**Survival curves: comparison of staging systems**

Figure 2 depicts Kaplan–Meier curves for time to death/last observation during each clinical stage for the King’s College (Fig. 2a) and MITOS (Fig. 2b)
staging systems, followed by log-rank test and Cox analyses between pairs of subsequent stages.

**Comparison of prognostic stratification of staging systems**

Table 4 shows the two staging systems' discriminatory ability and homogeneity for prediction of time to death/last observation. The King's College system shows both a higher homogeneity within stages and a higher linear trend.

**Discussion**

The present study was aimed at assessing the advantages and drawbacks of two recently developed staging systems, followed by log-rank test and Cox analyses between pairs of subsequent stages.

**Table 2** Patient characteristics and median time to death in different subgroups

|                          | Median time to death/last observation (months ± SD) | P-value | Dead at last observation [n (%)] | P-value |
|--------------------------|--------------------------------------------------|---------|---------------------------------|---------|
| Sex                      |                                                  |         |                                 |         |
| Male                     | 41.3 ± 22.4                                      | P = 0.30| 151 (50.3)                      | P = 0.83|
| Female                   | 39.3 ± 23.3                                      |         | 121 (49.4)                      |         |
| ALS onset                |                                                  |         |                                 |         |
| Bulbar                   | 35.9 ± 22                                        | P < 0.01| 88 (57.9)                       | P < 0.01|
| Spinal                   | 41.8 ± 23                                        |         | 184 (46.6)                      |         |
| Phenotype (542 patients) |                                                  |         |                                 |         |
| Bulbar                   | 34.4 ± 21.5                                      | P < 0.01*| 100 (57.8)                      | P = 0.02|
| Classic                  | 40.3 ± 21.5                                      |         | 107 (46.9)                      |         |
| Flail arm                | 47.9 ± 17.2                                      |         | 14 (42.4)                       |         |
| Flail leg                | 49.1 ± 27.5                                      |         | 26 (39.4)                       |         |
| UMN                      | 49.9 ± 25                                        |         | 11 (42.3)                       |         |
| Respiratory              | 30.2 ± 20.9                                      |         | 12 (75)                         |         |
| Enteral nutrition        |                                                  |         |                                 |         |
| Yes                      | 41.9 ± 20.9                                      | P = 0.24| 105 (62.1)                      | P < 0.01|
| No                       | 39.4 ± 23.7                                      |         | 167 (44.4)                      |         |
| Non-invasive ventilation |                                                  |         |                                 |         |
| Yes                      | 40.8 ± 21.1                                      | P = 0.63| 130 (62.8)                      | P < 0.01|
| No                       | 39.8 ± 23.9                                      |         | 142 (42)                        |         |
| Invasive ventilation     |                                                  |         |                                 |         |
| Yes                      | 43.7 ± 20.2                                      | P = 0.13| 48 (58.5)                       | P = 0.09|
| No                       | 39.6 ± 23.3                                      |         | 224 (48.5)                      |         |
| Riluzole                 |                                                  |         |                                 |         |
| Yes                      | 40.7 ± 22.8                                      | P = 0.25| 226 (49.3)                      | P = 0.55|
| No                       | 37.6 ± 23.3                                      |         | 46 (52.9)                       |         |
| Total                    | 40.2 ± 22.9                                      |         | 273 (50.1)                      |         |

ALS, amyotrophic lateral sclerosis; UMN, upper motor neuron predominant phenotype.
Significant results in bold.
*Post hoc test: bulbar versus classic, P < 0.01; bulbar versus flail arm, P < 0.01; bulbar versus flail leg, P < 0.01; bulbar versus UMN, P < 0.01; flail arm versus respiratory, P < 0.01.

**Figure 1** Standardized median times (SMTs) to each milestone. (a) SMT (median value, 25th–75th percentile, lower and upper adjacent values) to King’s College stages. (b) SMT (median value, 25th–75th percentile, lower and upper adjacent values) to Milano-Torino staging system stages.
staging systems for patients with ALS, when applied in an incident, population-based cohort.

Standardized median time to each milestone and cohort effects on timings

According to the King’s College staging system, SMT from onset to weakness in a second region, weakness in a third region and the need for gastrostomy or respiratory support (stages 2b, 3, 4a or 4b, respectively) correspond approximately to 40%, 60% and 80% of the disease course, respectively. Our data are very similar to theirs, with the above milestones occurring at 42%, 58%, 81% and 73% of the disease course if we exclude patients with dementia, as they did. The inclusion of patients with dementia accelerates median time to weakness in a third region (occurring after an SMT of 50%).

Stages 0–4 of the MITOS staging system are reached after an SMT of 35%, 67%, 79%, 100% and 104% of the disease course in our cohort. Overall, the King’s College milestones are more evenly spaced out throughout the disease course, whereas the MITOS milestones are mostly skewed towards later stages of the disease, with SMT to stages 3 and 4 being equal to or longer than median time to death. This is probably due to the fact that each stage is reached only once a complete loss of function has occurred and this occurs towards the end of the disease course.

### Table 3 Median and standardized median times (SMTs) from onset to each milestone

| King’s College staging system (median) from onset (IQR) | SMT | Equality of medians test |
|--------------------------------------------------------|-----|-------------------------|
| Stage 2a (n = 90)                                       | 8 (5–13) | 33 |
| Stage 2b (n = 123)                                      | 10 (6–17) | 42 |
| (P < 0.01)                                              | Stage 0 (n = 192) | 9 (5–13) |
| Stage 3 (n = 130)                                       | 12 (8–22) | 50 |
| (P < 0.01)                                              | Stage 1 (n = 143) | 16 (9–23) |
| Stage 4a (n = 112)                                      | 20 (14–29) | 81 |
| (P < 0.01)                                              | Stage 2 (n = 95) | 19 (13–31) |
| Stage 4b (n = 148)                                      | 19 (13–29) | 79 |
| (P = 0.28)                                              | Stage 3 (n = 51) | 24 (14–38) |
| Death (n = 272)                                         | 24 (16–37) | 100 |
| (P < 0.01)                                              | Death (n = 272) | 24 (16–37) |

| Milano-Torino staging system (median) from onset (IQR) | SMT | Equality of medians test |
|--------------------------------------------------------|-----|-------------------------|
| Stage 0 (n = 192)                                       | 9 (5–13) | 35 |
| Stage 1 (n = 143)                                       | 16 (9–23) | 67 |
| (P < 0.01)                                              | Stage 1 (n = 143) | 16 (9–23) |
| Stage 2 (n = 95)                                        | 19 (13–31) | 79 |
| (P < 0.01)                                              | Stage 3 (n = 51) | 24 (14–38) |
| Stage 3 (n = 51)                                        | 24 (14–38) | 100 |
| (P < 0.01)                                              | Stage 3 (n = 51) | 24 (14–38) |
| Stage 4 (n = 43)                                        | 25 (17–42) | 104 |
| (P < 0.01)                                              | Stage 4 (n = 43) | 25 (17–42) |
| Death (n = 272)                                         | 24 (16–37) | 100 |
| (P < 0.01)                                              | Death (n = 272) | 24 (16–37) |

IQR, interquartile range. Significant results in bold.
The median time spent in each stage varies from 2 to 8 months for the King’s College system, similar to data from two large phase three clinical trials assessed by Balendra et al. [8], in which the median duration of transition time from one stage to another varied from 3 to 7 months. For MITOS systems the median duration of stages 0–2 ranged from 3 to 9 months, whereas the median time from onset to stages 3, 4 and 5 overlapped.

As for subgroups of patients, median time to weakness in a third region is shorter in patients with a bulbar onset in both our cohort (SMT: 43%) and the King’s College cohort (SMT: 45%). This is consistent with the worse prognosis of the bulbar forms.

Survival curves during each stage

In the King’s College system there is a decrease in survival from the earliest to the most advanced stages when considering time to death/last observation during each stage and survival curves are all significantly distinct from one another.

In the MITOS staging system, survival during stage 2 does not differ significantly from survival during stage 3 and, paradoxically, there seems to be an inversion of the curves with patients dying sooner during stage 2 of the disease as opposed to those that have reached stage 3 (Fig. 2b). Although not specifically addressed, data in the study by Chiò et al. [5] are in line with our observations; the probability of transition from stage 2 to death and from stage 3 to death at 1 year is 33% for both stages in the Quality of Care in ALS study [13], whereas in the LITALS study [9], the probability even decreases from 29% to 25% for stage 2 and 3, respectively. We hypothesize that this may be due to the fact that patients who do not die after the complete loss of function in two domains may belong to a group of ‘long survivors’.

Tracheostomized patients

Eighty-two (15%) patients underwent tracheostomy; of these, 47 (57%) had died by the end of the follow-up. In our incident cohort, as expected, 90% of patients underwent tracheostomy during the last King’s College stage (stage 4), which occurs at approximately 80% of the disease course. According to the MITOS system, which considers tracheostomy as the loss of one function (the respiratory function), the percentage of tracheostomies was similar throughout stages 0–3. As these patients would have died without tracheostomy, it is not clear, from a methodological point of view, whether or not they should be considered as patients who have reached the end of the disease course (stage 5 for both staging systems).

Strengths and limitations

The strength of the present study is its population-based, real-life setting with a long follow-up and with inclusion of patients with dementia, who have not been considered in staging systems thus far, but who should not be excluded from attempts to stage the disease as 15% of patients with ALS have concomitant fronto-temporal dementia [16].

A limitation of the study is that data on time to clinical milestones are incomplete in some patients, especially in the more advanced stages. Furthermore, time to clinical stage was not collected prospectively, but was estimated retrospectively from ALSFRS-R (collected at mean 3-monthly intervals). A prospective study with a shorter duration between study visits may reveal that transition time between stages is shorter.

Conclusions

In the present population, the King’s College milestones appear to be more evenly spaced out throughout the disease course and their distribution is comparable to that described by Roche et al. [4], whereas the MITOS milestones are mostly skewed towards later stages of the disease.

The King’s College staging system has a higher homogeneity (i.e. smaller differences in survival among patients in the same stage within each system) and a higher discriminatory ability (i.e. greater differences in survival among patients in different stages within each system) compared with the MITOS system, suggesting a higher prognostic competency for the King’s College staging system, especially for individual prognosis and as an outcome measure for clinical trials. However, the MITOS system, based on the complete loss of function in different domains, may be more useful for estimating health costs and resource allocations [5].

Neither system included patients with dementia or addressed the question as to whether patients undergoing tracheostomy should be considered as patients who have reached the end of the disease course. Future studies should deal with these issues.
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Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

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