**SUPPLEMENTARY DATA**

**Multi-state models**

An excellent review of various multi-state models is presented by Andersen and Keiding (1). A brief overview of time-homogenous Markov models is presented below.

Multi-state models are an extension of time-to-event Cox models. In these models, the rate at which an event occurs in time *t* assuming that the event did not occur earlier than time *t* is defined by the hazard function

Multistate models extend the single-event hazard to multiple states, each with a *transition intensity* that represents the rate per unit of time of moving between two states. The Markov process assumes that the future of the process, is dependent only on the current state at time For example, the transition intensity between stage 0 and is given as:

The *transition intensity matrix*, or matrix, is composed of the transition intensities between each pair of stages. Given stages, the matrix will have the dimensions with diagonal entries being equal to the negative of the sum of the off-diagonal entries in that row. These diagonal entries are the rate per unit of time leaving the associated stage, and their inverses are estimated *sojourn times*. *Transition probabilities* after an interval are explicit functions of the transition intensities expressed in matrix form as:

Implying

is computed as a Taylor expansion, or using eigendecomposition, and can be estimated using maximum likelihood estimation from data (2). Given probabilities (or distribution) of states at time in vector form ), future probabilities of states at time are represented as:

Estimates of total duration in states are obtained by integrating the above expression over the period of interest.

Should the Markov process be an unreasonable assumption, non-Markov, semi-Markov, and non-homogenous models exist for applications where intensities are dependent on the duration and/or full history of the process. We consider an application of piecewise constant transition intensities to test the assumption of time-homogeneity.

**Other considerations**

An important consideration in epidemiological data is the fact that the documentation of disease stage may be incomplete or inconsistent. Interval censoring is a common assumption which assumes the actual time of transition to a stage is unobserved; it is only known that the transition occurred in the time interval . Another complication of disease staging is the likely misclassification of individuals by clinicians. Given that staging systems are progressive, misclassification is obvious when an individual transitions backwards to a stage of less severity. These misclassification can be incorporated into the multi-state model but increases model complexity and computational difficulty because of the introduction of additional parameters in the form of a misclassification probability matrix.

1. Andersen PK, Keiding N. Multi-state models for event history analysis. Stat Methods Med Res. 2002 Apr;11(2):91–115.

2. Kalbfleisch JD, Lawless JF. The Analysis of Panel Data under a Markov Assumption. J Am Stat Assoc. 1985 Dec 1;80(392):863–71.

**Table S1:** Population characteristics

|  |  |  |  |
| --- | --- | --- | --- |
| **n=3199** | **Median or counts** | **Interquartile range** | **Missing, comments** |
| Age (at study entry) | 57 years | 48, 64 | 695 |
| Sex | Male: 2005  Women: 1194 |  |  |
| Onset site | Bulbar: 645  Non-bulbar: 2079 |  | 475 |
| Days from onset | 516 days | 345, 731 | 134 |
| Initial ALSFRS-R | 39 points | 35, 42 |  |
| Pre-slope | - 0.534 points/month | - 0.857, - 0.324 | 134 |
| Observations per subject | 8 | 6, 13 | Total number of observations = 29947 |
| Follow-up duration | 11.96 months | 8.36, 13.64 |  |
| Recorded date of death | 719 |  |  |

**Table S2:** Two-way distributions of prevalence of stage by three staging systems of ALS throughout the period of observation.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **29,947 observations** | **MITOS 0** | **MITOS 1** | **MITOS 2** | **MITOS 3** | **MITOS 4** | **FT9 0** | **FT9 1** | **FT9 2** | **FT9 3** | **FT9 4** |
| King's 1 | 3800 | 405 | 8 | 0 | 0 | 744 | 3211 | 244 | 14 | 0 |
| King's 2 | 4931 | 1915 | 60 | 0 | 0 | 301 | 1773 | 4554 | 266 | 12 |
| King's 3 | 4426 | 3427 | 567 | 156 | 32 | 54 | 486 | 3518 | 3616 | 934 |
| King's 4a | 2453 | 1957 | 527 | 185 | 52 | 147 | 1147 | 1868 | 1515 | 497 |
| King's 4b | 354 | 1661 | 1850 | 650 | 531 | 25 | 189 | 554 | 1757 | 2521 |
| MITOS 0 |  |  |  |  |  | 1252 | 6048 | 6168 | 2220 | 276 |
| MITOS 1 |  |  |  |  |  | 19 | 746 | 4420 | 3114 | 1066 |
| MITOS 2 |  |  |  |  |  | 0 | 12 | 149 | 1589 | 1262 |
| MITOS 3 |  |  |  |  |  | 0 | 0 | 1 | 228 | 762 |
| MITOS 4 |  |  |  |  |  | 0 | 0 | 0 | 17 | 598 |

**Table S3:** Counts of transitions for each staging system. Each matrix element represents the number of transitions from row state to column state for consecutive pairs of observations.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **King’s transition counts** | | | | | |  | **MITOS transition counts** | | | | | |
|  | **1** | **2** | **3** | **4a** | **4b** | **Death** |  | **0** | **1** | **2** | **3** | **4** | **Death** |
| 1 | 3133 | 681 | 109 | 40 | 40 | 6 | 0 | 12921 | 1838 | 198 | 23 | 6 | 80 |
| 2 | 340 | 4789 | 1050 | 60 | 170 | 44 | 1 | 461 | 6625 | 1013 | 146 | 24 | 188 |
| 3 | 43 | 497 | 6436 | 210 | 454 | 201 | 2 | 13 | 304 | 1669 | 327 | 66 | 221 |
| 4a | 13 | 28 | 109 | 4089 | 389 | 138 | 3 | 1 | 11 | 86 | 451 | 169 | 126 |
| 4b | 9 | 16 | 100 | 90 | 3853 | 330 | 4 | 0 | 0 | 5 | 41 | 350 | 104 |
|  |  |  |  |  |  |  |  | **FT9 transition counts** | | | | | |
|  |  |  |  |  |  |  |  | **0** | **1** | **2** | **3** | **4** | **Death** |
|  |  |  |  |  |  |  | 0 | 786 | 343 | 78 | 10 | 3 | 1 |
|  |  |  |  |  |  |  | 1 | 185 | 4740 | 1290 | 204 | 37 | 14 |
|  |  |  |  |  |  |  | 2 | 17 | 501 | 7491 | 1603 | 252 | 93 |
|  |  |  |  |  |  |  | 3 | 2 | 63 | 611 | 4437 | 1089 | 222 |
|  |  |  |  |  |  |  | 4 | 0 | 3 | 38 | 462 | 2503 | 389 |

**Table S4:** Q (transition intensity) matrices for each staging system, baseline models. Each matrix entry is the estimated transition rate (events per month) moving from the row state to the column state. . Negative entries along the diagonal the rate leaving each state. Death is an absorbing state, therefore the last row is zero (no probability of leaving that state). 95% confidence intervals are provided in parentheses.

(A) **King’s:** Non-sequential model. Note that transitions from stages 1 and 2 to 4a, and from 1, 2 and 3 to 4b are permitted, as is transition to death from stage 2 on.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **1** | **2** | **3** | **4a** | **4b** | **death** |
| 1 | -0.228 | 0.211 | 0 | 0.009 | 0.007 | 0 |
|  | (-0.244, -0.213) | (0.197, 0.227) |  | (0.007, 0.013) | (0.005, 0.012) |  |
| 2 | 0.068 | -0.285 | 0.189 | 0.006 | 0.02 | 0.002 |
|  | (0.062, 0.076) | (-0.299, -0.272) | (0.178, 0.201) | (0.004, 0.009) | (0.016, 0.025) | (0.001, 0.004) |
| 3 | 0 | 0.076 | -0.171 | 0.024 | 0.054 | 0.017 |
|  |  | (0.071, 0.083) | (-0.181, -0.163) | (0.021, 0.027) | (0.049, 0.060) | (0.014, 0.020) |
| 4a | 0 | 0 | 0.019 | -0.080 | 0.050 | 0.011 |
|  |  |  | (0.016, 0.022) | (-0.086, -0.074) | (0.045, 0.056) | (0.009, 0.014) |
| 4b | 0 | 0 | 0.020 | 0.014 | -0.085 | 0.052 |
|  |  |  | (0.016, 0.023) | (0.011, 0.017) | (-0.092, -0.078) | (0.046, 0.057) |
| death | 0 | 0 | 0 | 0 | 0 | 0 |

(B) **MITOS:** Sequential model. Non-adjacent transitions are not permitted except to death from stages 1 on.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **0** | **1** | **2** | **3** | **4** | **death** |
| 0 | -0.120 | 0.120 | 0 | 0 | 0 | 0 |
|  | (-0.126, -0.115) | (0.115, 0.126) |  |  |  |  |
| 1 | 0.049 | -0.196 | 0.137 | 0 | 0 | 0.011 |
|  | (0.044, 0.053) | (-0.205, -0.188) | (0.129, 0.144) |  |  | (0.009, 0.014) |
| 2 | 0 | 0.113 | -0.330 | 0.169 | 0 | 0.047 |
|  |  | (0.101, 0.126) | (-0.351, -0.310) | (0.155, 0.185) |  | (0.039, 0.058) |
| 3 | 0 | 0 | 0.120 | -0.433 | 0.217 | 0.096 |
|  |  |  | (0.098, 0.147) | (-0.477, -0.394) | (0.19, 0.248) | (0.075, 0.122) |
| 4 | 0 | 0 | 0 | 0.081 | -0.206 | 0.124 |
|  |  |  |  | (0.06, 0.11) | (-0.242, -0.175) | (0.103, 0.151) |
| death | 0 | 0 | 0 | 0 | 0 | 0 |

(C) **FT9:** Sequential model. Non-adjacent transitions are not permitted except to death from stages 1 on.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **0** | **1** | **2** | **3** | **4** | **death** |
| 0 | -0.379 | 0.379 | 0 | 0 | 0 | 0 |
|  | (-0.417, -0.344) | (0.344, 0.417) |  |  |  |  |
| 1 | 0.037 | -0.270 | 0.233 | 0 | 0 | 0.001 |
|  | (0.032, 0.043) | (-0.283, -0.258) | (0.221, 0.245) |  |  | (0, 0.002) |
| 2 | 0 | 0.059 | -0.249 | 0.187 | 0 | 0.003 |
|  |  | (0.054, 0.064) | (-0.259, -0.239) | (0.179, 0.195) |  | (0.002, 0.005) |
| 3 | 0 | 0 | 0.104 | -0.300 | 0.185 | 0.011 |
|  |  |  | (0.096, 0.112) | (-0.313, -0.287) | (0.175, 0.196) | (0.008, 0.015) |
| 4 | 0 | 0 | 0 | 0.128 | -0.212 | 0.084 |
|  |  |  |  | (0.117, 0.140) | (-0.227, -0.198) | (0.076, 0.092) |
| death | 0 | 0 | 0 | 0 | 0 | 0 |

**Table S5:** Akaike information criteria (AIC) for various unadjusted, univariable, and multivariable Markov multistate models for each staging system.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model description | **King’s** | | **MITOS** | | **FT9** | |  |
| **df** | **AIC** | **df** | **AIC** | **df** | **AIC** | **n** |
|  | **UNADJUSTED MODELS** | | | | | |  |
| Unadjusted  non-sequential | **18** | **38303 $** | 16 | 36535 | 16 | 46632 | 3199 |
| Unadjusted sequential | 12 | 42201 | **12** | **36537 $** | **12** | **46665 $** |
|  | **ADJUSTED MODELS\*** | | | | | |  |
|  | UNIVARIABLE MODELS | | | | | |  |
| Unadjusted  (complete cases bulbar data) | 18 | 31563 | 12 | 29681 | 12 | 38243 | 2724 |
| Adjusted (bulbar, unconstrained)¶ | 31 | 31315 | 20 | 29594 | 20 | 38056 |
| Unadjusted (complete cases pre-slope data) | 18 | 37737 | 12 | 35291 | 12 | 45266 | 3065 |
| Adjusted (pre-slope, constrained) | 26 | 37432 | 16 | 34639 | 16 | 44801 |
| Adjusted (pre-slope, unconstrained)¶ | 44 | 37445 | 28 | 34590 | 28 | 44783 |
| Unadjusted  (complete cases age data) | 18 | 30409 | 12 | 25859 | 12 | 35324 | 2504 |
| Adjusted (age, constrained) | 22 | 30255 | 14 | 25757 | 14 | 35222 |
| Adjusted (age, unconstrained)¶ | 31 | 30249 | 20 | 25763 | 20 | 35162 |
| Adjusted (sex, unconstrained)¶ | 31 | 38276 | 20 | 36520 | 20 | 46658 | 3199 |
|  | MULTIVARIABLE MODELS | | | | | |  |
| Unadjusted  (complete cases age and pre-slope data) | 18 | 29727 | 12 | 24588 | 12 | 33910 | 2370 |
| Adjusted (age, constrained) | 22 | 29581 | 14 | 24483 | 14 | 33809 |
| Adjusted (pre-slope, constrained) | 26 | 29483 | 16 | 24049 | 16 | 33551 |
| **Adjusted (age and pre-slope, constrained)§** | **30** | **29344** | **18** | **23948** | **18** | **33459** |

df = degrees of freedom (number of free or estimated parameters)

AIC (Akaike information criteria) are measures of model fit, penalized for model complexity. A lower value implies a better fit. AIC is not comparable across staging systems, unless one system is a “coarse” version of another system nested in it. Also, within one system, comparison is not possible if differing subsets are used for model generation because of missing data. Within each system, comparison is possible between similarly shaded contiguous cells within each column, and between the adjusted (sex, unconstrained) cells and the unadjusted models at the top of the table. With 2 exceptions, more complex models exhibited better fit than simpler models.

$ unadjusted models used throughout the paper, including for Q matrix estimation, 3- and 6-month probability tables, predicted prevalence plots, and construction of adjusted models, are sequential for MITOS and FT9 (12 dfs each), and non-sequential for King’s (18 dfs).

\* All adjusted models build upon unadjusted sequential (MITOS, FT9) and non-sequential (King’s) models marked by the $ indicator above. Unadjusted models are again constructed under the adjusted models section for AIC comparison, including only the subset of patients with complete variable data.

¶ Transition-specific hazard rations (HRs) from these unconstrained univariable models are presented in Table S7, Supplementary Data.

§ hazard ratio (HR) estimates from these multivariable models that include age and pre-slope as covariates are presented in Table 4 of the main paper. To reduce the number of parameters, HRs were constrained so that they are equal for sequential progression (states 1 through 5), and separate but equal for transitions to death (from state 2 to 5 to death). Additional HR estimates are permitted for King’s for non-sequential transitions to stages 4a and 4b. Similar constraints on HR values are applied in other constrained uni- and multivariable models.

**Table S6:** Estimated total duration in different states by staging system

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **King’s** | | **MITOS** | | **FT9** | |
| Stage | months | Stage | months | Stage | months |
| 1 | 6.8 | 0 | 12.8 | 0 | 3.3 |
| 2 | 8.1 | 1 | 11.0 | 1 | 7.2 |
| 3 | 11.3 | 2 | 5.5 | 2 | 11.5 |
| 4a | 7.2 | 3 | 2.7 | 3 | 11.4 |
| 4b | 13.9 | 4 | 2.9 | 4 | 10.0 |

**Table S7:** Hazard ratios (HRs) for prognostically important variables by transition, for each staging system (univariate analyses, unconstrained HRs). 95% confidence intervals are presented in paretheses. Non-significant hazard ratios are greyed out for easier visualization. Point estimates of significant HRs are presented in directed acyclic graph form in Figure 5 of the paper.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Transitions** | **Bulbar onset** | **Steep pre-slope**  **≤ -0.733 points/mo** | **Less steep pre-slope**  **> -0.393 points/mo** | **Age (per decade)** | **Female sex** |
| King’s stage transitions | 1-2 | 0.83 | 1.37 | 0.63 | 0.96 | 1.09 |
|  | (0.69, 0.99) | (1.07, 1.74) | (0.54, 0.74) | (0.90, 1.03) | (0.95, 1.26) |
| 1-4a | 33.50 | 0.48 | 0.26 | 2.16 | 2.79 |
|  | (5.53, 202.96) | (0.09, 2.71) | (0.12, 0.55) | (1.42, 3.29) | (1.32, 5.89) |
| 1-4b | 2.22 | 1.04 | 0.65 | 1.44 | 0.45 |
|  | (0.61, 8.07) | (0.16, 6.92) | (0.22, 1.89) | (0.92, 2.24) | (0.13, 1.63) |
| 2-3 | 1.46 | 1.36 | 0.66 | 1.06 | 1.12 |
|  | (1.25, 1.71) | (1.18, 1.58) | (0.58, 0.76) | (1.01, 1.12) | (0.99, 1.27) |
| 2-4a | 31.51 | 0.66 | 0.50 | 1.94 | 4.40 |
|  | (6.85, 144.89) | (0.18, 2.46) | (0.20, 1.25) | (1.25, 3.00) | (1.69, 11.46) |
| 2-4b | 1.72 | 0.89 | 0.49 | 1.07 | 0.88 |
|  | (0.98, 3.04) | (0.51, 1.56) | (0.30, 0.81) | (0.88, 1.30) | (0.54, 1.43) |
| 2-death | 0.44 | 5.67 | 0.39 | 1.77 | 0.86 |
|  | (0.02, 8.05) | (0.34, 94.89) | (0.00, 42.84) | (0.53, 5.89) | (0.04, 20.10) |
| 3-4a | 3.59 | 1.58 | 0.77 | 1.26 | 1.54 |
|  | (2.61, 4.94) | (1.15, 2.18) | (0.50, 1.21) | (1.11, 1.42) | (1.16, 2.05) |
| 3-4b | 0.97 | 1.73 | 0.94 | 1.33 | 1.00 |
|  | (0.75, 1.27) | (1.39, 2.17) | (0.69, 1.27) | (1.22, 1.46) | (0.82, 1.22) |
| 3-death | 0.73 | 1.29 | 0.86 | 1.59 | 0.86 |
|  | (0.44, 1.21) | (0.86, 1.94) | (0.51, 1.45) | (1.31, 1.94) | (0.59, 1.26) |
| 4a-4b | 1.06 | 1.60 | 0.72 | 1.19 | 0.79 |
|  | (0.84, 1.35) | (1.26, 2.04) | (0.54, 0.95) | (1.02, 1.40) | (0.64, 0.98) |
| 4a-death | 2.49 | 1.30 | 0.28 | 1.38 | 1.20 |
|  | (1.47, 4.23) | (0.79, 2.11) | (0.12, 0.64) | (1.09, 1.76) | (0.75, 1.92) |
| 4b-death | 0.9 | 1.39 | 0.96 | 1.33 | 1.17 |
|  | (0.69, 1.18) | (1.08, 1.77) | (0.69, 1.35) | (1.16, 1.53) | (0.94, 1.46) |
| MITOS stage transitions | 0-1 | 1.11 | 1.73 | 0.46 | 1.08 | 1.15 |
|  | (1.00, 1.23) | (1.56, 1.92) | (0.41, 0.51) | (1.03, 1.12) | (1.05, 1.25) |
| 1-2 | 1.68 | 1.59 | 0.79 | 1.14 | 1.13 |
|  | (1.48, 1.92) | (1.41, 1.79) | (0.67, 0.93) | (1.08, 1.21) | (1.02, 1.26) |
| 1-death | 1.35 | 0.93 | 1.14 | 1.66 | 0.46 |
|  | (0.78, 2.34) | (0.54, 1.6) | (0.66, 1.96) | (1.29, 2.14) | (0.25, 0.87) |
| 2-3 | 1.49 | 1.39 | 0.91 | 1.07 | 1.08 |
|  | (1.23, 1.81) | (1.14, 1.70) | (0.66, 1.25) | (0.96, 1.18) | (0.91, 1.29) |
| 2-death | 0.45 | 0.99 | 0.83 | 1.44 | 1.62 |
|  | (0.22, 0.89) | (0.64, 1.53) | (0.41, 1.66) | (1.13, 1.85) | (1.08, 2.42) |
| 3-4 | 1.30 | 1.53 | 0.89 | 1.00 | 0.95 |
|  | (0.98, 1.74) | (1.11, 2.12) | (0.52, 1.53) | (0.83, 1.19) | (0.73, 1.23) |
| 3-death | 0.74 | 0.63 | 1.01 | 1.37 | 0.51 |
|  | (0.40, 1.36) | (0.37, 1.06) | (0.51, 1.97) | (0.99, 1.88) | (0.29, 0.90) |
| 4-death | 1.46 | 1.04 | 0.98 | 1.45 | 1.36 |
|  | (0.96, 2.22) | (0.63, 1.73) | (0.43, 2.22) | (1.05, 2.00) | (0.92, 2.01) |
| FT9 stage transitions | 0-1 | 1.04 | 2.58 | 0.66 | 1.07 | 1.27 |
|  | (0.83, 1.32) | (1.58, 4.19) | (0.51, 0.85) | (0.97, 1.18) | (1.03, 1.58) |
| 1-2 | 1.03 | 1.66 | 0.56 | 0.94 | 0.94 |
|  | (0.92, 1.16) | (1.43, 1.93) | (0.50, 0.63) | (0.90, 0.99) | (0.85, 1.04) |
| 1-death | 0.80 | 1.52 | 0.53 | 1.67 | 0.84 |
|  | (0.04, 18.01) | (0.03, 81.57) | (0.02, 15.27) | (0.34, 8.11) | (0.04, 19.51) |
| 2-3 | 2.23 | 1.46 | 0.69 | 1.11 | 1.15 |
|  | (2.00, 2.48) | (1.32, 1.61) | (0.61, 0.77) | (1.07, 1.16) | (1.05, 1.25) |
| 2-death | 0.95 | 2.01 | 0.72 | 1.91 | 0.35 |
|  | (0.23, 3.99) | (0.63, 6.39) | (0.16, 3.33) | (1.11, 3.31) | (0.08, 1.53) |
| 3-4 | 1.17 | 1.40 | 0.86 | 1.28 | 1.06 |
|  | (1.03, 1.33) | (1.24, 1.58) | (0.73, 1.02) | (1.21, 1.36) | (0.95, 1.18) |
| 3-death | 0.68 | 0.93 | 1.04 | 1.41 | 0.67 |
|  | (0.25, 1.88) | (0.43, 2.02) | (0.41, 2.62) | (1.04, 1.90) | (0.31, 1.47) |
| 4-death | 0.89 | 0.88 | 1.06 | 1.36 | 1.05 |
|  | (0.70, 1.12) | (0.71, 1.09) | (0.77, 1.46) | (1.20, 1.54) | (0.86, 1.28) |

**Figure S1:** Longitudinal mixed effects model estimates of subscore trajectories by site of onset, obtained from PRO-ACT ALSFRS-R data (see reference 10 in paper). Only observed data points were used to build these models. The unobserved (time 0, subscore 12) point was not included. Solid lines are linear time term model estimates, whereas dotted lines are quadratic time term model estimates. Improved model fit with the quadratic time term indicates curvilinear trajectory of subscores. Fine’til9 (FT9) stages by how many subscores have reached or crossed the threshold of 9. Inspection of these plots suggests that the threshold of 9 is least sensitive to choice of model (linear and quadratic time term model estimates coincide the best at that level).



**Figure S2:** Modeled survival probabilities by stage for King’s, MITOS and FT9 staing systems. These modeled probabilities underestimate mortality beyond the first year.

**Figure S3:** Stacked prevalence plots of stages and death for each system over the first 24 months of observation. The shaded areas depict observed prevalences by stage (marked with corresponding labels), whereas areas separated by dotted lines depict modeled prevalences employing time-inhomogenous Markov models (changing transition intensities at 6 and 12 month points of observation). Note that modeled prevalences approximate observed prevalences up to about 12 months of observation, beyond which time point the model underestimates progression and mortality. Similar plots for time homogenous Markov models are presented in Figure 4 of the paper.

