Application of ALS Staging Systems to an American ALS Population

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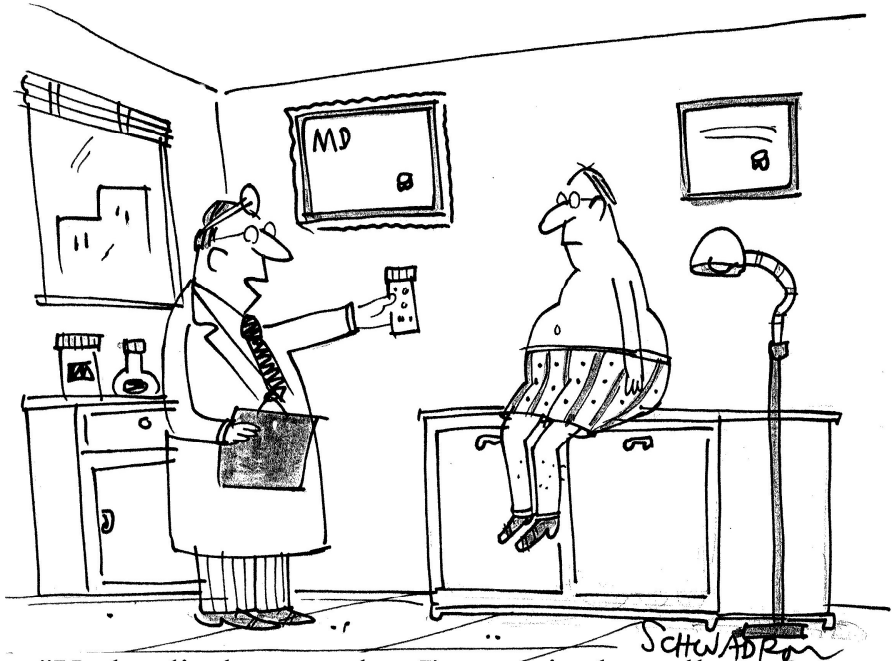
Disclosure statement

- I have no conflicts of interest to report
- I do not have financial or other relationships with any commercial interest
- I will not be discussing off label use of pharmaceuticals or devices



"Under disclosure rules, I'm required to tell you I own stock in the company whose drug I'm prescribing."

Current ALS “classifications”

- Site of onset
- Gene mutation
- Cognitive impairment

Revised El Escorial diagnostic criteria

- Revised El Escorial diagnostic criteria
  - Characterizes the extent of upper and lower motor neuron signs

- Clinically definite ALS
  - Upper motor neuron (UMN) as well as lower motor neuron (LMN) signs in the bulbar region and at least two spinal regions or the presence of UMN and LMN signs in three spinal regions
- Clinically probable ALS
  - UMN and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs
- Clinically probable ALS: laboratory supported
  - UMN and LMN signs are only in one regions or UMN signs alone are in one or more regions, and LMN signs defined by EMG criteria in at least two regions
- Clinically possible ALS
  - UMN and LMN in one region (together) or
  - UMN in 2 or more regions
  - UMN and LMN signs in 2 regions with no UMN signs rostral to LMN signs

El Escorial criteria limitations

- Goal of the criteria is to determine clinical certainty of ALS diagnosis
- Criteria is sensitive to the “extent of disease” rather than to the “burden of disease”
- Up to 10% of patients may not fulfill “definite ALS” criteria at the time of death
- Does not provide prognostic information

ALS-FRS-R

- 48 point scale with 4 major domains (48 = normal)
  - Bulbar
    - Speech
    - Salivation
    - Swallowing
  - Upper limb
    - Handwriting
    - Cutting food and handling utensil (with and without gastrostomy)
    - Dressing and hygiene
  - Lower limb
    - Turning in bed and adjusting bed clothes
    - Walking
    - Climbing stairs
  - Respiratory
    - Dyspnea
    - Orthopnea
    - Respiratory insufficiency

ALS-FRS-R

- Measure of disability and not “stage” of disease
- Patients with different stages of disease may have the same ALS-FRS-R

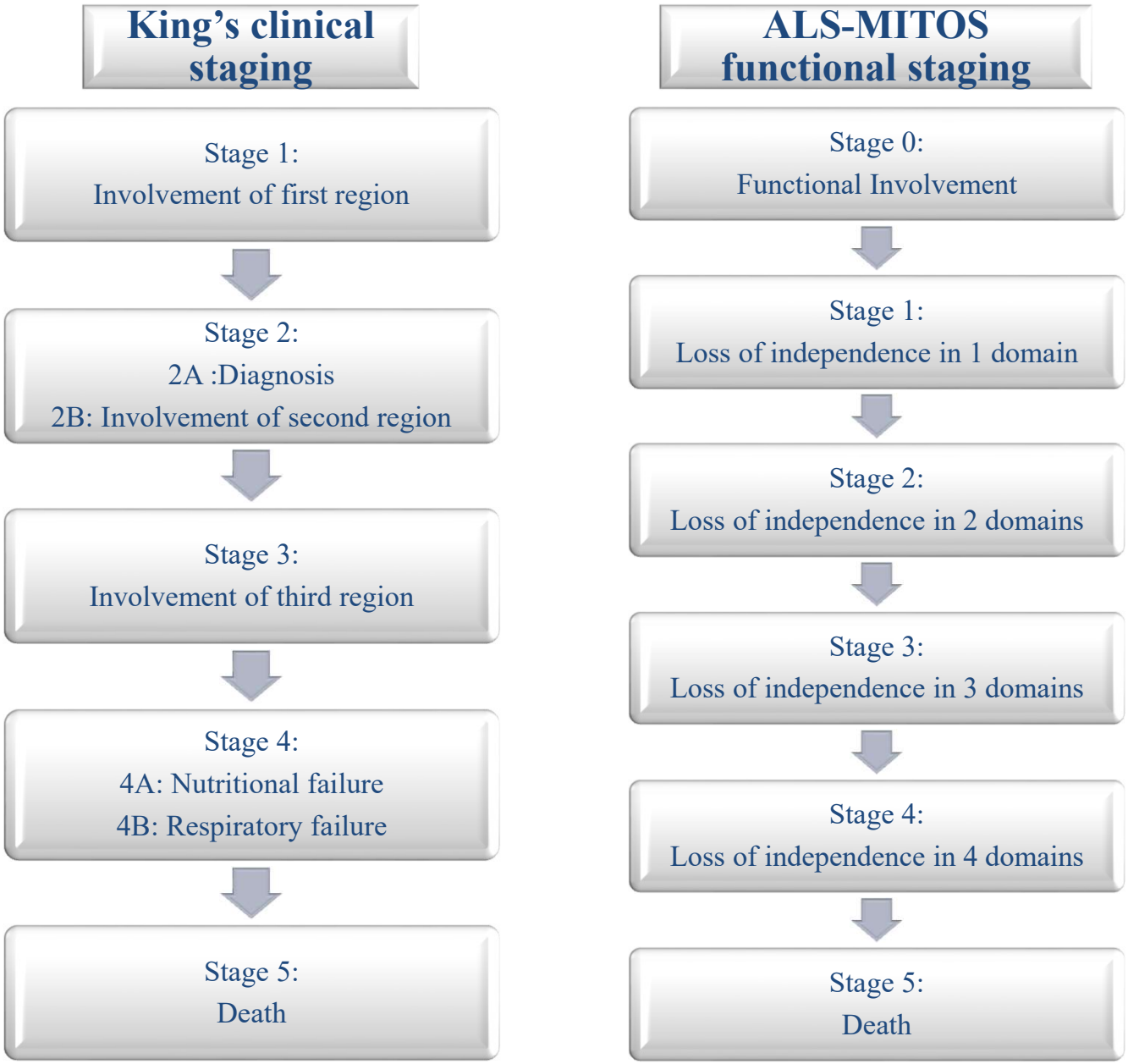
What is staging and why is it important?

- Define specific milestones over the course of the disease and reflects:
  - Disease severity
  - Prognosis
  - Options for treatment
- Purpose:
  - Tool of rehabilitation
  - Rapid functional assessment
  - Biomarker analysis
  - Effective research design
  - Health economics

Proposed staging systems

- King's clinical staging (2012)
  - 5 stages based on disease burden as measured by clinical involvement and significant feeding or respiratory failure
  - Can be estimated from ALSFRS-R
- Milano-Torino functional staging (2015)
  - Uses 6 stages based on functional ability as assessed by ALS Functional Rating Scale-Revised

- King’s clinical staging system differentiates early to mid disease
  - Focus on anatomical disease spread and significant involvement of respiration
- MiToS differentiate late stages in detail
  - Functional status tends to follow anatomical involvement therefore MiToS stages tend to lag behind King’s stages


King's clinical staging
Stage 1:
Involvement of first region
Stage 2:
2A :Diagnosis
2B: Involvement of second region
Stage 3:
Involvement of third region
Stage 4:
4A: Nutritional failure
4B: Respiratory failure
Stage 5:
Death
ALS-MITOS functional staging
Stage 0:
Functional Involvement
Stage 1:
Loss of independence in 1 domain
Stage 2:
Loss of independence in 2 domains
Stage 3:
Loss of independence in 3 domains
Stage 4:
Loss of independence in 4 domains
Stage 5:
Death

- Objective:
  - Apply the King's clinical staging to an American ALS population

Methods

- IRB approved retrospective chart review of 139 patients who presented to the University of Maryland ALS Clinic between January 2007 to August 2015
- ALS patient fulfilled the revised El Escorial Diagnostic criteria for clinical definite, probable, possible ALS

- Statistics:
  - Mean milestone time: Time elapsed from symptom onset to time of last clinical milestone reached
  - Fraction of total survival to onset of stages: Proportion of time spent in each milestone from symptom onset to death

Demographics

Onset		N (%)	Onset (years)	Duration to Diagnosis (months)	Survival (months)
All	**Total**	**139**	**60.7**	**14.0**	**35.0**
	Male	82 (59%)	59.8	14.9	34.0
	Female	57 (41%)	61.9	13.7	37.1
Bulbar	**Total**	**45 (32%)**	**62.7**	**13.9**	**27.3**
	Male	23 (51%)	61.3	15.2	27.4
	Female	22 (49%)	64.4	12.3	27.3
Limb	**Total**	**91 (66%)**	**59.8**	**14.7**	**39.2**
	Male	57 (63%)	59.1	14.2	37.1
	Female	34 (37%)	60.8	14.8	42.4
Spine	**Total**	**3 (2%)**	**56.7**	**12.0**	**33.5**
	Male	2 (66%)	60.5	15.5	33.5
	Female	1 (33%)	49.0	5.0	--

Demographics

		UMD	King's
Total		139	1459
Male		82 (59%)	892 (61%)
Female		57 (41%)	577 (39%)
Bulbar onset		45 (32%)	371 (25%)
Limb onset		91 (66%)	1088 (75%)
Age at onset (years)		60.7	60
Survival (months)	**All**	35	42
	Bulbar	27	30
	Limb	39	48

Mean Times (Months) To Reach Disease Stages

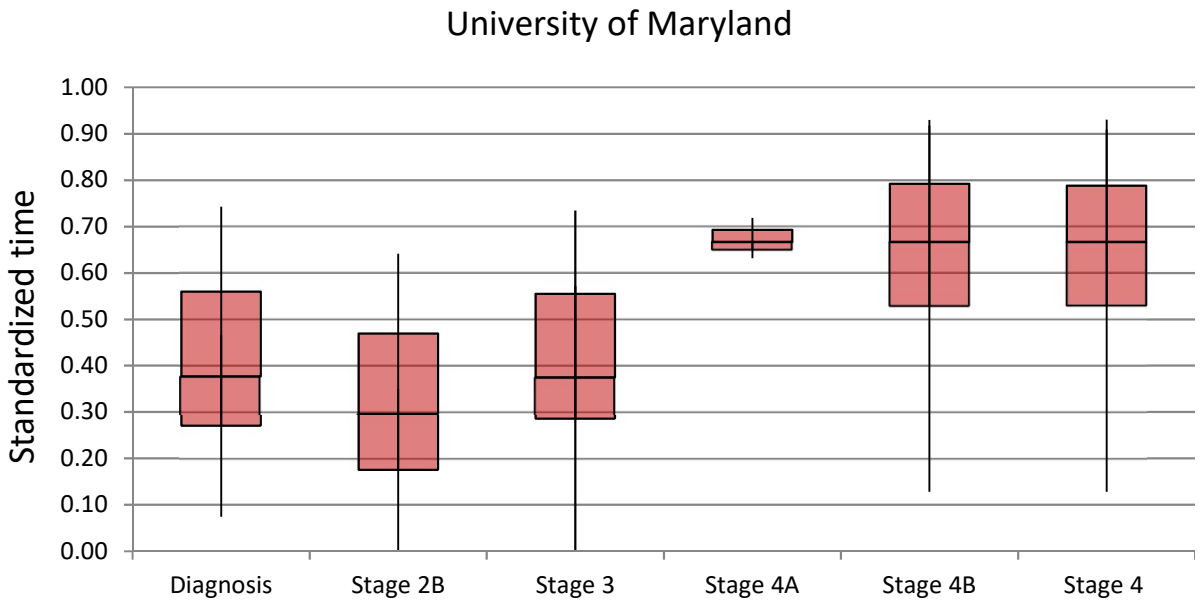
	University of Maryland	King's clinical staging
Stage 2B	12.4 (8.5 - 16.3)	17.7 (15.5 - 19.8)
Stage 3	15.4 (12.7 - 18.1)	23.3 (20.8 - 25.7)
Stage 4A	16.3 (9.7 - 23.0)	27.7 (25.1 - 30.2)
Stage 4B	24.4 (20.6 - 28.3)	30.3 (26.4 - 34.2)

Fraction of total survival to onset of the stages (with 95% CI)

Stage	Overall Population		Bulbar Onset		Limb Onset	
	UMD	**King's**	**UMD**	**King's**	**UMD**	**King's**
2	0.33 (0.27-0.39)	0.40 (0.37-0.42)	0.32 (0.19-0.46)	0.39 (0.32-0.45)	0.34 (0.28, 0.39)	0.40 (0.37-0.43)
3	0.41 (0.37-0.46)	0.59 (0.57-0.62)	0.37 (0.30-0.43)	0.45 (0.40-0.51)	0.44 (0.38-0.50)	0.63 (0.60-0.66)
4a	0.67 (0.62-0.72)	0.76 (0.73-0.78)	0.68 (0.59-0.76)	0.71 (0.68-0.74)	0.67	0.81 (0.77-0.84)
4b	0.66 (0.61-0.70)	0.75 (0.72-0.79)	0.60 (0.51-0.70)	0.81 (0.77-0.86)	0.68 (0.63-0.73)	0.73 (0.69-0.78)
4	0.65 (0.61-0.70)		0.60 (0.50-0.69)		0.68 (0.63-0.73)	

Note that time spent in each stage is expressed as a fraction of 1, which represents 100% of the illness course.

Time to reach each milestone



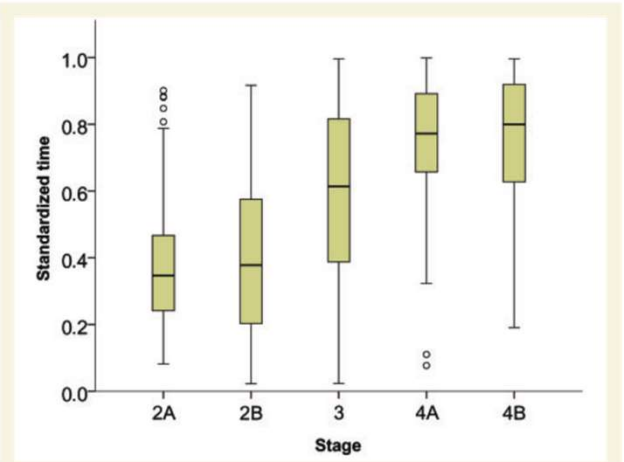
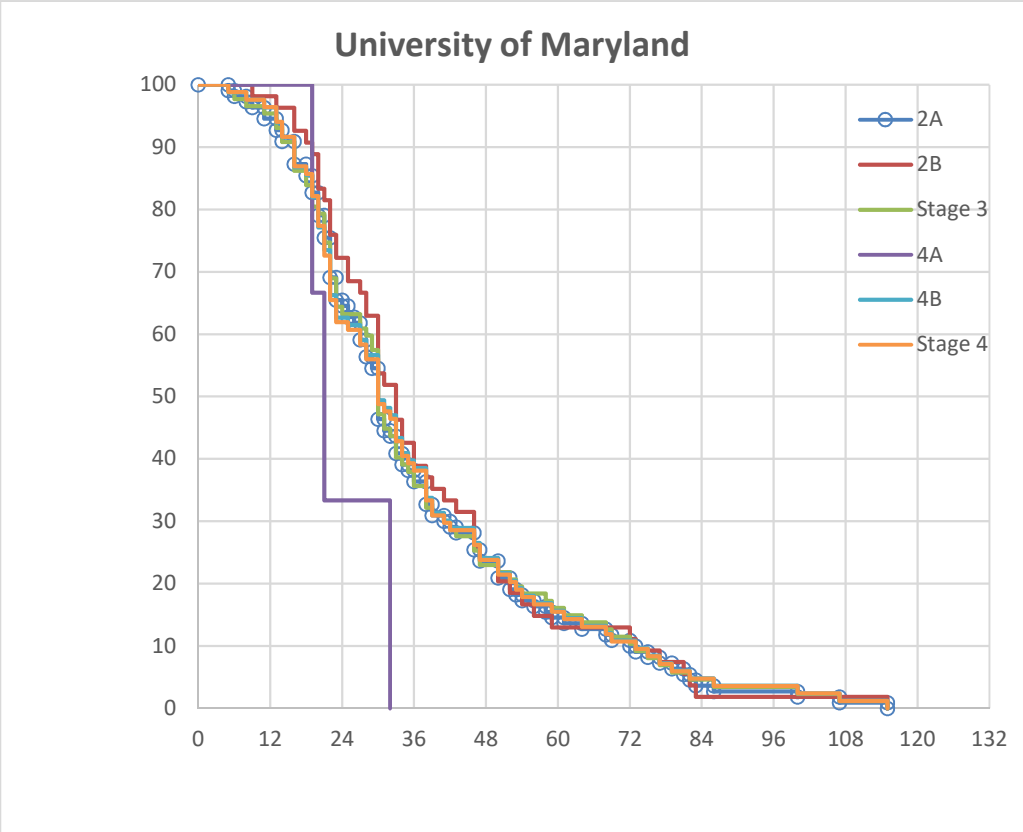


Figure 1 Boxplot showing standardized times to last recorded milestone (where 0 is onset of disease and 1 is death) for each stage in the entire cohort with ALS. Stage 1 (onset) is not explicitly shown but occurs at the origin; 2A = diagnosis; 2B = second region involved; 3 = third region involved; 4A = gastrostomy needed; 4B = respiratory support (non-invasive ventilation) needed. The line marks the median with the shaded box showing the interquartile range.

Roche et al 2012



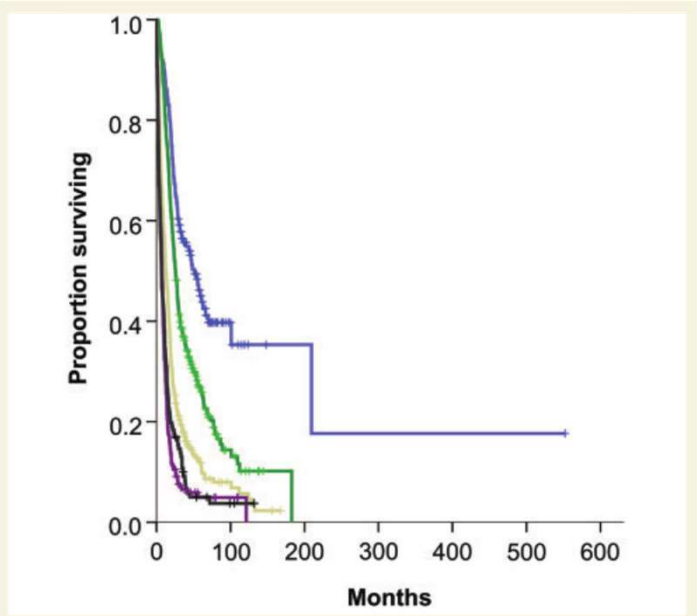


Figure 2 Kaplan–Meier curve showing survival for entire cohort from last recorded milestone to death or censor date. The separation of the curves is evidence of construct validity Blue = diagnosis; green = second region involved; grey = third region involved; black = gastrostomy needed; purple = respiratory support needed.

Roche et al 2012

US versus European data

Similarities

- Similar demographics
- Comparable time to reach the next milestone

Differences

- Shorter survival in US
  - May be driven by the limb onset group (39 [US] vs 48 [European] months)
- More time spent in the early stages in King's and later stages in UMD
  - Bulbar onset patient spent more time in stage 4 in UMD
  - Limb onset transition faster to later stages in UMD

Summary

- Apply and validate the King's staging in a US ALS population
- Differences in health insurance systems in US versus UK
  - Access to specialized equipment such as NPPV
- Limitation
  - Smaller US population
  - Retrospective review

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