Poster 325

Time from ALS Symptom Onset to Key Disease Milestones for Slow, Intermediate, and Fast Progressors: a Real-World Cross-Sectional Survey

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INTRODUCTION

- Amyotrophic lateral sclerosis (ALS) is a heterogeneous neurodegenerative disease with mean survival of 36–60 months from symptom onset.[1,2]
- Clinical milestones reflect disease progression and functional loss in people living with ALS and occur at specific points in the disease course.
  - Healthcare resource utilization and medical costs increase substantially with each milestone.[3,4]

Objective

- To estimate the time from symptom onset to key disease milestones in people with ALS with slow, intermediate, or fast disease progression, using multinational real-world data.

METHODS

- Data were drawn from the Adelphi ALS Disease Specific Programme™ (DSP) – a multinational, cross-sectional survey of neurologists and the patients with ALS under their care in the United States and Europe (France, Germany, Italy, Spain, UK).
  - The data were collected between July 2020 and March 2021.
- The DSP methodology details were previously published.[5]
  - Briefly, neurologists completed questionnaires about people living with ALS under their care, such as demographics, disease milestones, and clinical outcomes, including ALS Functional Rating Scale-Revised (ALSFRS-R) scores and symptom duration; this was used to calculate their disease progression rate (48 minus ALSFRS-R score divided by symptom duration in months).
- Disease progression within this dataset was divided into tertiles of slow (≤0.36 points/month), intermediate (0.36 to <0.77), and fast (≥0.77) rates.
- Disease milestones were defined as key events occurring during the disease course, and some (but not all) may reflect disease progression and functional loss in ALS.
- From symptom onset, mean time in months to key milestones for slow, intermediate, and fast progressors was reported. Each analysis included only patients reaching the respective milestones.
- For the United States and Europe, patient characteristics and time to key milestones were compared with analysis of variance, chi-squared, Fisher's exact, or *t*-tests ($P<0.05$ considered significant).

RESULTS

Table 1. Demographic and clinical characteristics

Characteristic	Slow (n=285)	Intermediate (n=287)	Fast (n=295)	*P* value[a]
Age, mean (SD), years	59.1 (11.1)	61.3 (11.5)	63.3 (10.3)	<0.001
Male, n (%)	180 (63.2)	174 (60.6)	188 (63.7)	0.715
White, n (%)	250 (87.7)	263 (91.6)	259 (87.8)	0.331
BMI, mean (SD), kg/m²	24.6 (5.4)	24.1 (3.4)	24.2 (3.5)	0.301
ALSFRS-R total score, mean (SD)	42.0 (6.6)	33.8 (10.2)	24.8 (11.8)	<0.001
Time since diagnosis, mean (SD), months	26.3 (33.7)	19.2 (16.1)	12.7 (9.8)	<0.001
Time since 1st symptom, mean (SD), months	37.8 (40.3)	26.6 (18.5)	18.0 (10.8)	<0.001
ALS site of onset: bulbar, n (%)	48 (16.8)	51 (17.8)	70 (23.7)	<0.001
On riluzole alone, n (%)	197 (69.1)	189 (65.9)	155 (52.5)	<0.001
On edaravone alone, n (%)[b]	32 (11.2)	28 (9.8)	33 (11.2)	
On riluzole plus edaravone, n (%)[b]	12 (4.2)	23 (8.0)	26 (8.8)	

[a] Chi-squared test comparing slow, intermediate, and fast progressors. [b] Edaravone is not approved in Europe.
ALSFRS-R, ALS Functional Rating Scale-Revised; BMI, body mass index.

Time from symptom onset to key disease milestones for all patients

- Time to reach milestones demonstrated the variability of progression with this disease, including rapid functional loss in many people (**Figure 1**).
  - For all subgroups, requiring nutritional support (gastrostomy) was the milestone reached after the longest time, at a mean of 19, 40, and 102 months from symptom onset for fast, intermediate, and slow progressors, respectively.
- For intermediate or fast progressors, the difference in time from symptom onset was statistically significant for every disease milestone compared with slow progressors (**Table 2**).

Figure 1. Time to key milestones from symptom onset for slow, intermediate, and fast progressors

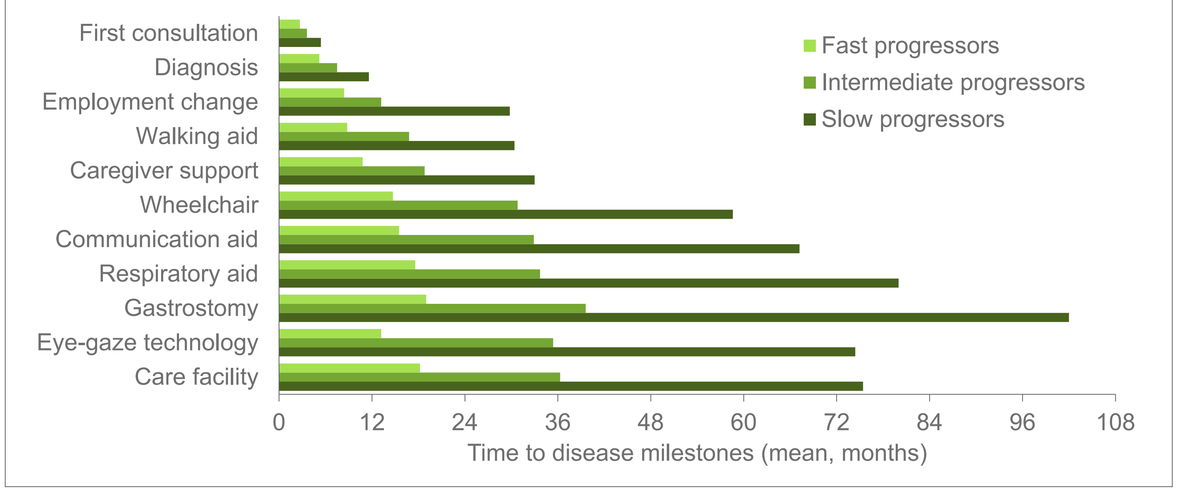

Table 2. Time (months) from symptom onset to key milestones for all patients

Disease milestones	Slow		Intermediate		Fast		Fast vs slow	Intermediate vs slow	Fast vs intermediate
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	Mean difference (95% CI), *P* value	Mean difference (95% CI), *P* value	Mean difference (95% CI), *P* value
First consultation	261	5.37 (4.41, 6.32)	267	3.59 (3.09, 4.08)	279	2.67 (2.33, 3.02)	−2.69 (−2.08, −3.30) <0.001	−1.78 (−1.32, −2.24) <0.001	−0.91 (−0.76, −1.06) 0.136
Diagnosis	275	11.59 (9.38, 13.81)	284	7.52 (6.81, 8.24)	291	5.20 (4.71, 5.69)	−6.39 (−4.67, −8.12) <0.001	−4.07 (−2.57, −5.57) <0.001	−2.32 (−2.10, −2.55) 0.046
Employment change	73	29.80 (21.96, 37.63)	75	13.21 (11.38, 15.05)	99	8.44 (7.15, 9.74)	−21.35 (−14.82, −27.89) <0.001	−16.58 (−10.59, −22.58) <0.001	−4.77 (−4.23, −5.31) 0.318
Walking aid	98	30.38 (25.35, 35.40)	135	16.84 (15.05, 18.63)	135	8.80 (8.03, 9.58)	−21.58 (−17.33, −25.83) <0.001	−13.54 (−10.30, −16.77) <0.001	−8.04 (−7.03, −9.06) <0.001
Caregiver support	124	33.01 (25.96, 40.07)	205	18.78 (17.17, 20.39)	246	10.85 (9.88, 11.81)	−22.17 (−16.07, −28.26) <0.001	−14.23 (−8.78, −19.68) <0.001	−7.94 (−7.29, −8.58) <0.001
Wheelchair	14	58.58 (27.59, 89.57)	60	30.75 (27.71, 33.80)	121	14.73 (13.32, 16.13)	−43.85 (−14.27, −73.44) <0.001	−27.83 (0.12, −55.77) <0.001	−16.03 (−14.39, −17.67) <0.001
Communication aid	11	67.25 (22.83, 111.67)	50	32.88 (28.17, 37.59)	97	15.52 (13.77, 17.27)	−51.73 (−9.05, −94.41) <0.001	−34.37 (5.35, −74.08) <0.001	−17.36 (−14.40, −20.33) <0.001
Respiratory aid	17	80.01 (48.82, 111.21)	91	33.67 (29.95, 37.39)	153	17.64 (16.03, 19.26)	−62.37 (−32.79, −91.95) <0.001	−46.34 (−18.87, −73.82) <0.001	−16.03 (−13.92, −18.14) <0.001
Gastrostomy	9	101.97 (44.46, 159.47)	43	39.58 (34.40, 44.77)	117	18.98 (17.16, 20.80)	−82.99 (−27.30, −138.67) <0.001	−62.38 (−10.06, −114.71) <0.001	−20.60 (−17.24, −23.96) <0.001
Eye-gaze technology	7	74.39 (5.21, 143.57)	26	35.39 (28.01, 42.77)	28	13.24 (10.17, 16.31)	−61.16 (4.95, −127.27) <0.001	−39.01 (22.79, −100.81) 0.004	−22.15 (−17.84, −26.46) 0.013
Care facility	6	75.39 (−15.86, 166.63)	21	36.33 (29.20, 43.47)	33	18.23 (14.34, 22.12)	−57.16 (30.20, −144.51) <0.001	−39.05 (45.06, −123.17) 0.014	−18.11 (−14.87, −21.35) 0.081

Time from symptom onset to key disease milestones for patients in the US and Europe

- For all subgroups, the mean time from symptom onset to key disease milestones was generally faster for patients in the United States compared with patients in Europe (**Tables 3, 4**).
  - For fast vs slow progressors in the United States and Europe, the difference in time from symptom onset was statistically significant for every disease milestone (**Tables 3, 4**).
  - The mean time from symptom onset to diagnosis was shorter in the United States compared with Europe by 3.7, 3.7, and 2.9 months for slow, intermediate, and fast progressors, respectively (**Tables 3, 4**).

Table 3. Time (months) from symptom onset to key milestones for patients in the US

Disease milestones	Slow		Intermediate		Fast		Fast vs slow	Intermediate vs slow	Fast vs intermediate
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	Mean difference (95% CI), *P* value	Mean difference (95% CI), *P* value	Mean difference (95% CI), *P* value
First consultation	90	5.47 (3.34, 7.61)	87	2.59 (1.62, 3.57)	134	2.03 (1.69, 2.36)	−3.44 (−1.65, −5.24) <0.001	−2.88 (−1.72, −4.04) 0.006	−0.56 (0.08, −1.20) 1.000
Diagnosis	96	9.21 (6.83, 11.58)	95	5.09 (4.00, 6.17)	138	3.67 (3.24, 4.09)	−5.54 (−3.59, −7.49) <0.001	−4.12 (−2.83, −5.41) <0.001	−1.42 (−0.76, −2.08) 0.411
Employment change	26	24.25 (13.07, 35.42)	19	10.80 (7.61, 13.99)	58	7.35 (6.06, 8.64)	−16.90 (−7.01, −26.78) <0.001	−13.45 (−5.47, −21.43) 0.009	−3.45 (−1.54, −5.35) 1.000
Walking aid	38	26.96 (18.72, 35.20)	52	14.94 (11.59, 18.28)	77	8.35 (7.32, 9.39)	−18.60 (−11.39, −25.82) <0.001	−12.02 (−7.13, −16.92) <0.001	−6.58 (−4.27, −8.90) 0.029
Caregiver support	45	24.70 (16.83, 32.57)	55	15.20 (12.20, 18.20)	124	9.48 (8.23, 10.74)	−15.22 (−8.60, −21.83) <0.001	−9.49 (−4.62, −14.37) 0.002	−5.72 (−3.98, −7.46) 0.036
Wheelchair	6	40.19 (4.66, 75.73)	13	28.91 (20.21, 37.60)	52	13.73 (11.68, 15.79)	−26.46 (7.02, −59.94) <0.001	−11.29 (15.55, −38.12) 0.229	−15.17 (−8.53, −21.82) 0.001
Communication aid	8	45.64 (12.10, 79.18)	13	28.01 (16.28, 39.73)	54	13.75 (11.93, 15.57)	−31.89 (−0.17, −63.61) <0.001	−17.64 (4.17, −39.45) 0.047	−14.26 (−4.34, −24.17) 0.014
Respiratory aid	8	79.54 (45.25, 113.83)	22	26.87 (19.68, 34.05)	87	14.89 (13.07, 16.71)	−64.65 (−32.18, −97.12) <0.001	−52.68 (−25.58, −79.77) <0.001	−11.98 (−6.60, −17.35) 0.002
Gastrostomy	3	110.33 (40.51, 180.16)	11	31.44 (20.51, 42.38)	64	16.59 (14.45, 18.73)	−93.74 (−26.05, −161.42) <0.001	−78.89 (−20.00, −137.78) <0.001	−14.85 (−6.06, −23.65) <0.001
Eye-gaze technology	4	47.49 (−18.66, 113.62)	9	19.59 (13.98, 25.19)	25	12.40 (9.18, 15.61)	−35.09 (27.84, −98.02) <0.001	−27.90 (32.63, −88.43) 0.007	−7.19 (−4.80, −9.59) 0.604
Care facility	3	67.71 (−88.31, 223.73)	4	44.45 (24.55, 64.34)	20	18.29 (14.24, 22.35)	−49.42 (102.54, −201.38) 0.002	−23.27 (112.86, −159.39) 0.433	−26.15 (−10.32, −41.99) 0.079

Table 4. Time (months) from symptom onset to key milestones for patients in Europe

Disease milestones	Slow		Intermediate		Fast		Fast vs slow	Intermediate vs slow	Fast vs intermediate
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	Mean difference (95% CI), *P* value	Mean difference (95% CI), *P* value	Mean difference (95% CI), *P* value
First consultation	171	5.31 (4.37, 6.25)	180	4.07 (3.51, 4.62)	145	3.27 (2.70, 3.84)	−2.04 (−1.67, −2.41) <0.001	−1.24 (−0.85, −1.63) 0.041	−0.80 (−0.82, −0.78) 0.389
Diagnosis	179	12.87 (9.72, 16.02)	189	8.75 (7.87, 9.63)	153	6.58 (5.79, 7.37)	−6.29 (−3.93, −8.65) <0.001	−4.13 (−1.86, −6.40) 0.009	−2.17 (−2.07, −2.26) 0.408
Employment change	47	32.87 (22.19, 43.54)	56	14.03 (11.81, 16.25)	41	9.99 (7.44, 12.54)	−22.88 (−14.76, −31.00) <0.001	−18.83 (−10.38, −27.29) <0.001	−4.05 (−4.38, −3.71) 1.000
Walking aid	60	32.55 (26.08, 39.01)	83	18.04 (16.00, 20.07)	58	9.40 (8.21, 10.58)	−23.15 (−17.87, −28.43) <0.001	−14.51 (−10.08, −18.94) <0.001	−8.64 (−7.79, −9.49) 0.003
Caregiver support	79	37.75 (27.64, 47.86)	150	20.10 (18.21, 21.98)	122	12.23 (10.79, 13.67)	−25.52 (−16.85, −34.18) <0.001	−17.65 (−9.43, −25.88) <0.001	−7.86 (−7.42, −8.31) 0.017
Wheelchair	8	72.37 (19.34, 125.40)	47	31.26 (28.01, 34.52)	69	15.47 (13.53, 17.42)	−56.90 (−5.81, −107.98) <0.001	−41.11 (8.67, −90.88) <0.001	−15.79 (−14.48, −17.10) <0.001
Communication aid	3	124.87 (−115.75, 365.49)	37	34.60 (29.46, 39.73)	43	17.74 (14.56, 20.92)	−107.13 (130.31, −344.57) <0.001	−90.28 (145.21, −325.77) <0.001	−16.86 (−14.90, −18.81) 0.001
Respiratory aid	9	80.44 (21.44, 139.43)	69	35.84 (31.53, 40.15)	66	21.28 (18.59, 23.96)	−59.16 (−2.85, −115.47) <0.001	−44.60 (10.09, −99.28) <0.001	−14.57 (−12.94, −16.19) 0.001
Gastrostomy	6	97.78 (0.60, 194.97)	32	42.38 (36.49, 48.27)	53	21.87 (18.89, 24.84)	−75.92 (18.29, −170.13) <0.001	−55.40 (35.89, −146.70) <0.001	−20.52 (−17.60, −23.43) 0.002
Eye-gaze technology	3	110.27 (−148.07, 368.61)	17	43.75 (35.14, 52.36)	3	20.25 (5.20, 35.30)	−90.02 (153.27, −333.31) 0.019	−66.52 (183.21, −316.25) 0.025	−23.50 (−29.94, −17.06) 0.936
Care facility	3	83.06 (−218.94, 385.06)	17	34.43 (26.18, 42.67)	13	18.12 (9.53, 26.72)	−64.93 (228.47, −358.34) 0.020	−48.63 (245.12, −342.38) 0.098	−16.30 (−16.65, −15.95) 0.636

Limitations

- Data from the survey are cross-sectional, with limited information about individual patient journeys or disease history.
- Participation was affected by the willingness to complete the survey and may not reflect a random sample of neurologists or people living with ALS.

CONCLUSIONS

- In intermediate and fast progressing ALS, times to disease milestones were shorter than for slow progressing ALS, illustrating the heterogeneity of disease progression.
- Across the board, milestones were consistently reached earliest by those with the fastest disease progression rates and latest by those with the slowest rates.
- The rapid loss of mobility, respiratory, and bulbar function is consistent with the rapid progression of this disease.
- The mean time from symptom onset to key disease milestones was generally faster for patients in the United States compared with patients in Europe, irrespective of disease progression rate subgroup.
- Effective therapies that slow disease progression may have the potential to reduce burden of ALS and help people living with ALS, physicians, and caregivers to better plan optimal care in relation to these key milestones.

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