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ORIGINAL COMMUNICATION

Tollgate-based progression pathways of ALS patients

Özden O. Dalgıç[1,2] · F. Safa Erenay[3] · Kalyan S. Pasupathy[4,5] · Osman Y. Özaltın[6] · Brian A. Crum[7] · Mustafa Y. Sir[4,5,8]

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Abstract

Objective To capture ALS progression in arm, leg, speech, swallowing, and breathing segments using a disease-specific staging system, namely tollgate-based ALS staging system (TASS), where tollgates refer to a set of critical clinical events including having slight weakness in arms, needing a wheelchair, needing a feeding tube, etc.

Methods We compiled a longitudinal dataset from medical records including free-text clinical notes of 514 ALS patients from Mayo Clinic, Rochester-MN. We derived tollgate-based progression pathways of patients up to a 1-year period starting from the first clinic visit. We conducted Kaplan–Meier analyses to estimate the probability of passing each tollgate over time for each functional segment.

Results At their first clinic visit, 93%, 77%, and 60% of patients displayed some level of limb, bulbar, and breathing weakness, respectively. The proportion of patients at milder tollgate levels (tollgate level <2) was smaller for arm and leg segments (38% and 46%, respectively) compared to others ($>65\%$). Patients showed non-uniform TASS pathways, i.e., the likelihood of passing a tollgate differed based on the affected segments at the initial visit. For instance, stratified by impaired segments at the initial visit, patients with limb and breathing impairment were more likely (62%) to use bi-level positive airway pressure device in a year compared to those with bulbar and breathing impairment (26%).

Conclusion Using TASS, clinicians can inform ALS patients about their individualized likelihood of having critical disabilities and assistive-device needs (e.g., being dependent on wheelchair/ventilation, needing walker/wheelchair or communication devices), and help them better prepare for future.

Keywords ALS progression · Tollgate-based staging system · Phenotypes · Kaplan–Meier analysis

Introduction

Patients with amyotrophic lateral sclerosis (ALS) lose control of voluntary movements over time due to degeneration of motor neurons [1]. ALS typically begins as focal weakness or dysfunction affecting arm, leg, speech, swallowing, or breathing; and the progression can be in any anatomical

Brian A. Crum, Mustafa Y. Sir contributed equally as senior authors to this work.

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✉ Mustafa Y. Sir
sir.mustafa@mayo.edu

[1] Harvard Medical School, Boston, 25 Shattuck St, Boston, MA 02115, USA

[2] Institute for Technology Assessment, Massachusetts General Hospital, 101 Merrimac Street, Boston, MA 02114, USA

[3] Department of Managements Sciences, University of Waterloo, 200 University Ave., Waterloo, ON N2L3G1, Canada

[4] Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

[5] Mayo Kern Center for the Science of Health Care Delivery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

[6] Edward P. Fitts Department of Industrial and Systems Engineering, North Carolina State University, 400 Daniels Hall, Raleigh, NC 27695, USA

[7] Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

[8] Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, 200 First Street SW, Rochester, MN 55905, USA

direction at various paces [2, 3]. Although there exist general "average" progression expectations, the information is insufficient to counsel patients about their own specific likely progression pathways [4]. Therefore, there is a need for instruments to better educate patients/caregivers about what critical events, referred to as tollgates in the remainder, to expect and when to expect them, and provide patients with a timeframe for critical life decisions (e.g., when to retire or remodel a house) [5].

Most studies have investigated ALS progression based on ALSFRS-R (revised ALS Functional Rating Scale) and factors such as the site of onset [6–11]. However, using ALSFRS-R to determine the timing of particular clinical tollgates or to foresee future needs of ALS patients is challenging due to aggregation when calculating scores and the lack of specific questions to determine passing of a tollgate. Other staging systems are also utilized to capture ALS progression over time, including King's staging system, which is based on the number of body regions affected by ALS, and the Milano–Torino system (MiToS), which is based on the number of the lost functional domains in the ALSFRS-R scale [12, 13]. However, research analyzing ALS progression regarding the timing of certain critical clinical events [beyond either involvement of an anatomical region (King's) or complete loss of function of a domain (MiToS)] still remains limited, and existing research considers only a few specific events (e.g., needing respiratory support or wheelchair) [14–17].

Inspired from King's and MiToS staging systems, we define a Tollgate-based ALS staging system (TASS), that can capture ALS progression (in a straightforward manner) relevant to the patient perspective based on a comprehensive set of critical events, referred to as tollgates, such as having slight weakness in a functional segment or using an assistive device. TASS follows MiToS's loss-of-function stages in a more granular manner (each functionality loss is divided into tollgate levels to indicate specific patient needs). We use TASS to translate detailed information from ALSFRS-R into a more patient-centered form that can help patients, physicians, and caregivers to plan for the anticipated progression of ALS. Using a detailed longitudinal dataset from Mayo Clinic Rochester, MN, we characterized ALS progression through tollgates at the functional segment and patient levels over time and showed how the progression varies among patients based on their individualized tollgate history.

Materials and methods

Patients and clinical data

To analyze possible tollgate-based progression pathways, we compiled a longitudinal dataset from medical records of 514 ALS patients, who attended their quarterly follow-up examinations at the ALS Clinic of Mayo Clinic, Rochester, MN between 2006 and 2016. Each patient underwent at least one examination. We extracted the medical records of these patients from Mayo Clinic ALS Evaluation and Neurologic Examination Forms. The derived longitudinal data include demographics, diagnosis records, ALSFRS-R scores, and assessment reports from the ALS Clinic team, composed of neurologists, physiatrists, nurses, speech pathologists, speech therapists, dieticians, and social workers, for each examination. The assessment reports provided detailed medical information mostly in free-text format including assessments of the disease progression and patients' medical history, e.g., use of medication and assistive devices. This study was reviewed by the Mayo Clinic Institutional Review Board and deemed as an exempt study.

Tollgate-based ALS staging system (TASS)

TASS consists of a set of critical events (i.e., tollgates) specifying impairment levels and associated assistive technology/equipment needs for each functional segment based on opinions of an expert panel composed of the ALS Clinic team members practicing at Mayo Clinic, Rochester, MN. Table 1 provides a detailed description of tollgates in TASS, which is associated with each of the five functional segments (referred to as segments hereafter): arms, legs, speech, swallowing, and breathing. Tollgates are labeled with numbers signifying the impairment level; a higher number means more significant impairment. For example, the leg tollgate "No weakness" is the initial tollgate (level 0) when the disease has not affected a patient's legs, whereas "Dependent on a wheelchair" is the final tollgate (level 5) when a patient can no longer walk and is always in need of a wheelchair. Due to the irreversible nature of ALS, patients reach tollgates in each segment in a non-improving manner [18].

Extracting tollgate data from medical records

The exact timing of reaching a specific tollgate level is not readily available in the medical records because they reflect patients' conditions at regular clinic visits, while patients may advance several tollgates between two visits in any segment based on their progression rate. Therefore, from clinical notes, we can only determine the most recently reached tollgate in each segment at a clinic visit. To extract tollgate information from clinical notes, we first employed *NLTK*, a natural language processing package in *Python* [19], to extract two- or three-word phrases (i.e., bigrams and trigrams) that frequently repeat in clinical notes indicating that patient has reached a specific tollgate. For example, the trigram "right", "arm", "useless" in a clinical note in the respective order usually indicates reaching tollgate level 3

Table 1 Tollgates and their definitions for each segment

Level	Tollgate	Definition
Leg		
0	No weakness	No leg weakness
1	Slight weakness	The patient's leg(s) is/are weak. However, the weakness does not prevent the patient from performing daily activities such as walking, climbing stairs, or running, etc.
2	Modifying activities	The weakness in the legs requires modification in patients' daily activities, such as avoiding long-distance walks, or tripping/falling when walking, but still, no assistance is required
3	Requiring assistance with walking	The patient uses a lightweight assistance tool such as a walker, or cane, but does not use heavyweight assistance tools (e.g., wheelchair, scooter)
4	Using a wheelchair	The patient uses a wheelchair occasionally but still can walk with a lightweight assistance tool
5	Dependent on a wheelchair	The patient cannot walk with a lightweight assistance tool and/or has no (or very little) use of legs
Arm		
0	No weakness	No arm weakness
1	Slight weakness	ALS has started weakening the arm(s). However, the weakness does not prevent the patient from performing daily activities such as dressing, grooming, bathing
2	Modifying activities	The weakness in the arms requires modification in patients' activities, such as using a button-hook, not being able to raise arms or open lids. Some assistance may be required
3	Losing useful function of one arm	One arm becomes completely useless. Assistance is required with most of the daily activities
4	Losing useful function of both arms	Both arms become entirely useless. Constant assistance required with all daily activities
Swallowing		
0	No weakness	ALS has not yet affected the patient's swallowing ability
1	Affected eating/drinking	Some difficulty when eating and drinking but still following a regular diet
2	Modifying what you eat	Eating/drinking is significantly affected. The patient avoids certain foods and/or drinks that are hard to swallow
3	Using a feeding tube	The patient cannot swallow consistently; thus, has a feeding tube
Breathing		
0	No weakness	ALS has not yet affected the patient's breathing ability
1	Limited activity because of SOB	The patient reports shortness of breath (SOB) with exertion or when performing daily activities
2	Using BiPAP device at night	The patient uses Bi-level Positive Airway Pressure (BiPAP) device when sleeping. However, BiPAP is not required when awake
3	Using BiPAP device during the day	The patient uses BiPAP device during the day
4	Using a ventilator	The patient is using a ventilator
Speech		
0	No weakness	ALS has not yet affected the patient's speaking ability
1	Affected speech	The patient's speaking ability is slightly affected resulting in slurred speech. Verbal communication is still possible
2	Using a device to assist communication	The patient's speaking ability is significantly affected. It is difficult to understand the patient. The patient occasionally uses a communication device such as iPad, writing tablet, or writing to communicate
3	Losing the ability to talk	The patient is not able to verbally communicate and requires a communication device all the time

for the arm segment (losing useful function of one arm). Second, because not all bigrams or trigrams had predictive power, we estimated the tollgates reached using a classification tree with bigrams and trigrams as the predictors [20]. We trained the classification tree model using tollgate data manually extracted from clinical notes for 10% of all patient clinic visits. Then, we estimated the tollgates for the remaining 90%. This classification tree approach provided a fast-initial tollgate classification and helped determine which section of the clinical notes to review for verifying whether the classification was correct or not. To ensure quality and accuracy of the extracted data, we verified the accuracy and

consistency of the tollgate estimations from the classification tree through a manual review of the associated sections of the clinical notes.

Handling missing data

514 patients visited the ALS Clinic at least once with a median of 2 visits per patients. Among patients who had more than one visit, the median time between consecutive visits was 3.13 months. ALS Clinic's recommended visit frequency is every 3 months. Therefore, to simplify statistical analysis, we assumed evenly spaced data points collected for each patient in every 3 months for a follow-up period of up to 1-year from the first visit. Around 90% of the evenly spaced visits matched the actual visits. However, the remaining 10% (143 visits) were missed/postponed (i.e., more than 1.5 months away from the closest actual visit). The missing data points (i.e., regular clinic visits that were missed) were imputed by a linear interpolation technique (see Online Resource I for details) [21, 22]. In addition, 83 data points (6% of actual visits) had missing ALSFRS-R scores which were imputed using a classification tree approach implemented in the *MICE* package in *R* [23].

Statistical analysis

We conducted Kaplan–Meier analyses using the *Survival* package in *R* to derive the probability of reaching (and passing beyond) each tollgate at each clinic visit for all segments considering a 12-month follow-up period after the first clinic visit [24]. That is, our analysis captured ALS progression in the first five consecutive clinic visits. Patients who dropped out or died before the end of this follow-up period were censored [24]. Note that Kaplan–Meier analysis is a reliable approach to analyze censored data, as it incorporates the effect of drop-outs into the resulting estimations [25, 26]. The illustrations (see Figs. 1b, 3) from the Kaplan–Meier analyses are presented in the form of reverse Kaplan–Meier (reverse-KM) curves, representing the probability of reaching at or being worse than a tollgate level, to increase their interpretability.

Data availability

To facilitate further research in the development of clinical decision support systems for ALS clinics, anonymized data not published within the article could be shared by request from a qualified investigator with the condition that the request is approved by the institutional review board and a data use agreement is signed between Mayo Clinic and the institution of the requesting investigator.

Results

Patient characteristics

In our patient cohort, there were slightly more males (55% male), the median age was 64 (min 24, max 93), and the mean ALSFRS-R score at the first clinic visit was 36 out of 48 (a lower score indicates more significant overall impairment). In total, 514 (100%), 346 (67%), 264 (51%), 199 (38%), and 164 (32%) patients attended their first, second, third, fourth, and fifth visits, respectively. At the first clinic visit, 437 patients out of 514 reported that they were either taking (25%) or not taking (75%) riluzole. At their first clinic visit, 93% of patients displayed some level of limb weakness. Among them, 17% had only arm weakness, 10% had only leg weakness, and both arms and legs were affected in the remainder (73%). Around 77% had bulbar weakness at the first clinic visit, with 21% (of 77%) having only speech difficulties without any swallowing involvement and 8% (of 77%) having only swallowing difficulties without any speech involvement. The breathing segment was affected in 60% of the patients at their first clinic visit. At the first clinic visit, 20% of the patients used a non-invasive breathing support (breathing-level = 2–3), 8% had a feeding tube (swallowing-level = 3), and 5% were anarthric (speech-level = 3). Moreover, 17% of the patients used a wheelchair (leg-level = 4) at the first clinic visit and 7% of the patients were completely dependent on a wheelchair (leg-level = 5).

Tollgate profile over time

Figure 1a illustrates the proportions of patients at each tollgate at each visit (among those who attended the visit) for all segments over a 12-month period. In each segment, the majority (60–83%) of the patients had mild weakness/disability or worse (tollgate level ≥ 1) at the first visit. The proportion of patients at lower tollgate levels (less clinically affected, i.e., levels 0–1) was greater for the speech (80%), swallowing (65%) and breathing (80%) segments compared to arm (38%) and leg (46%) segments. The proportions of patients at higher tollgates (i.e., levels 3–5) in each segment naturally increased at each visit due to the irreversible nature of ALS. The rates of progression to higher tollgate levels were greater in the arm, leg, and swallowing segments than the speech and breathing segments. For example, over a 12-month period, the lowest and highest rate of progression from lower (i.e., levels 0–2) to higher tollgates (i.e., levels 3–5) were observed in breathing (3%) and swallowing (16%) segments, respectively.

The reverse Kaplan–Meier (reverse-KM) curves in Fig. 1b show the probability of reaching at or being

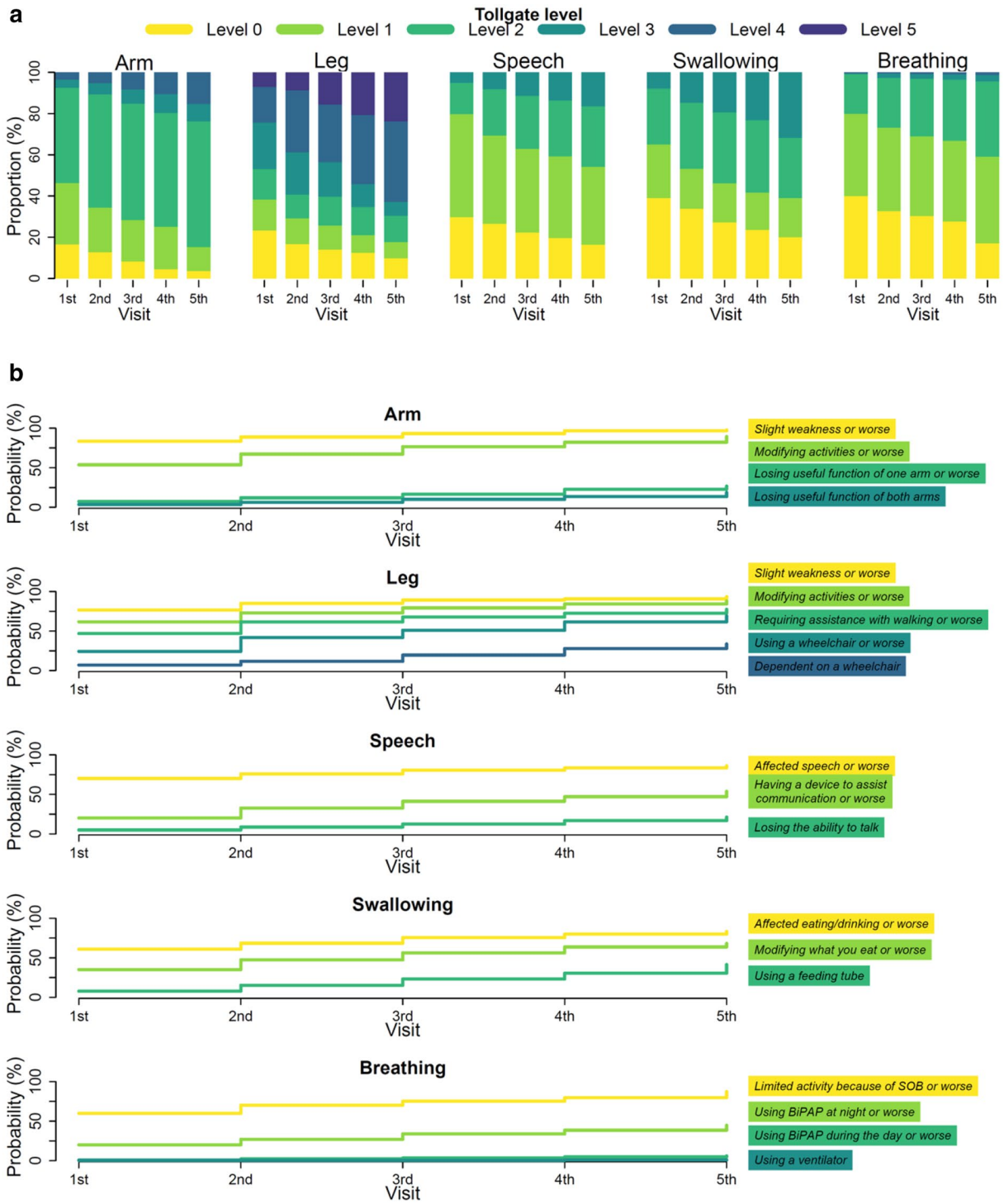

Fig. 1 **a** Proportion of patients at each tollgate at each clinic visit over the 12-month period from the initial ALS clinic visit. **b** Reverse Kaplan–Meier curves representing the probability of patients reaching at or being worse than a certain tollgate level over the 12-month period from the initial ALS clinic visit. Note that level 4 is not applicable to speech and swallowing segments, and level 5 is only applicable to leg segment. Please refer to Table 1 for the definition of tollgate levels

worse than a certain tollgate at each visit for the overall patient cohort. The curves with steeper increase over time imply more aggressive ALS progression. Figure 1b helps identify segments and tollgate levels associated with aggressive ALS progression and informs about the likelihood and timing of needing assistive devices within

our patient cohort. For instance, the likelihood of using a wheelchair or similar equipment drastically increases from 24.3% (CI 20.5–27.9%) to 69.2% (CI 63.1–74.2%) within 1 year leading to 33.7% (CI 27.6–39.3%) of ALS patients becoming dependent on a wheelchair (leg-level = 5) by the end of the year. Similarly, the likelihood of using a feeding tube (swallowing-level = 3) or BiPAP (breathing-level > 1) increases from 7.8% (CI 5.4–10.1%) to 41.4% (CI 34.9–47.3%) and from 20% (CI 16.5–23.4%) to 44.8% (CI 38.6–50.3%) within 1 year, respectively. Using BiPAP day-and-night or ventilator was uncommon within the 1st year (< 7%). Half of all patients were eventually at a level requiring a communication-assistive device or worse (speech-level ≥ 2) and the likelihood of completely losing the ability to speak 12 months after the first clinic visit (speech-level = 3) was relatively lower (21.5%, CI 16.2–26.4%).

Segment-based tollgate pathways

Figure 2 illustrates individual-level ALS progression in the leg segment for our patient cohort. Patients are stratified by their initial tollgate levels at the first clinic visit, each of which is represented by a single tree. Each tree has multi-colored and weighted branches manifesting the number of patients progressed to different tollgates from one visit to the next. Note that dropouts are not illustrated for the sake of brevity. Following connected branches allows building different disease progression pathways. For instance, patients who needed assistance with walking at the first clinic visit (leg-level = 3) are illustrated by the tree under the red arrow. This tree has 116 patients. 81 of these patients had a second visit (35 patients dropped out after the first visit); 39 (48%) stayed at the same tollgate, while 38 patients (47%) progressed to the tollgate "using a wheelchair at least sometimes" (leg-level = 4), and the remaining 4 (5%) patients became dependent on the wheelchair (leg-level = 5). In the third visit (month 6), among 39 patients who were at leg-level 3 in the second visit, 10 (12%) patients dropped out, 19 (23%) patients stayed at the same tollgate, 9 (11%) patients moved to leg-level 4. Similar illustrations for other segments can be found in Online Resource II.

Tollgate-specific ALS progression based on the affected segments at the first clinic visit

The reverse-KM curves in Fig. 3 characterize the tollgate-based ALS progression for different patient phenotypes defined by the affected segments at the first clinic visit. With this phenotype definition, we captured the effect of initial ALS progression on the future ALS progression. We classified each patient into a phenotype by designating a code for each affected (level > 0) functional segment at the first visit: A = arm, L = leg, Sp = speech, Sw = swallowing, and B = breathing. Like in Fig. 1b, the reverse-KM curves in Fig. 3 specify the likelihood of being at a specific tollgate or worse at each visit for each patient phenotype. For instance, Fig. 3g shows that the likelihood of requiring assistance with walking or worse increases from 46.9% (CI 42.4–51%) to 77.5% (CI 72.3–81.7%) in a year for the overall cohort

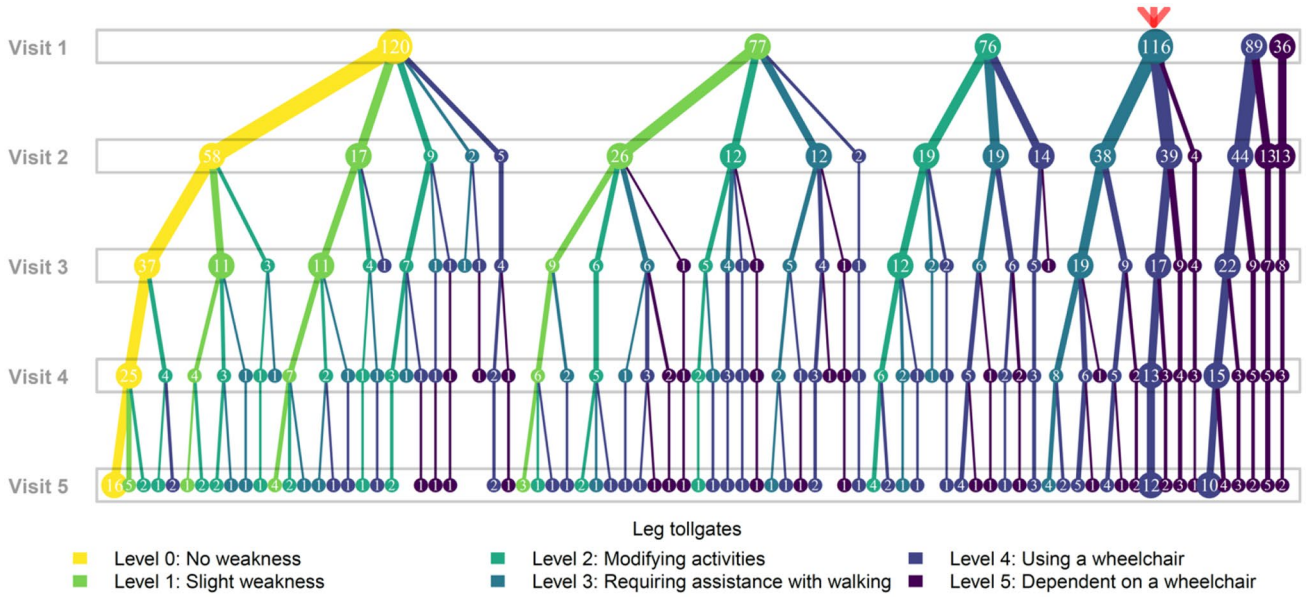

Fig. 2 Individual tollgate progression pathways for the leg segment over the 12-month period following the first ALS clinic visit. Please refer to Online Resource II for the tollgate pathways of other segments

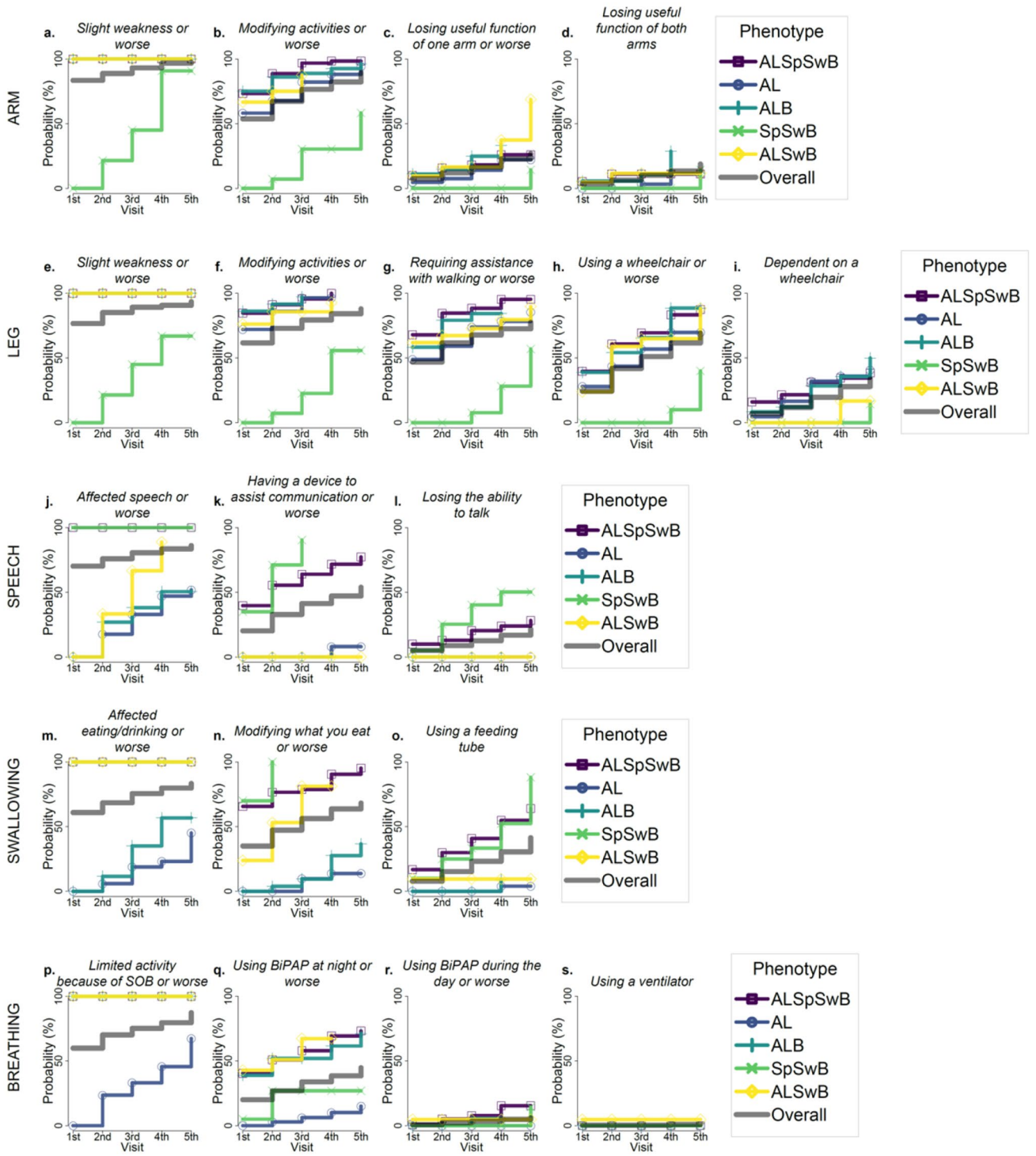

Fig. 3 Reverse Kaplan–Meier curves representing the probability of being at a particular tollgate level or worse for a set of patient phenotypes over the 12-month period from the first ALS clinic visit. Each graph is for a specific segment and tollgate level. Patients are stratified by phenotypes based on the affected segments at the first clinic visit. Each line in the graphs corresponds to a patient phenotype where the initially affected segments are denoted by a combination of the letters: A (arm), L (leg), Sp (speech), Sw (swallowing), B (breathing). The lines labeled as "Overall" illustrate the corresponding probabilities for the entire cohort of patients in the study. Note that, among all possible patient phenotypes, only the results for the most common five are illustrated: *ALSpSwB* (131 patients), *AL* (43 patients), *ALB* (36 patients), *SpSwB* (20 patients), *ALSwB* (21 patients). *SOB* shortness of breath, *BiPAP* bi-level positive airway pressure

patients in the study, while the same likelihood for patients with *ALSpSwB* (all segments affected at the initial visit) and *ALB* (arm, leg, and breathing segments affected) phenotypes increases from 67.9% (CI 59–75%) to 95.4% (CI 84–98.7%) and from 58.3% (CI 38.7–71.7%) to 84.4% (CI 60.6–93.8%), respectively.

Figure 3 provides important observations and insights. First, the reverse-KM curves in Fig. 3 inform about the timing of various interventions and assistive device needs within 1 year from the initial visit for various phenotypes. For instance, Fig. 3h shows that patients with phenotypes *ALSpSwB* and *ALB* are very likely to use a wheelchair (69% and 66%, respectively) by their third visit, and up to 45% of those patients may be dependent on a wheelchair by the end of the year. On the other hand, for patients who had weakness only in speech, swallowing, and breathing (*SpSwB*), 10% may need a wheelchair at their fourth visit and 40% will require it at the 1-year mark.

The above examples imply that the timing of the transition from one tollgate level to the next may significantly differ among patients with different phenotypes. The differences are especially notable for speech, swallowing, and breathing segments. For example, Fig. 3k shows that for phenotypes *ALSwB, ALB*, and *AL*, whose speech segment was not affected at the first visit, the likelihood of having a device to assist communication or worse (level 2 and above) remains low (< 10%) within 1 year, whereas the same probability jumps from 39.7% (CI 30.7–47.5%) to 77.4% (CI 62.1–86.5%) for *ALSpSwB* patients and from 35% (CI 10.3–52.9%) to 90.4% (CI 98.4–42.4%) for *SpSwB* patients within the same follow-up period. This indicates that ALS patients without any speech involvement at first visit in ALS Clinic are very unlikely to have a need for assistive communication devices in the subsequent year. Moreover, Fig. 3o illustrates that a mere 2% of patients with no swallowing involvement (AL and ALB) at their first visit may require a feeding tube in 6 months (by the 3rd visit). This number is much higher (38%) for those patients with involvement in the swallowing segment at their first visit.

As expected, for most phenotypes, the reverse-KM curves corresponding to segments with involvement in the first visit are above the ones with no involvement, e.g., compare phenotypes with speech segment involvement (*ALSpSwB* and *SpSwB*) versus the others (*AL, ALB*, and *ALSwB*) in the reverse-KM curves for the speech segment. However, the reverse-KM curves corresponding to a specific tollgate level for two different phenotypes with some common segment involvements at the initial visit may still display significant differences. For example, Fig. 3q shows the likelihood of using BIPAP at night or a worse tollgate level. While the breathing segment is initially affected for both *ALB* and *SpSwB* phenotypes, the reverse-KM curve for *SpSwB* (the likelihood increased from 5 to 26.973.1% in a year) is much lower than that for *ALB* (the likelihood increased from 38.9 to 71.2% in a year).

Discussion

We have introduced a new staging system, TASS, to monitor ALS progression. TASS was designed based on expert opinion provided by the ALS Clinic team members practicing at Mayo Clinic, Rochester, MN and analyzed using a unique dataset from the same clinic. Our patient cohort reasonably represents the general ALS population. There are more males in our patient cohort (55%) and majority of them are older than 50 (mean age 62.8), comparable to other studies which report that around 60% of ALS patients are male and the mean age of diagnosis is 58–63 [27, 28]. The mean ALSFRS-R score at the first visit and the mean follow-up period in our patient cohort (i.e., 36 and 3.76 months) is also close to that reported in similar studies (e.g., 34 and 3.5 months, respectively [29]).

The overall patterns in the distribution of impairments as measured by the tollgate levels among the patient cohort are also consistent with observations reported in the literature. In our patient cohort, the proportion of ALS patients reaching high tollgate levels (level ≥ 2) within a year of follow-up was greater in the limb segments than the bulbar and breathing segments. This is expected as the literature commonly reports higher prevalence of limb-onset in ALS patients [4]. Breathing was usually the least affected segment across all patients and clinic visits in our patient cohort, as respiratory functions are typically affected in later stages of ALS [30]. Very few patients in our cohort ever used BiPAP during the day or a ventilator within the 1st year of follow-up, which is consistent with the literature [31].

By categorizing patients into phenotypes based on the segments clinically involved at the time of the first ALS clinic visit, we observed diverse sets of ALS progression pathways as illustrated in Fig. 2. For instance, if a patient is already using a cane to assist walking at the first clinic visit, there is a high likelihood (74%) of using a wheelchair in the next 6 months. However, the likelihood is much lower if he or she did not need a cane in the first visit (48%). While these results are qualitatively not surprising, the quantitative data can be useful for individual patient counseling. Moreover, based on the combination of affected segments at the first clinic visit, the likelihood of reaching specific tollgates over time may vary significantly (see Fig. 3). For example, the likelihood of requiring a wheelchair for patients, who have no limb weakness but are affected in all other segments, is below 15% for the entire year following the first clinic visit. Thus, practitioners may recommend delaying the acquisition of a wheelchair for these patients.

As illustrated above, TASS efficiently depicts ALS progression pathways and is straightforward to interpret. Using the information from tollgate-based ALS progression pathways, clinicians can better inform their patients about how their condition will progress, when to expect critical functional ability losses and assistive device needs for different functional segments, and how to prepare themselves for prospective changes in their lives. Providing such recommendations based on segments involved at the first clinic visit (phenotype) would facilitate individualized care of ALS patients.

In the current practice, ALSFRS-R is a commonly used tool for estimating survival and exploring risk factors for ALS progression [7, 11, 32]. Although there are studies estimating how the aggregate ALSFRS-R will change in future for individuals [33, 34], the aggregate score in future visits does not necessarily specify what new levels of impairment or device needs are to be expected. In the best case, the ALSFRS-R-based progression models might indicate the occurrence of a specific critical event once the ALSFRS-R score passes a certain threshold (e.g., ALSFRS-R of 21 or less implies significant disability) [35]. The usage of aggregate ALSFRS-R score as a metric has been criticized in the literature and there have been suggestions to consider the score for each question in ALSFRS-R separately [36]. TASS offers an effective alternative to fill this gap. Estimating the order and timing of tollgates can prove to be valuable information for the patients, their caregivers, and clinicians to better prepare for the future. TASS could be a useful instrument to track the ALS natural history and predict the future progression. While there is overlap between the tollgates of TASS and the items in ALSFRS-R (see Online Recourse III—Figure OR-6 for a correlation analysis between the tollgates of each functional segment and scores of relevant ALSFRS-R questions), these two instruments have some differences. First, ALSFRS-R scores are generally based on the declaration of a patient (or a caregiver), whereas tollgates are extracted from clinical notes from a comprehensive examination [37] at a clinic visit. Therefore, the assessment of the progression captured by the tollgate mechanism might be a more reliable source of data compared to that by ALSFRS-R, considering that patients' self-assessments of their physical impairments may be highly associated with their psychological status [38]. Second, by design, ALSFRS-R captures a patient's current condition independent of the patient's disease history. As a result, the score of individual ALSFRS-R items may increase from one survey point to the next implying an improvement in the patient condition despite the fact that ALS is an irreversible disease [18]. Therefore, TASS, which is a non-improving staging scheme, might be more suitable for modeling progression pathways. We acknowledge the existence of other staging systems for ALS progression which are effective in tracking the overall progression of the disease. Our system is attempting to combine involvement (King's) and loss-of-function (MiToS) and also include degrees of impairment of functioning.

There are certain limitations of our study. First, the sample size is limited, which is a common issue as ALS is a rare disease [39]. Second, because the disease onset dates are not readily available in our dataset, we have based our analysis on the time of the first ALS clinic visit, which is a common practice in the medical literature [40, 41]. We realize that categorizing patients into groups based on segments involved at the first clinic visit may result in combining some patients who experienced varying progression pathway until that moment in time; for example, a bulbar-onset patient and limb-onset patient may be in the same TASS segment category by the time they are first seen in the ALS Clinic. Nonetheless, our approach closely mimics the situation faced by providers in the ALS Clinic; namely to assist with counseling based on current clinical status. Future work will focus on understanding the pre-ALS Clinic pathway and assess how that information may improve our current work and also to incorporate a learning component to modify models of progression based on newly acquired data (e.g., at subsequent ALS Clinic visits).

Another limitation of our study is that around 70% of the patients in our cohort dropped out and did not have all follow-up clinic visits by the end of 1-year period. In addition, we were not able to reliably track progression past the 1-year mark given the low follow-up numbers. We realize that censored data may bias our results to some extent. Patients progressing more rapidly or those more severely affected may not be able to travel to the ALS Clinic; on the other hand, patients progressing very slowly may not feel the need to attend all scheduled clinic visits. As these factors were not controlled (and we do not know the specific reason why patients did not complete a full 1-year follow-up), it is difficult to estimate this effect; our conclusions pertain to those patients who are attending the ALS Clinic for follow-up. Additional analysis did reveal that the ALSFRS-R scores of dropout patients were always lower (3–6 points, p value < 0.01) than those of non-dropout patients at each visit, suggesting the loss of follow-up was likely related to more severe disease. We feel, however, that the information provided by our analysis is still very important as this study reflects on the patients we are following at the ALS Clinic over time. Note that when estimating the likelihood of passing each tollgate level, we performed the Kaplan–Meier analysis, which is specifically designed to incorporate the effect of censoring [26].

Conclusion

We show that TASS can be a useful clinical tool capable of capturing ALS progression and variability among patients. Although TASS could be useful for clinicians to improve

their practice for the management of ALS patients, there are some issues to be addressed in future studies. First, while ALSFRS-R scores are widely available, some of the tollgate information needs to be extracted from free-text clinical notes. However, deriving tollgate-based progression pathways is still feasible given the recently developed efficient natural language processing tools and expanded ability to capture and analyze more discrete clinical data from electronic health records. Moreover, we investigated the association between the tollgates of each functional segment and scores of relevant ALSFRS-R questions and observed strong correlations between them (see Online Resource III). This suggests that ALSFRS-R scores combined with other factors such as ALS history (onset time, onset type, etc.) and demographics may be used to accurately estimate the tollgate levels of a patient at a particular time (i.e., mapping associated scores of ALSFRS-R questions to tollgate levels).

Second, although the analysis in Fig. 3 demonstrates the significance of the ALS phenotype (based on affected segments in the first visit) on future ALS progression, more comprehensive studies utilizing patients' ALS symptoms or impairments at multiple time points and several other factors (e.g., age, onset age, onset region) may result in a better characterization and prediction of ALS progression [42]. Further studies are needed to estimate tollgate-based ALS progression beyond a 1-year follow-up period with a goal of better educating patients, caregivers, and providers on the anticipated progression of their disease. Although achieving this requires tollgate information from a larger patient cohort, future work will explore whether a dataset can be attained by mapping the ALSFRS-R data in the available databases, such as the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database [43], into tollgates in TASS. If ALSFRS-R information in the PRO-ACT database can be accurately translated into tollgate information for TASS, the analysis we presented in the result section could be extended to a longer follow-up period. Such a prospective analysis would also eliminate all limitations of this analysis such as small sample size, high drop-out rates (drop-outs are less common in PRO-ACT data), and lack of onset data (available for a large number of participants). Our initial findings about this future research direction are quite promising (see Figure OR-7).

In conclusion, our main contribution is capturing the future ALS progression of patients and illustrating it using an alternative staging system, TASS, which can be clinically useful to ALS patients, caregivers, and clinicians to estimate the timing of critical life events and assistive device needs. Future work will focus on validation in larger and more robust clinical datasets and exploration of individualized predictive modeling of the course of ALS progression.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard This study was reviewed by the Mayo Clinic Institutional Review Board and deemed as an exempt study.

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