Development and validation of a clinically useful risk score for dysphagia onset in persons diagnosed with amyotrophic lateral sclerosis

A thesis submitted by

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Abstract

Dysphagia is common, increases mortality, and reduces quality of life in persons diagnosed with ALS. As such, timely and informed decision-making surrounding dysphagia management is critical. The goal of this work was to develop a risk prediction model for the timing of dysphagia onset in this population.

Data from the Pooled Resource Open-Access ALS Clinical Trials Database was used for model development and validation. Dysphagia onset was defined as a score of <4 on the swallowing question of the ALS Functional Rating Scale (ALSFRS). A multivariable Cox proportional hazards regression model was created and used to estimate the 3, 6, and 12-month risk of dysphagia onset. Model discrimination and calibration were calculated. External model validation was completed.

A total of 3,948 participants were included in the study, 2057 in development cohort and 1891 in the validation cohort. The final model included 7 regularly collected clinical variables. These included spinal onset, ALSFRS bulbar, fine and gross motor scores, presence of respiratory impairment, rate of decline, and time from diagnosis. The model had an optimism corrected c-statistic of 0.70 and a calibration slope of .96. The model demonstrated good discrimination (C statistic = .75) and calibration on external validation.

Results of this work are expected to improve the timeliness of dysphagia diagnosis by identifying those at high risk for dysphagia development, and therefore in need of a comprehensive swallowing assessment.

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List of Abbreviations

(ALS) Amyotrophic Lateral Sclerosis
(ALSFRS) ALS Functional Rating Scale
(ALSFRS-R) ALS Functional Rating Scale-Revised
(NEALS) Northeast ALS Consortium
(PALS) Person's diagnosed with amyotrophic lateral sclerosis
(PEG) Percutaneous endoscopic gastronomy
(PRO-ACT) Pooled Resource Open-Access Clinical Trial Database
(PROBAST) Prediction model study Risk of Bias Assessment Tool
(SLP) Speech language pathologist
(TRIPOD) Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

Chapter 1: Introduction

Amyotrophic Lateral Sclerosis (ALS) is a fatal neuromuscular disease characterized by the rapid degeneration of both upper and lower motor neurons of the brain and spinal cord, resulting in progressive deterioration of muscle function throughout the body.[1] With a national prevalence estimate of nearly 16,000 persons,[2] ALS is one of the most common disabling neuromuscular diseases among adults in the United States. The average life span after diagnosis is approximately two to five years.[3,4] Symptom onset of the disease is variable with the initial presentation of ALS observed in the limbs (spinal onset, 70% of cases) throat, tongue, jaw and face (bulbar onset, 25% of cases), or respiratory system (respiratory onset, 5%). Regardless of the site of symptom onset, the loss of swallowing function is expected over the course of the disease as a result of the deterioration of muscle function of the face, mouth, pharynx and larynx.[5]

Difficulty swallowing (dysphagia), caused by weakness and/or spasticity of the muscles of mastication, affects up to 85% of persons diagnosed with ALS and is one of the most severe and debilitating symptoms of the disease.[6–8] The timing of the development of dysphagia is highly variable and ranges from 8 to 50 months.[9,10] Dysphagia-related complications, including aspiration pneumonia and malnutrition, markedly increase the risk of death.[11,12] Furthermore, functional swallowing impairments, including coughing/choking during meals, increased fatigue with eating, and prolonged eating duration have a significant impact on psychosocial well-being and quality of life in this population.[13]

Because treatment options for persons with ALS (PALS) are limited, best practice management of these patients involves symptom management and palliative care through multidisciplinary care clinics.[14] Multidisciplinary care has been found to extend survival, reduce hospitalization, and improve quality of life in PALS.[14] Typical members of a multidisciplinary care team for PALS include physicians, physical therapists, occupational therapists, dietitians, social workers, respiratory therapists, nurse case managers and speech language pathologists (SLP). SLP's assess, manage, and educate patients on the loss of both speech and swallowing.[14] Physicians caring for PALS need to carefully select which patients to refer to which specialties at which times, and, because time is short in contemporary clinical encounters, clinicians often perform abbreviated evaluations and defer their referral decisions to a later time.[15]

At present, there are no clinical guidelines for the identification, evaluation, and management of dysphagia in PALS and as such, there is large variability in practice patterns.[15] A recent survey of multidisciplinary care clinics in the US revealed that, despite the high prevalence of dysphagia and the significant impact it has on overall well-being in this population, regular referral patterns for SLP evaluations were low, averaging approximately 60% percent.[15] Although routinely collected measures such as weight loss, bulbar scales and site of symptom onset would appear at the surface to be indicators of dysphagia, even among PALS referred to SLP's, clinical evaluations of swallowing are performed only 55% of the time.[15] Moreover, practice patterns for the placement and timing of percutaneous endoscopic gastronomy (PEG) tubes are highly variable.[15] This suggests PALS with dysphagia are inadequately prepared to make timely decisions surrounding eating and drinking which significantly impact their quality of life.

Best practice management of dysphagia should include the early identification of swallowing impairment, appropriate diet modifications and postural adjustments during meals, and timely implementation of PEG tube placement.[13] However, variability in the clinical presentation and progression of swallowing impairment in PALS in conjunction with the significant time constraints faced by SLPs assessing these patients make early identification and clinical management of dysphagia a significant contemporary challenge.[16] Delayed management of dysphagia is a risk factor for malnutrition,[17] which is related to increased mortality in this population.[1] Research directed at improving the early identification of dysphagia has been limited to physiologically-driven, single-institution studies with small sample sizes, making it difficult to control for the significant heterogeneity within this patient population. Additionally, assessment methodologies used in these studies are not well-suited for widespread use in busy multidisciplinary clinical settings and no practical clinical models are presently available to predict the onset of dysphagia.

All PALS are faced with making several critical decisions that directly impact their survival and quality of life as dysphagia develops, including the implementation of diet modifications and/or compensatory postural adjustments during meals and the placement of a feeding tube. Clinicians working with PALS need to provide patients with evidence-based information to help them make timely and informed decisions. At present, under-referral to SLPs, and underutilization of formal swallowing evaluations, place PALS at a significant disadvantage when the time comes for them to make timely and informed decisions regarding the management of their swallowing impairments.[15] When communication between clinicians and PALS regarding symptom management is

lacking, critical decisions are delayed.[18] Poorly timed decisions have been found to increase emergency hospital admissions, compromise patient health, safety, and quality of life, and place increased burden on caretakers.[19]As such, early identification of patients at varying risks for developing dysphagia is critical to improving the health and quality of life for PALS.

To address the lack of evidence-based guidelines for the assessment and management of speech and swallowing impairments in PALS, the Northeast ALS Consortium (NEALS) recently formed a committee of practicing clinicians who are working to establish best practice guidelines for dysphagia management.[20] Research is currently underway to determine clinically feasible methodologies by which to evaluate and monitor the physiologic declines of swallowing function in PALS. Our work proposes to address the critical need for a relatively brief clinical tool by which to identify PALS at high risk for the development of dysphagia. Determining the presence of dysphagia by self-report has known limitations but several strengths.[21,22] Self-reported dysphagia scores are regularly collected in busy multidisciplinary ALS clinics[15] and may be helpful in identifying patients who require referral to an SLP and more comprehensive assessments of their swallowing function. However, a recently published reflection on the management of bulbar function in this patient population expresses concerns regarding the cost and feasibility of implementing routine physiologic bulbar assessment into clinical practice and highlights the urgent need for a quick, clinically accessible tool to help guide timely clinical management of bulbar impairments.[23]

As such, the goal of this work is to develop a simple, clinically useful, prediction model that identifies PALS at varying risk for developing dysphagia. Dysphagia risk

prediction models have been used to predict swallowing impairments after radiation in persons diagnosed with head and neck cancer [24], in persons following radiation for lung cancer [25], and to predict recovery of swallow function and placement of PEG tubes in persons following a stroke.[26,27] We expect that a dysphagia risk score for persons diagnosed with ALS will help facilitate appropriate early referrals to SLPs and identify those in greatest need for comprehensive dysphagia evaluations, the first step towards improving the timeliness of dysphagia diagnosis and improving decision making surrounding feeding management.

Chapter 2: Predicting dysphagia development in persons diagnosed with amyotrophic lateral sclerosis.

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2.1 Introduction

Difficulty swallowing (dysphagia) occurs in 63-85% of persons diagnosed with ALS depending on their site of symptom onset.[10] The timing of dysphagia onset in this population varies widely with limited understanding of the risk factors and timing for dysphagia development. Dysphagia-related complications, including aspiration pneumonia and malnutrition increase mortality and reduce quality of life in this population.[13,28] As such, timely and informed decision-making surrounding dysphagia evaluation and management, including diet modifications and feeding tube placement, is of great importance.

In the absence of life-prolonging treatments for persons with ALS, best practices involve symptom management and palliative care through multidisciplinary care clinics.[14] Physicians caring for patients diagnosed with ALS carefully select which patients to refer to which specialties at which times, but unanticipated referral decisions may be postponed to a later time.[15] At present, in the absence of clinical guidelines, large variability in practice patterns for the identification, evaluation, and management of dysphagia in PALS exist.[15] A clinically accessible and reliable tool to identify patients at high risk for dysphagia development could facilitate comprehensive dysphagia assessment.

Clinical prediction models allow for an individualized approach to medical decision-making and have become widely used across fields in medicine. Potential benefits of a dysphagia prediction tool for persons diagnosed with ALS include improved timely dysphagia diagnosis and intervention. Leveraging data from the Pooled Resource Open-Access ALS Clinical Trials Database (PRO-ACT), which includes more than

10,700 de-identified clinical patient records pooled from 23 Phase II/III ALS clinical trials across the world,[29] the objective of this work was to develop and externally validate a multivariable clinical predictive model determining the 3-month, 6-month, and 12-month risk of self-perceived dysphagia development in persons diagnosed with ALS.

2.2 Methods

2.2.1 Study Population

The development cohort was derived from the PRO-ACT database.[29] PRO-ACT is the largest database containing clinical trial data from persons diagnosed with ALS and, at present, includes over 10,700 de-identified clinical patient records pooled from 23 Phase II/III clinical trials between the years of 1990-2015 across the world. None of the interventions tested proved to be clinically effective. This dataset was selected for its size and inclusion of easily and reliably obtainable clinical variables relevant for model development. Participants were excluded from this study if they 1) had no reported ALS Functional Rating Scale or Functional Rating Scale - Revised (ALSFRS or ALSFRS-R) scores in the dataset or 2) had a score of less than 4 on the swallowing question of the ALSFRS or ALSFRS-R on their first study visit, indicating the presence of dysphagia at time of study entrance. The ALSFRS-R differs from the ALSFRS only in the respiratory subscale, as two additional respiratory questions were added to the ALSFRS to create the ALSFRS-R.

Prior to model development, the more recent participant PRO-ACT data, (i.e. participants with ALSFRS-R scores) were set aside for external model validation. The study was reviewed and approved by the Institutional Review Board at Tufts Medical

Center in Boston, Massachusetts. Informed consent was waived due to the de-identifiable nature of the data.

2.2.2 Outcome

The outcome of interest was time to the development of dysphagia at 3, 6, and 12-month time horizons and was defined as a change in score from 4 (i.e. no impairment) to <4 (i.e. any impairment) on the swallowing question of the ALSFRS or ALSFRS-R. These time horizons were selected as they represent typical times that patients would be returning for regularly scheduled clinic visits and thereby can help healthcare providers identify if and when a comprehensive swallowing assessment by a speech language pathologist might be appropriate. Participants who did not develop dysphagia were censored at their last recorded ALSFRS score or at 365 days, whichever came first.

2.2.3 Variable Selection

Based on the published literature[1,30] and expert opinion, the selected candidate variables included age, sex, race, site of symptom onset, time from diagnosis, weight, height, forced vital capacity, slow vital capacity, riluzole use, family history of ALS, ALSFRS bulbar subscale score, ALSFRS fine motor subscale score, ALSFRS gross motor subscale score, ALSFRS respiratory subscale score, and whether or not the participant received the placebo or treatment in the clinical trial. ALSFRS bulbar, fine motor, and gross motor scale scores each range from 0-12 with 12 being no impairment and 0 being severe impairment. The ALSFRS respiratory subscale includes one question and ranges from 0-4, with 4 being no impairment and 0 being severe impairment. To account for disease progression, a rate of decline variable was calculated as the total ALSFRS score at the first visit in the dataset divided by the time since symptom onset in

months.[31] ALSFRS total scores were calculated by summing the 4 ALSFRS subscale scores. Total ALSFRS scores range from 0-40 with 40 being no impairment and 0 being severe impairment. For participants with ALSFRS-R scores rather than ALSFRS scores, we derived total ALSFRS scores from ALSFRS-Revised (ALSFRS-R) scores, by excluding the scores on the two added respiratory questions when summing the subscale scores.[32] To account for disease progression, a rate of decline variable was calculated as the total ALSFRS score at the first visit in the dataset divided by the time since symptom onset in months.[31] Rate of decline was log transformed to normalize its skewed relation to the outcome. Site of symptom onset data were binary and categorized as either spinal or not spinal. All predictor variables were obtained at the first visit recorded in the dataset.

Missing data for candidate variables were imputed by multiple imputation to create 10 complete data sets using predictive mean matching for imputing continuous variables; logistic regression for imputation of binary variables; and polytomous logistic regression for imputation of categorical variables. Variables missing over 50% including family history of ALS, forced vital capacity scores, and slow vital capacity scores, were excluded from the model.

2.2.4 Statistical Analysis

A multivariable Cox proportional hazards regression model was fit to each of the 10 imputed data sets using all candidate variables as described above. Parameter estimates and standard errors were then pooled using Rubin's rules. Variables in the full model that were not associated with time to dysphagia development ($p>.05$) were removed in the estimation of a simplified model, with the exception of site of symptom

onset which was forced into the model because of its well-accepted association with the dysphagia outcome. A likelihood ratio test was performed to assess for differences between the full and simplified model.

Both the full and simplified models were assessed for discrimination, calibration, and potential for over-fitting and optimism. Concordance statistics (c-statistics) were used to assess model discrimination. To assess model calibration, calibration plots at 3, 6, and 12-months compared observed and predicted outcomes. Internal model validation was used to assess for over-fitting and optimism using bootstrap resampling.[33] We used 200 bootstrap samples on each of the 10 imputed datasets to calculate a uniform shrinkage factor for both models. The uniform shrinkage factor from the full model was used to calculate optimism corrected model coefficients in the simplified model in order to avoid over-fitness. The c-statistic from the bootstrapped samples was averaged to calculate an optimism corrected c-statistic for both the full and simplified models.

The simplified model was evaluated in the split sample external validation dataset. The baseline hazard at 3, 6, and 12 months and shrunk beta coefficients from the developed model were applied to the external validation data set to estimate predicted outcomes. To determine clinical utility, decision curves were plotted for the simplified model. All statistical analyses were performed using RStudio version 1.2.1335.[34]

2.3 Results

The dataset contained a total of 10,723 participants. Of those, 4,216 participants were excluded as ALSFRS or ALSFRS-R data were not available. Initial scores <4 on the swallowing question of the ALSFRS or ALSFRS-R indicated the baseline presence of dysphagia, so these 2,559 participants were also excluded. Thus, 3,948 participants

remained eligible for study inclusion. After splitting the dataset, the model development cohort included 2,057 persons with 1,891 in the external validation cohort (Figure 2.1).

Participant characteristics for those with and without dysphagia development are included in Table 2.1. Participant characteristics by development and validation cohort are in included in Appendix Table 4.1. On average, those in the development cohort were heavier, had less time since diagnosis, were less likely to have spinal onset, were more likely to have respiratory impairment at baseline, were more likely to have been prescribed riluzole, and had a slightly higher rate of developing dysphagia within 12 months.

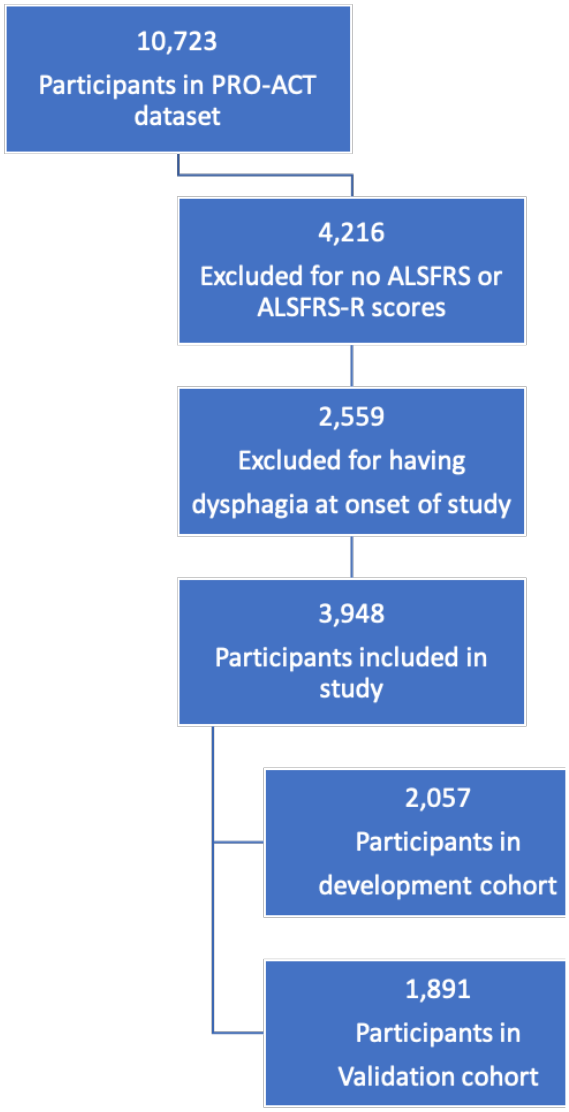


Figure 2.1. CONSORT diagram for study

The full model had good discrimination with a C statistic of 0.71. The model was well calibrated at each time horizon. Full model calibration plots are shown in Appendix Figure 4.2. The simplified model included site of symptom onset, presence of bulbar impairment at baseline, ALSFRS bulbar, fine motor, and gross motor subscale scores, presence of respiratory impairment at baseline, rate of decline and time since diagnosis.

The simplified model had good discrimination (C statistic = .71). Calibration was adequate across the three different time horizons (Figure 2.2. A-C). A likelihood ratio test revealed no differences in model fit between the full and simplified models (p=.29). Optimism corrected c-statistics were .70 for both models. The uniform shrinkage factor was .98 and .96 for the full and simplified models, respectively. Hazard ratios for both the full and simplified models are included in Table 2.2.

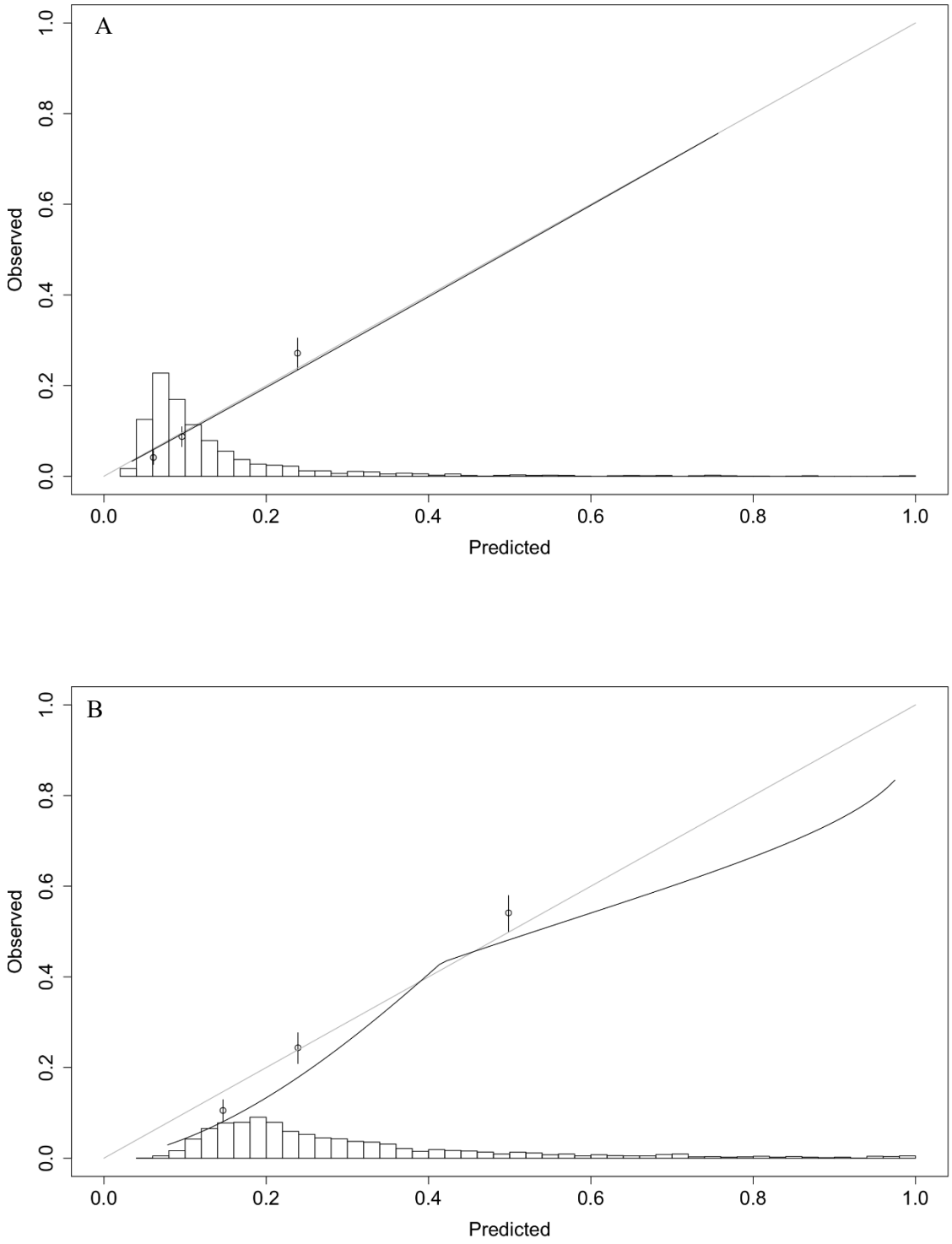
Table 2.1. Participant characteristics in the for those with and without dysphagia development

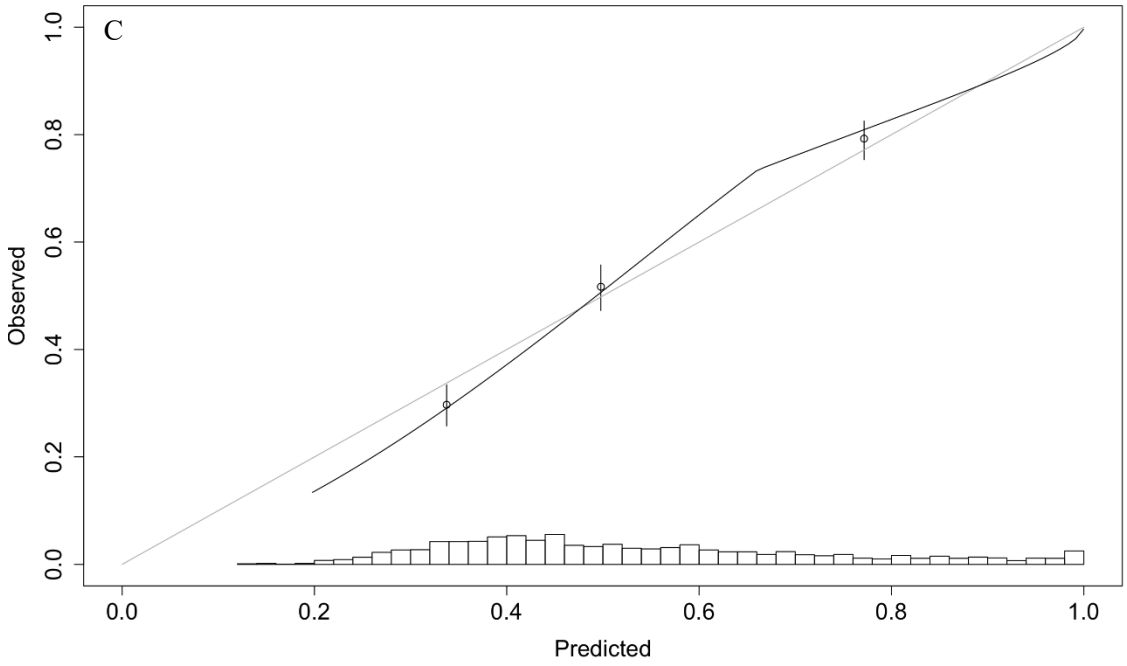
	No Dysphagia n=2265	Dysphagia n= 1683
Age (mean (sd))	55.11 (11.33)	55.37 (11.78)
Sex = Male (%)	1553 (68.6)	1091 (64.8)
Race (%)		
Caucasian	2082 (94.4)	1545 (94.4)
African American	24 (1.1)	18 (1.1)
Asian	46 (2.1)	34 (2.1)
Other	54 (2.4)	39 (2.4)
Height, cm (mean (sd))	171.66 (9.41)	171.03 (9.67)
Weight, kg (mean (sd))	78.21 (18.39)	77.38 (18.18)
Months from Diagnosis (mean (sd))	8.79 (9.34)	8.21 (9)
Rate of Decline, points per month (median (IQ range))	1.68 (1.06, 2.77)	1.81 (1.07, 2.84)
Site of Onset = Not Spinal (%)	188 (8.3)	341 (20.3)
ALSFRS Bulbar Subscale Score (0-12) (mean (sd))	11.75 (.6)	11.11 (1.15)
ALSFRS Fine Motor Subscale Score (0-12) (mean (sd))	8.63 (2.66)	7.69 (2.98)
ALSFRS Gross Motor Subscale Score (0-12) (mean (sd))	7.84 (2.87)	7.36 (2.96)
ALSFRS Respiratory Subscale Score (0-4) (mean (sd))	3.82 (.46)	3.7 (.57)
Riluzole Use = Yes (%)	1285 (73.2)	894 (72.6)

Table 2.2. Hazard ratios for full and simplified models

	Hazard Ratio Full Model (CI)	Hazard Ratio Simplified Model (CI)
Age	1.01 (1.00-1.01)	–
Sex = Male	0.94 (0.79-1.13)	–
Race		
African American	0.80 (0.45-1.44)	–
Asian	0.92 (0.57-1.50)	–
Other	0.89 (0.61-1.31)	–
Height (cm)	1.00 (0.99-1.01)	–
Weight (kg)	1.00 (0.99-1.00)	–
Months from Diagnosis	0.98 (0.97-1.00)	0.98 (0.97-1.00)
Rate of Decline (points per month)	1.50 (1.29-1.75)	1.48 (1.28-1.73)
Site of Onset = Not Spinal	1.05 (0.89-1.25)	1.07 (0.91-1.25)
ALSFRS Bulbar Subscale Score (0-12)	0.57 (0.53-0.60)	0.57 (0.53-0.60)
ALSFRS Fine Motor Subscale Score (0-12)	0.89 (0.86-0.91)	0.89 (0.87-0.92)
ALSFRS Gross Motor Subscale Score (0-12)	0.94 (0.92-0.97)	0.94 (0.91-0.96)
ALSFRS Respiratory Subscale Score (0-4)	0.78 (0.71-0.87)	0.78 (0.70-0.86)
Riluzole Use = Yes	0.94 (0.76-1.15)	–
Study Arm = Placebo	.96 (0.83-1.11)	–

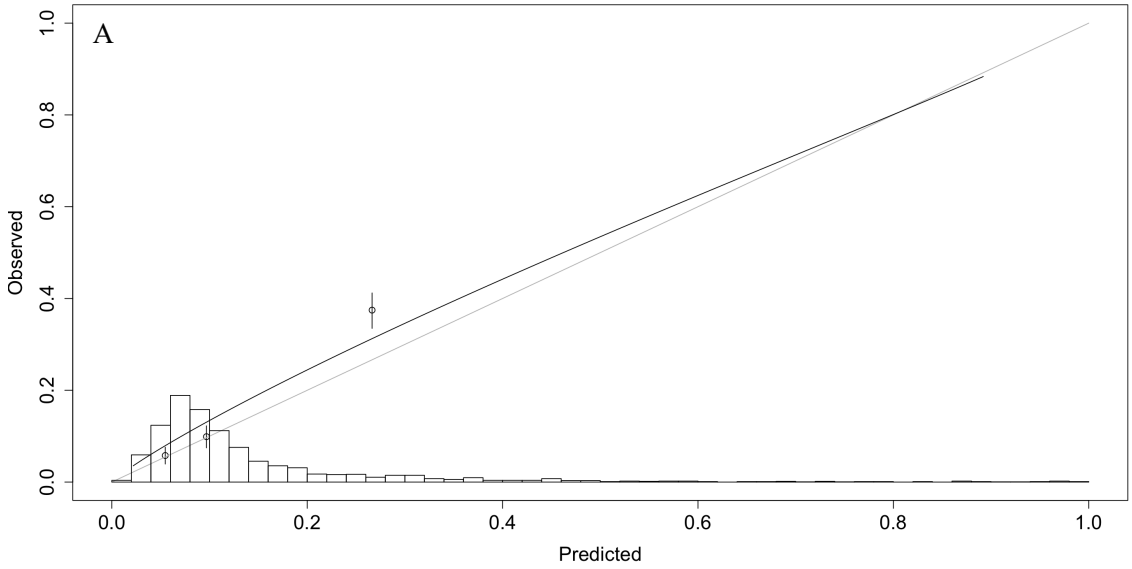
Figure 2.2. Calibration plots at 3-months (A), 6 months (B), and 12 months (C) for the simplified model

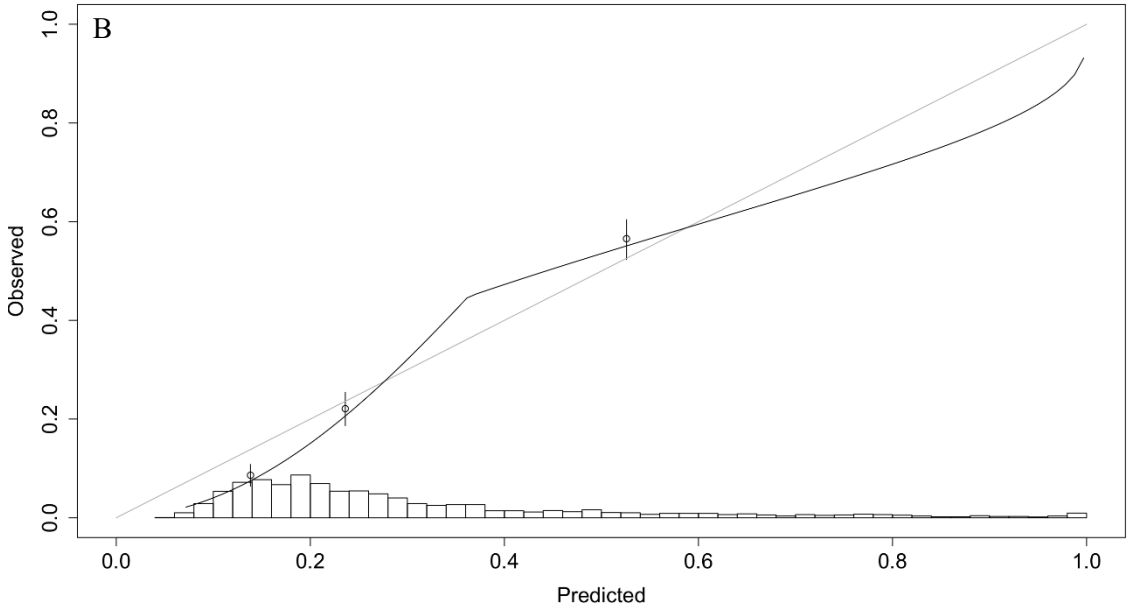


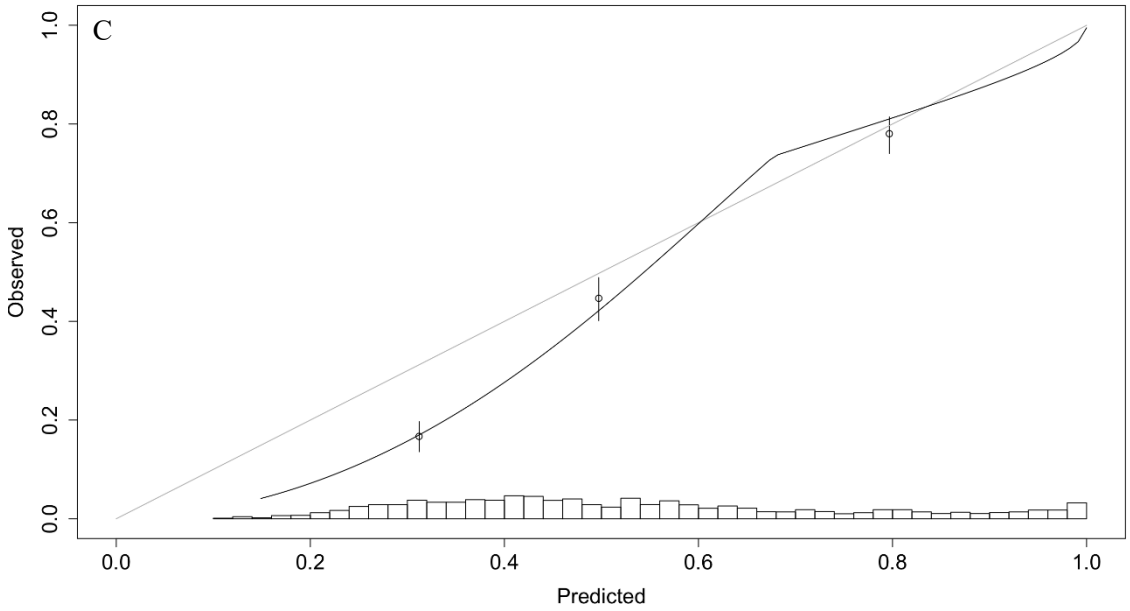


External validation using the validation cohort found that model discrimination improved modestly with a c-statistic of 0.75 at 3 months, 0.75 at 6 months, and 0.73 at 12 months. The cumulative incidence of dysphagia was 23% at 3-months, 29% at 6-months, and 45% at 12-months. At 3 months, the mean absolute error in predicted probabilities was .05 with a .9 quantile of absolute error of .08. At 6-months the mean absolute error in predicted probabilities was .04 with a .9 quantile of absolute error of .09. At 12-months the mean absolute error in predicted probabilities was .05 with a .9 quantile of absolute error of .10. Figure 2.3. (A-C) displays the external validation calibration plots.

Figure 2.3. External validation curves for the simplified model at 3-months (A), 6-months (B), and 12-months (C)

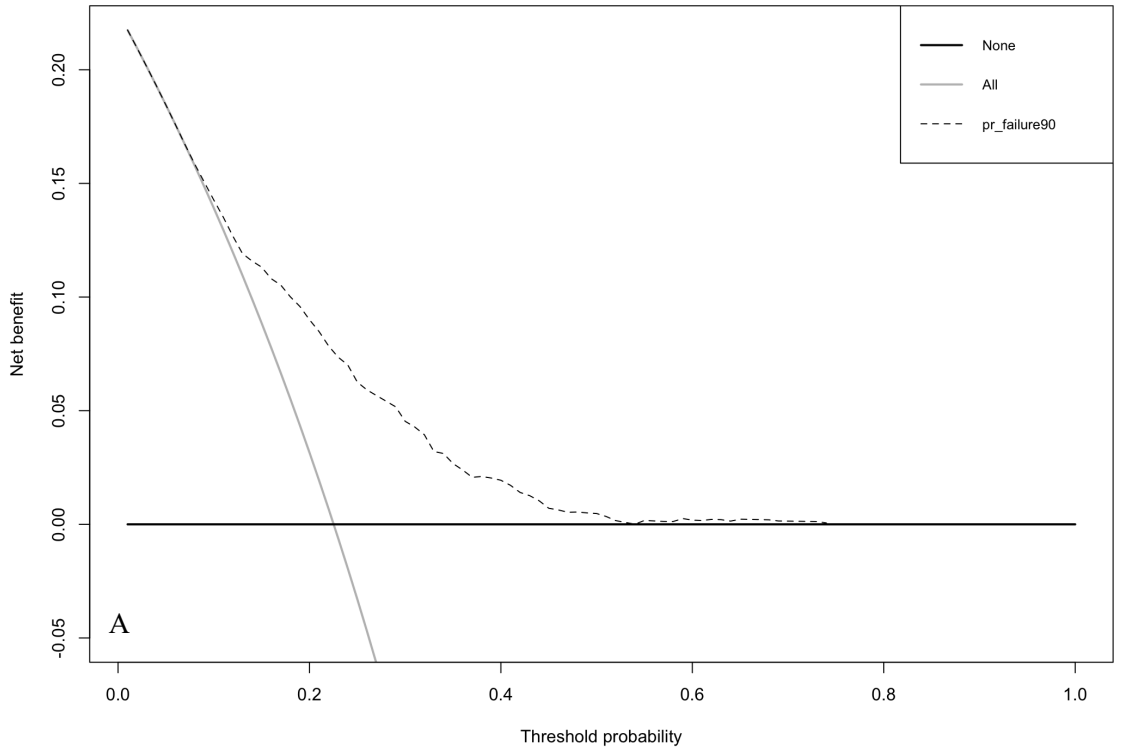


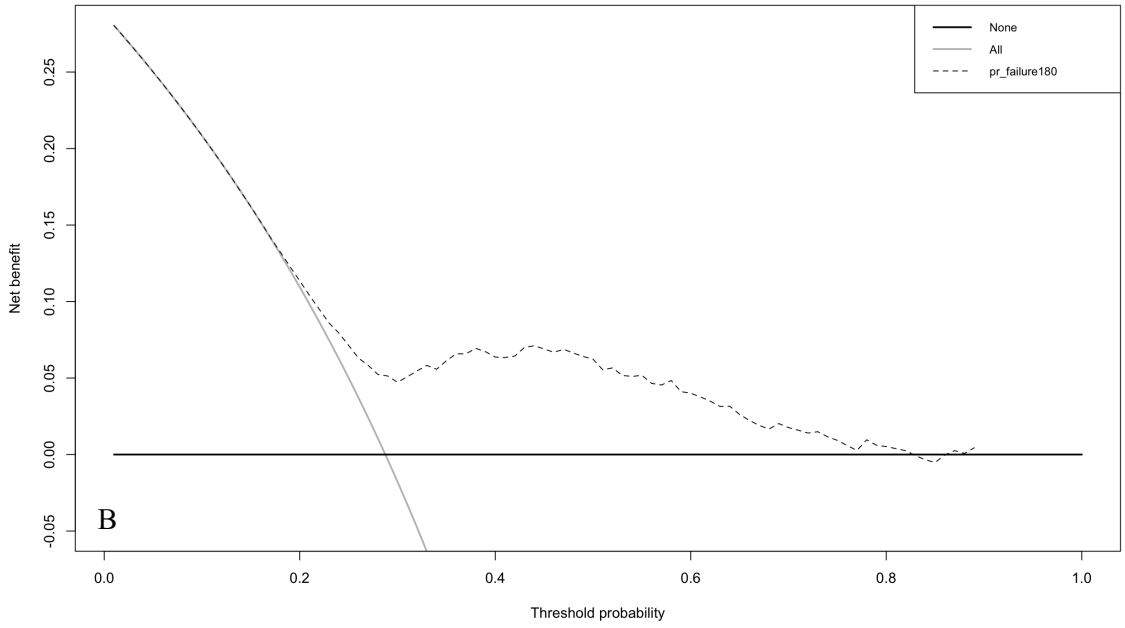


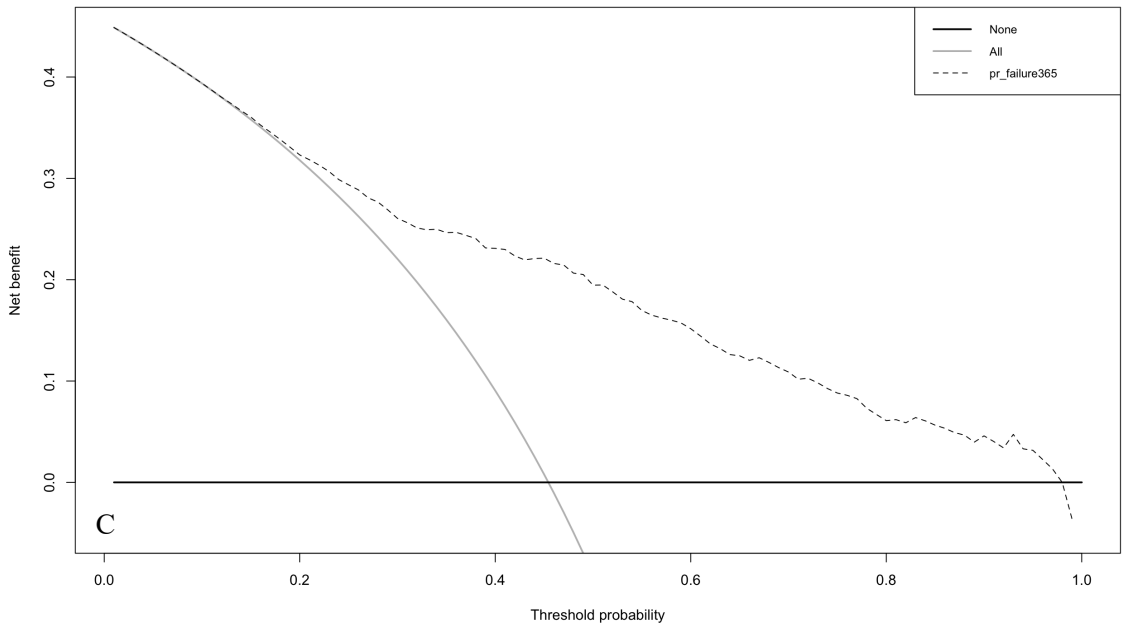


Decision curves for the simplified model were plotted with the external dataset and revealed clinical usefulness of the model at all three time horizons. The model performs at least as well as treat all or treat none approaches across threshold probabilities at all three time horizons. At 3-months, the model appears clinically useful over treat all or treat none approaches when the threshold for the treatment decision is between .15 and .55 (Figure 2.4A). At 6 months, the model appears clinically useful over the treat all or treat none approach when the threshold for the treatment decision is between .2-.8 (Figure 2.4B). At 12 months, the model appears to clinically useful over the treat all or treat none approach when the threshold for the treatment decision is between .2-.95 (Figure 2.4C).

Figure 2.4. Decisions curves for the simplified model at 3-months (A), 6-months (B), and 12-months (C)

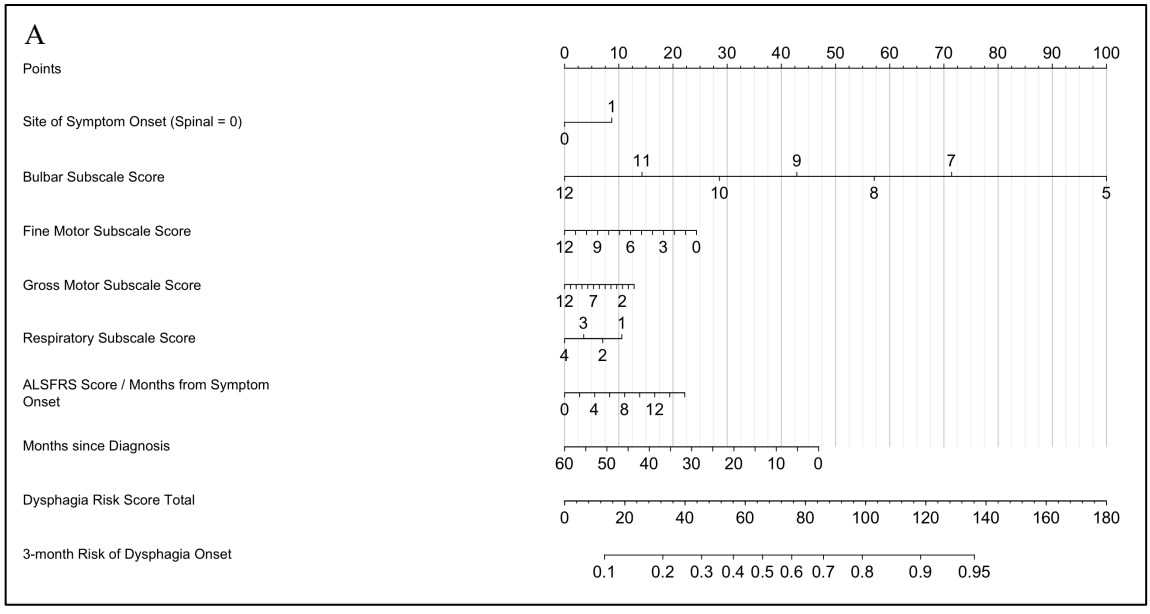


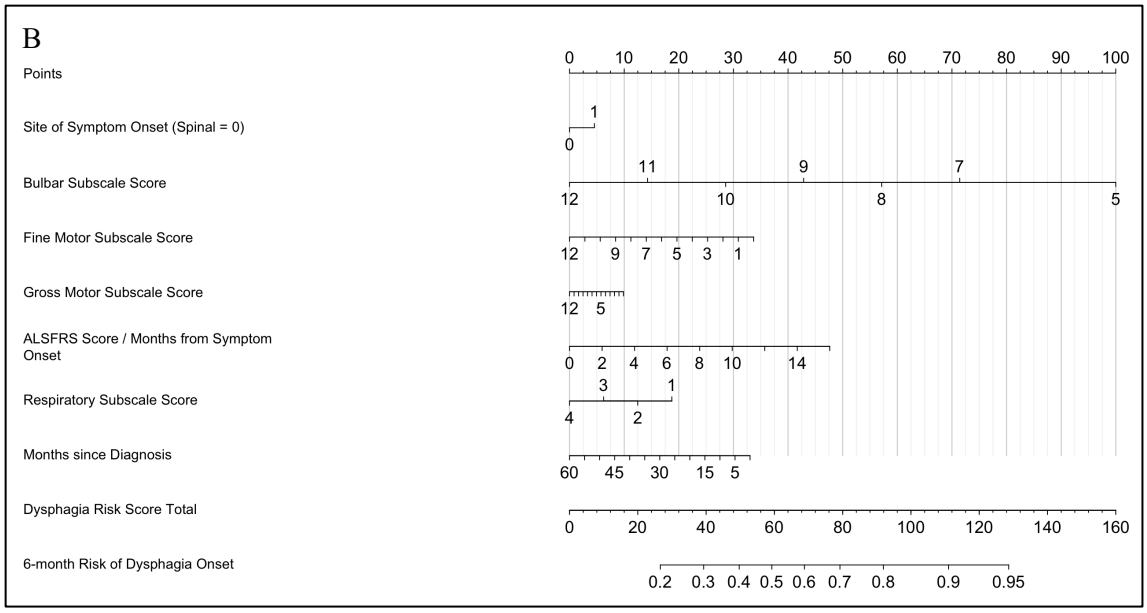


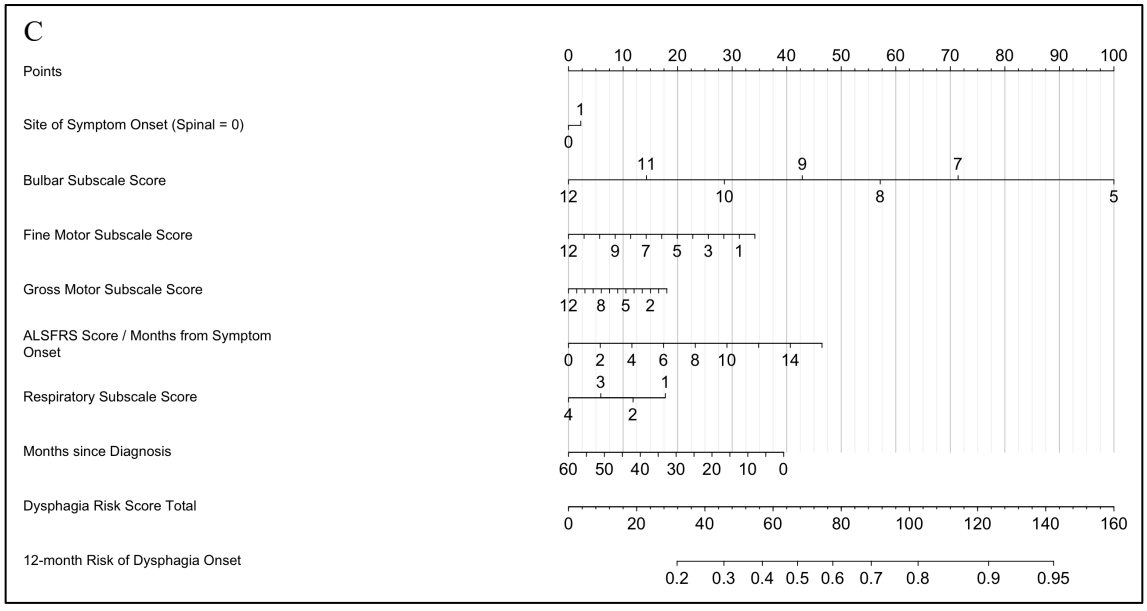


With no difference in model performance between the full and simplified models, the simplified model was chosen as the final model, as the simplified model would be easier to implement in the clinical setting. To calculate the ALS dysphagia risk score, we created a 3, 6 and 12-month nomograms (Figure 2.5A-C).

Figure 2.5. Nomograms for 3 (A), 6 (B) and 12 (C) risk of dysphagia onset.







2.4 Discussion

Using data from the PRO-ACT database, the ALS dysphagia risk score estimates an individual's likelihood of developing dysphagia at 3-months, 6-months, and 12-months. The final model contains seven variables that are regularly collected in the clinical setting and demonstrates strong discrimination and calibration upon external validation. Based on its parsimony, statistical characteristics and routinely collected

parameters, this model sufficiently identifies patients with ALS at high risk for dysphagia development to serve as a much-needed tool to identify those patients in greatest need of a comprehensive dysphagia evaluation by a speech language pathologist prospectively.

From the final model, six variables were significant predictors of dysphagia development. Presumably because those who developed dysphagia early in the disease course were excluded from the study, our study found no association between dysphagia development and site of symptom onset.

Unsurprisingly, however, the score on the ALSFRS bulbar subscale served as the strongest predictor of dysphagia development. Higher scores on this subscale (indicative of less bulbar impairment) not surprisingly were protective of dysphagia development. At baseline, approximately 30% of participants in our study reported speech and/or secretion management impairments but not swallowing impairments. This is consistent with literature suggesting that speech impairment often precedes swallowing impairments in this population.[35]

Our study found that the incidence of dysphagia increased in people with increased rates of decline. To our knowledge, no studies have explored the relation between rate of decline and the onset of swallowing impairments. A study by Rong et al.[30] found no association between the rate of speech loss and rate of disease decline as calculated as the time elapsed between initial and follow-up study assessment divided by change in ALSFR-R total scores between assessments. Research suggests that using time from symptom onset divided by total ALSFRS score is more sensitive to disease decline then using change in time over 4-month intervals and may explain differences in our findings.[31]

The ALSFRS respiratory score was strongly associated with dysphagia development. For each point decrease on question 10 of the ALSFRS or ALSFRS-R score, the hazard of dysphagia increased by 28%. This finding was consistent with previous literature that linked impaired respiratory function to both dysphagia and aspiration in persons diagnosed with ALS.[36] This association is also well documented in patients diagnosed with Parkinson's disease.[37,38]

Both ALSFRS fine motor and gross motor subscale scores were significantly associated with dysphagia development. Indicative of less severe disease status, higher ALSFRS fine motor and gross motor subscale scores were, as expected, protective of dysphagia development. To our knowledge, the relation between ALSFRS motor scores and dysphagia development has not been studied, however, associations between dysphagia and the loss of muscle mass[39] and hand grip strength[8,39] have been found.

Presently, no clinical guideline recommendations for when patient should be referred for comprehensive swallowing assessment exist. In a recent survey of 34 multidisciplinary ALS clinics across the United States, roughly half refer fewer than 15% of their patients for modified barium swallowing studies (MBSS), the "gold standard", and others refer over 70%. The known drawbacks to MBSS, e.g., an additional appointment and radiation exposure, would appear to be minor relative to complications from dysphagia, e.g., malnutrition, aspiration pneumonia and mortality. As such the threshold for the decision to refer patients for more comprehensive swallowing assessments should be relatively low. Decision curve analysis suggests that this model can substantially enhance referral for screening if the threshold for referring (i.e. that

probability at which clinicians and patients would consider evaluation worthwhile) was in the ~15% to ~40% range.

2.4.1 Limitations

Because the PRO-ACT database consists of data from participants in large clinical trials, the dataset may not be representative of the ALS population as a whole in both measured and unmeasured characteristics. Because the dataset does not include a trial indicator variable, the model was unable to account for clustering by trial which may impact our findings. Additionally, inclusion in this study is contingent upon both not developing dysphagia and surviving from the time of diagnosis to the start of a clinical trial. As such, the dysphagia risk score may not be well calibrated to those who develop dysphagia in the very early stages of the disease. Additionally, particularly given this selection, any causal interpretation of variable effects should be avoided.

Most importantly, this study relies on a single question is to define the development of dysphagia on a scale that is not reflective of the "gold-standard" diagnosis of dysphagia derived from a modified barium swallow study. One study suggests that impairments in swallowing efficiency and swallowing safety may precede dysphagia symptoms.[22] Large datasets containing "gold-standard" swallowing assessments do not currently exist. Furthermore, "gold-standard" dysphagia assessments are not regularly performed[15], so and their clinical usefulness to predict dysphagia onset remains unknown. Finally, patient reported outcomes are generally felt to be more clinically meaningful (even if less sensitive) than image-based tests, which may be viewed as surrogate outcomes. As such, we feel that a model containing regularly

collected clinical variables, such as the one proposed, could serve as a valuable tool to identify those who are in greatest need of a “gold-standard” dysphagia assessment.

2.4.2 Conclusions

The ALS dysphagia risk score includes seven easily accessible clinical variable and appears to sufficiently identify the 3, 6 and 12-month risk of dysphagia onset for persons’ diagnosed with ALS. Findings from this study are expected to help improve clinical decision-making surrounding dysphagia by identifying patients diagnosed with ALS who are at high risk for developing dysphagia and therefore, most in need for a comprehensive dysphagia assessment. Because all patients diagnosed with ALS are faced with making several critical decisions that directly impact their survival and quality of life as dysphagia develops, including the implementation of diet modifications and/or compensatory postural adjustments during meals and the placement of a feeding tube, we believe that early identification of patients at varying risks for developing dysphagia is critical to improving the health and quality of life for these patients.

Chapter 3: Discussion

In this study we aimed to fill a critical gap in our understanding of dysphagia development in persons diagnosed with ALS by developing and validating the ALS dysphagia risk score for the time to dysphagia onset in persons diagnosed with ALS. The final model includes seven regularly collected clinical variables, including time from diagnosis, rate of decline, respiratory impairment, spinal onset, ALSFRS bulbar subscale score, ALSFRS fine motor subscale score, and ALSFRS gross motor subscale score. The ALS dysphagia risk score provides clinicians with an evidence-based approach for identifying patients in greatest need of comprehensive swallowing evaluations.

At present, our understanding about the timing of the onset of dysphagia for person's diagnosed with ALS is limited. Published literature suggests large heterogeneity among the timing of dysphagia development with times frames ranging between 8-and-50 months' post disease onset. New research suggests that for those with spinal onset, the median time to dysphagia development is around 3 years.[10] For those without spinal onset whose presenting symptoms are not dysphagia, the median time to dysphagia development is around 2 years.[10] Our study went a step further than previous work by determining the contribution of key risk factors for dysphagia development that can be applied in a highly personalized way for use in both clinical practice and research.

Several important decisions, including the implementation of diet modifications and/or compensatory postural adjustments during meals and the placement of a feeding tube, are often made around the time of dysphagia onset. Timely and informed decisions surrounding nutritional management are key to minimizing complications that may arise from dysphagia and maximizing quality of life for patients diagnosed with dysphagia.

The dysphagia risk model is expected to help clinicians identify those at high risk for dysphagia development and thereby allow clinicians to assess swallowing function and provide swallowing intervention in a timely and efficient way.

Improved understanding of the timing of dysphagia development is also critical for ongoing research evaluating whether therapeutic strategies aimed at delaying the loss of swallowing function are effective in early stages of the disease. Presently available interventions targeting swallowing problems in this population are focused primarily on symptom management; however, recent data suggests that pharmacological intervention and/or exercise in early stages of the disease process may be useful in prolonging swallowing function.[36] Due to high variability in the timing of development of dysphagia in PALS, evaluating the effectiveness of interventions aimed at prolonging the development of swallowing impairment in early stages of the disease process is a significant challenge. This easy to administer tool capable of stratifying patients at varying risk for developing dysphagia may be of great benefit to those designing treatment trials aimed at prolonging the loss of swallowing function.

Strengths of our study include the use of the PRO-ACT dataset, which is the largest and most complete publicly available dataset comprised of persons diagnosed with ALS. It was important to us that the final model be easy to use in busy multidisciplinary clinic settings, where many patients with ALS receive care, therefore, the variables in final model are easy to collect and/or typically available in the patients' medical record. Additionally, with only 7 variables in the model, calculating the dysphagia risk score is not overly laborious.

There are several known limitations to this study. Because the PRO-ACT database is comprised only of data from participants in larger clinical trials, the dataset may not be representative of the ALS population as a whole as persons who choose to participate in clinical trials may be different than those who do not. As such, the generalizability of this study to the broader ALS population is unknown. Additionally, because of exclusion criteria for this study, the model may not be well suited for those patients who are fast-progressors or who develop dysphagia in the very early stages of the disease. Finally, in this study the development of dysphagia is defined by a single question on a scale that is not reflective of the "gold-standard" diagnosis of dysphagia which is typically derived from a modified barium swallow study. There is research to suggest that in this population, impairments in swallowing efficiency and swallowing safety may in fact be present prior to reported dysphagia,[22] however, in general, patient reported outcomes are thought to be more clinically meaningful (even if less sensitive) than image-based tests.

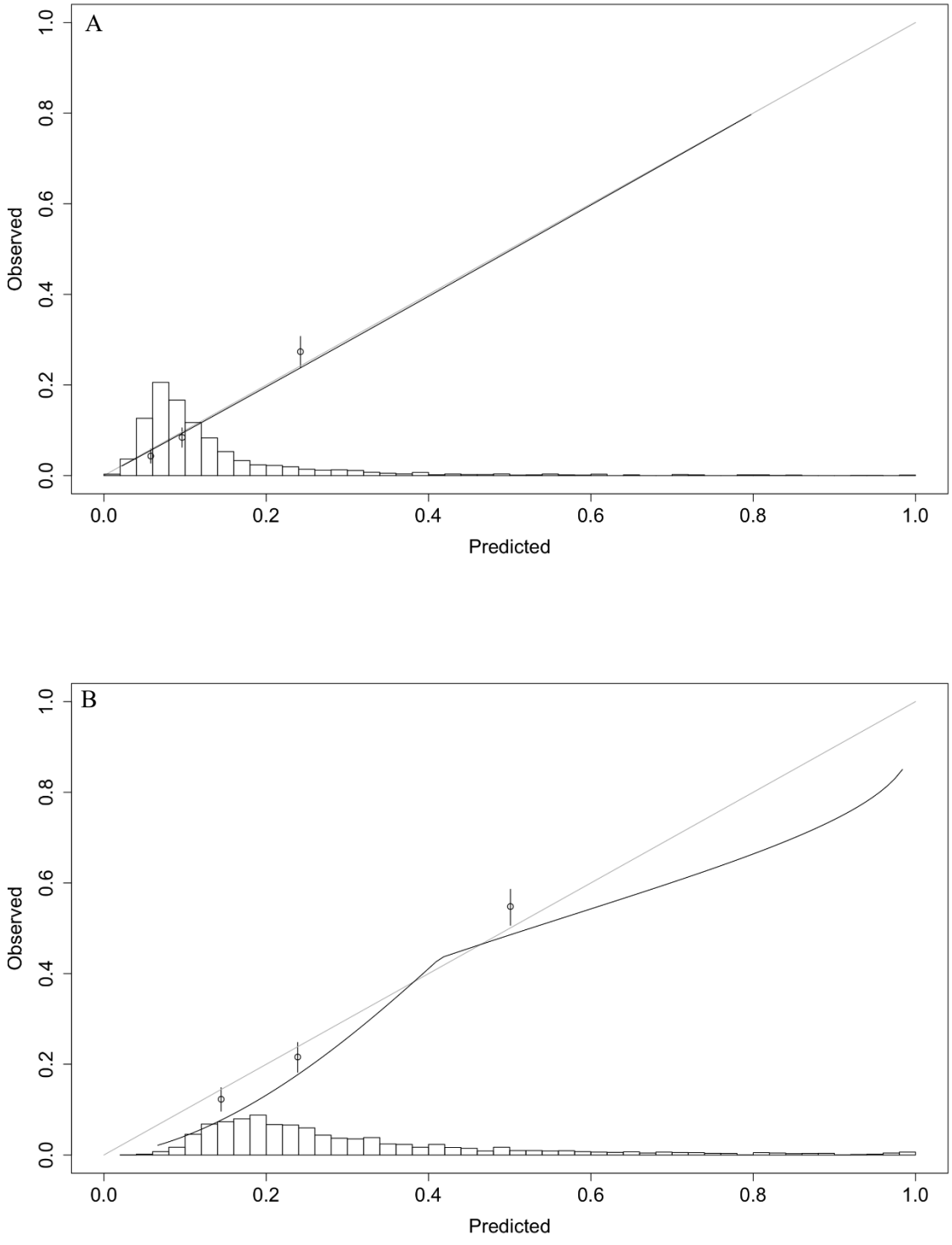
Work from this study serves as an important first steps towards improving the management of dysphagia in this patient population. Additional future work includes 1) determining patient characteristics that predict benefits and tradeoffs from various nutritional strategies for persons with ALS who develop dysphagia; 2) identifying patient's and physicians' preferences surrounding nutritional management strategies and outcomes among key stakeholders and 3) incorporating results from this work with results from the work described above to develop a personalized decision aid for nutritional decision making in patients diagnosed with ALS.

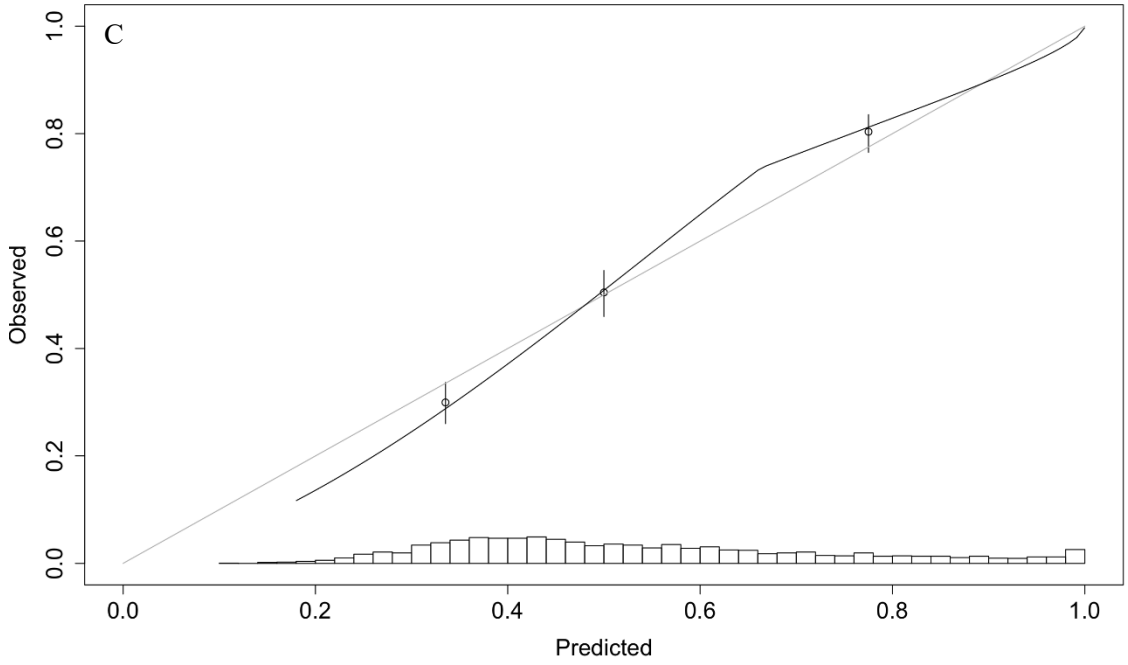
Chapter 4: Appendix

Table 4.1. Participant Characteristics in the development cohort and the validation cohort

	Development Cohort n=2057	Validation Cohort n= 1891
Age (mean (sd))	55.22 (11.42)	55.22 (11.61)
Sex = Male (%)	1390 (67.6)	1254 (66.3)
Race (%)		
Caucasian	1834 (93.5)	1793 (95.4)
African American	27 (1.4)	15 (0.8)
Asian	38 (1.9)	42 (2.2)
Other	63 (3.2)	30 (1.6)
Height, cm (mean (sd))	172.16 (9.23)	170.86 (9.69)
Weight, kg (mean (sd))	80.62 (20.72	75.06 (14.97)
Months from Diagnosis (mean (sd))	7.34 (7.72)	12.33 (12.10)
Rate of Decline, points per month (median (IQ range))	1.54 (.944, 3.66)	1.89 (1.21, 3.00)
Site of Onset = Not Spinal (%)	392 (19.1)	137 (7.2)
ALSFRS Bulbar Subscale Score (0-12) (mean (sd))	11.52 (0.87)	11.43 (.99)
ALSFRS Fine Motor Subscale Score (0-12) (mean (sd))	8.32 (2.66)	8.14 (3.02)
ALSFRS Gross Motor Subscale Score (0-12) (mean (sd))	7.71 (2.84)	7.54 (2.99)
ALSFRS Respiratory Subscale Score (0-4) (mean (sd))	3.75 (.57)	3.80 (.44)
Riluzole Use = Yes (%)	1350 (80.7)	829 (63.0)
Dysphagia Development = Yes (%)	924 (44.9)	787 (41.6)

Figure 4.1. Calibration plots at 3-months (A), 6-months (B), and 12-months (C) for the full model




C
Observed
Predicted
0.0
0.2
0.4
0.6
0.8
1.0

4.1. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) checklist[42] - Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	i
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	ii
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	7
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	7
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	8
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	8
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	8
	5b	D;V	Describe eligibility criteria for participants.	8
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	9
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA

Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	9
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	11
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	10
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	11
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	10
	10c	V	For validation, describe how the predictions were calculated.	10
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	10
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	12
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	12
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	12

	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	12
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	12
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	20-21
	15b	D	Explain how to the use the prediction model.	20-21
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	14-20
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	24
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	21-22
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	22-24
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	25
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	29
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	NA

4.2. Prediction model study Risk of Bias Assessment Tool (PROBAST)[43], Version of 15/05/2019, www.probast.org

Step 1: Specify your systematic review question

State your systematic review question to facilitate the assessment of the applicability of the evaluated models to your question. The following table should be completed once per systematic review.

Criteria	Specify your systematic review question
Intended use of model:	Determine the risk of dysphagia development in persons diagnosed with ALS
Participants including selection criteria and setting:	The development and validation cohort were derived from the PRO-ACT database. PRO-ACT is the largest database containing clinical trial data from persons diagnosed with ALS and, at present, includes over 10,700 de-identified clinical patient records pooled from 23 Phase II/III clinical trials between the years of 1990-2015 across the world. Participants were excluded if they did not ALS Functional Rating Scale Score outcomes or if they had dysphagia at the start of the clinical trial.
Predictors (used in prediction modelling), including types of predictors (e.g. history, clinical examination, biochemical markers, imaging tests), time of measurement, specific measurement issues (e.g., any requirements/ prohibitions for specialized equipment):	Selected candidate variables included age, sex, race, site of symptom onset, time from diagnosis, weight, height, forced vital capacity, slow vital capacity, riluzole use, family history of ALS, ALSFRS bulbar subscale score, ALFRS fine motor subscale score, ALSFRS gross motor subscale score, ALSFRS respiratory subscale score, and whether or not the participant received the placebo or treatment in the clinical trial.
Outcome to be predicted:	Time to development of dysphagia

Step 2: Classify the type of prediction model evaluation

Use the following table to classify the evaluation as model development, model validation or model update, or combination. Different signalling questions apply for different types of prediction model evaluation. If the evaluation does not fit one of these classifications then PROBAST should not be used.

Classify the evaluation based on its aim			
Type of prediction study	PROBAST boxes to complete	Tick as appropriate	Definition for type of prediction model study
Development only	Development		Prediction model development without external validation. These studies may include internal validation methods, such as bootstrapping and cross-validation techniques.
Development and validation	Development and validation	x	Prediction model development combined with external validation in other participants in the same article.
Validation only	Validation		External validation of existing (previously developed) model in other participants.

This table should be completed once for each publication being assessed and for each relevant outcome in your review.

Publication reference	
Models of interest	
Outcome of interest	

Step 3: Assess risk of bias and applicability

PROBAST is structured as four key domains. Each domain is judged for risk of bias (low, high or unclear) and includes signalling questions to help make judgements. Signalling questions are rated as yes (Y), probably yes (PY), probably no (PN), no (N) or no information (NI). All signalling questions are phrased so that "yes" indicates absence of bias. Any signalling question rated as "no" or "probably no" flags the potential for bias; you will need to use your judgement to determine whether the domain should be rated as "high", "low" or "unclear" risk of bias. The guidance document contains further instructions and examples on rating signalling questions and risk of bias for each domain. The first three domains are also rated for concerns regarding applicability (low/ high/ unclear) to your review question defined above. Complete all domains separately for each evaluation of a distinct model. Shaded boxes indicate where signalling questions do not apply and should not be answered.

DOMAIN 1: Participants			
A. Risk of Bias			
The PRO-ACT database consists of data from participants in large clinical trials, therefore, the dataset may not be representative of the ALS population as a whole in both measured and unmeasured characteristics.			
		Dev	Val
1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?		Y	Y
1.2 Were all inclusions and exclusions of participants appropriate?		Y	Y
Risk of bias introduced by selection of participants	RISK: (low/ high/ unclear)	Unclear	Unclear
Rationale of bias rating: It is unclear how different participants included in clinical trials might be from those who were not.			
B. Applicability			
Describe included participants, setting and dates: Participants were diagnosed with ALS, were selected and elected to enrol in a clinical trial between the years of 1999-2015.			
Concern that the included participants and setting do not match the review question	CONCERN: (low/ high/ unclear)	Low	Low
Rationale of applicability rating: With no cure for ALS and very few treatment options, participants included in this study are likely still reflective of the ALS population today.			

DOMAIN 2: Predictors			
A. Risk of Bias			
List and describe predictors included in the final model, e.g. definition and timing of assessment: Age at time of first study visit, sex, race, site of symptom onset (spinal or not spinal), months from diagnosis, weight, height, forced vital capacity, slow vital capacity, riluzole use (yes/no), family history of ALS (yes/no), ALSFRS bulbar subscale score, ALSFRS fine motor subscale score, ALSFRS gross motor subscale score, ALSFRS respiratory subscale score, rate of decline (ALSFRS Total score/Months since symptom onset) and whether or not the participant received the placebo or treatment in the clinical trial.			
		Dev	Val
2.1 Were predictors defined and assessed in a similar way for all participants?		YES	YES
2.2 Were predictor assessments made without knowledge of outcome data?		YES	YES
2.3 Are all predictors available at the time the model is intended to be used?		YES	YES
Risk of bias introduced by predictors or their assessment	RISK: (low/ high/ unclear)	Low	Low
Rationale of bias rating: The predictors were well defined, assessments were made without knowledge of the outcome, and all predictors would be available at the time the model is intended to be used.			
B. Applicability			
Concern that the definition, assessment or timing of predictors in the model do not match the review question	CONCERN: (low/ high/ unclear)	Low	Low
Rationale of applicability rating: The predictors seem well defined and appropriately suited to match the study question.			

DOMAIN 3: Outcome			
A. Risk of Bias			
Describe the outcome, how it was defined and determined, and the time interval between predictor assessment and outcome determination: The outcome was time to development of dysphagia. Development of dysphagia was defined as a change in scorefrom 4 to anything <4 on the ALS Functional Rating Scale swallowing question. Time to event was calculated as the time from the first study visit to the time of first study visit with a score change. Time was censored at 365 days, as the time horizons of interest were 3, 6, and 12 months.			
		Dev	Val
3.1 Was the outcome determined appropriately?		Yes	Yes
3.2 Was a pre-specified or standard outcome definition used?		Yes	Yes
3.3 Were predictors excluded from the outcome definition?		Yes	Yes
3.4 Was the outcome defined and determined in a similar way for all participants?		Yes	Yes
3.5 Was the outcome determined without knowledge of predictor information?		Yes	Yes
3.6 Was the time interval between predictor assessment and outcome determination appropriate?		Yes	Yes
Risk of bias introduced by the outcome or its determination	RISK: (low/ high/ unclear)	Low	Low
Rationale of bias rating: The outcome was clearly defined, pre-specified, and consistently measured across participants.			
B. Applicability			
At what time point was the outcome determined: The outcome was assessed a 3, 6, and 12 months If a composite outcome was used, describe the relative frequency/distribution of each contributing outcome: NA			
Concern that the outcome, its definition, timing or determination do not match the review question	CONCERN: (low/ high/ unclear)	Unclear	Unclear
Rationale of applicability rating: As the outcome was defined by a single self-reported question on the ALS Functional Rating Scale Score, the outcome represents patient reported dysphagia, and not dysphagia confirmed using “gold standard” assessment. It is unclear how accurately patients are able to self-report dysphagia in this population, however, patient reported outcomes are generally felt to be more clinically meaningful (even if less sensitive) than image-based tests, which may be viewed as surrogate outcomes.			

DOMAIN 4: Analysis
Risk of Bias
Describe numbers of participants, number of candidate predictors, outcome events and events per candidate predictor: 3,948 participants were eligible for study inclusion. The model development cohort included 2,057 persons and the external validation cohort included 1,891 participants. There were 18 candidate variables considered, 914 outcomes in the development cohort, and 769 outcomes in the validation cohort. There were 50 events per candidate variable in the development cohort.
Describe how the model was developed (for example in regards to modelling technique (e.g. survival or logistic modelling), predictor selection, and risk group definition): A multivariable Cox proportional hazards regression model was fit to each of the 10 imputed data sets using all candidate variables as described above. Parameter estimates and standard errors were then pooled using Rubin's rules. Variables in the full model that were not associated with time to dysphagia development ($p>.05$) were removed in the estimation of a simplified model, with the exception of site of symptom onset which was forced into the model because of its well-accepted association with the dysphagia outcome. A likelihood ratio test was performed to assess for differences between the full and simplified model.
Describe whether and how the model was validated, either internally (e.g. bootstrapping, cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, different type of participants): The model was externally validated using temporal validation.
Describe the performance measures of the model, e.g. (re)calibration, discrimination, (re)classification, net benefit, and whether they were adjusted for optimism: The model was assessed for calibration using calibration plots, and discrimination using the c-statistic. Bootstrapping was used to derive optimism corrected coefficients and c-statistics.
Describe any participants who were excluded from the analysis: Participants were excluded from the study if they did not have ALS Functional Rating Scale Scores reported or if they had the outcome at the first study visit in the dataset.
Describe missing data on predictors and outcomes as well as methods used for missing data: Missing data for candidate variables were imputed by multiple imputation to create 10 complete data sets using predictive mean matching for imputing continuous variables; logistic regression for imputation of binary variables; and polytomous logistic regression for imputation of categorical variables. Variables missing over

50%, family history of ALS, forced vital capacity scores, and slow vital capacity scores were excluded from the model.			
		Dev	Val
4.1 Were there a reasonable number of participants with the outcome?		Yes	Yes
4.2 Were continuous and categorical predictors handled appropriately?		Yes	Yes
4.3 Were all enrolled participants included in the analysis?		Yes	Yes
4.4 Were participants with missing data handled appropriately?		Yes	Yes
4.5 Was selection of predictors based on univariable analysis avoided?		Yes	
4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately?		Yes	Yes
4.7 Were relevant model performance measures evaluated appropriately?		Yes	Yes
4.8 Were model overfitting and optimism in model performance accounted for?		Yes	
4.9 Do predictors and their assigned weights in the final model correspond to the results from multivariable analysis?		Yes	
Risk of bias introduced by the analysis	RISK: (low/ high/ unclear)	Low	Low
Rationale of bias rating: The number of participants was large and the candidate to predictor ratio was sufficient. Missing data was handled appropriately, no univariate analysis was conducted, participants were censored appropriately, and model performance was measured sufficiently. The model accounted for overfitting and optimism.			

Step 4: Overall assessment

Use the following tables to reach overall judgements about risk of bias and concerns regarding applicability of the prediction model evaluation (development and/or validation) across all assessed domains. Complete for each evaluation of a distinct model.

Reaching an overall judgement about risk of bias of the prediction model evaluation	
Low risk of bias	If all domains were rated low risk of bias. If a prediction model was developed without any external validation, and it was rated as low risk of bias for all domains, consider downgrading to high risk of bias. Such a model can only be considered as low risk of bias, if the development was based on a very large data set and included some form of internal validation.
High risk of bias	If at least one domain is judged to be at high risk of bias.
Unclear risk of bias	If an unclear risk of bias was noted in at least one domain and it was low risk for all other domains.

Reaching an overall judgement about applicability of the prediction model evaluation	
Low concerns regarding applicability	If low concerns regarding applicability for all domains, the prediction model evaluation is judged to have low concerns regarding applicability.
High concerns regarding applicability	If high concerns regarding applicability for at least one domain, the prediction model evaluation is judged to have high concerns regarding applicability.
Unclear concerns regarding applicability	If unclear concerns (but no "high concern") regarding applicability for at least one domain, the prediction model evaluation is judged to have unclear concerns regarding applicability overall.

Overall judgement about risk of bias and applicability of the prediction model evaluation		
Overall judgement of risk of bias	RISK: (low/ high/ unclear)	Unclear
Summary of sources of potential bias: It is unclear how participants who enter clinical trials might differ from those who do not.		
Overall judgement of applicability	CONCERN: (low/ high/ unclear)	Unclear
Summary of applicability concerns: It is unclear how closely the patient perceived outcome of dysphagia development relates to the "gold standard" assessment of dysphagia development.		

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