

# Disease Progression in Multiple System Atrophy—Novel Modeling Framework and Predictive Factors

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**ABSTRACT: Background:** Multiple system atrophy (MSA) is a rare and aggressive neurodegenerative disease that typically leads to death 6 to 10 years after symptom onset. The rapid evolution renders it crucial to understand the general disease progression and factors affecting the disease course.

**Objectives:** The aims of this study were to develop a novel disease-progression model to estimate a population-level MSA progression trajectory and predict patient-specific continuous disease stages describing the degree of progress into the disease.

**Methods:** The disease-progression model estimated a population-level progression trajectory of subscales of the Unified MSA Rating Scale and the Unified Parkinson's Disease Rating Scale using patients in the European MSA natural history study. The predicted disease continuum was validated via multiple analyses based on reported anchor points, and the effect of MSA subtype on the rate of disease progression was evaluated.

**Results:** The predicted disease continuum spanned approximately 6 years, with an estimated average

duration of 51 months for a patient with global disability score 0 to reach the highest level of 4. The predicted continuous disease stages were shown to be correlated with time of symptom onset and predictive of survival time. MSA motor subtype was found to significantly affect disease progression, with MSA-parkinsonian (MSA-P) type patients having an accelerated rate of progression.

**Conclusions:** The proposed modeling framework introduces a new method of analyzing and interpreting the progression of MSA. It can provide new insights and opportunities for investigating covariate effects on the rate of progression and provide well-founded predictions of patient-level future progressions. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

**Key Words:** disease progression; multiple system atrophy; multivariate nonlinear mixed-effects models; motor subtype; neurodegenerative disease

Multiple system atrophy<sup>1-4</sup> (MSA) is a rare and rapidly progressive neurodegenerative disease characterized by autonomic and motor symptoms. Neuropathologically oligodendroglial  $\alpha$ -synuclein inclusion pathology (glial

cytoplasmic inclusions [GCIs]) is the hallmark of the disease.<sup>5</sup> A definite diagnosis of MSA requires postmortem evidence of widespread  $\alpha$ -synuclein-immunoreactive GCIs along with nigrostriatal or olivopontocerebellar atrophy.

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Two major motor subtypes of MSA exist. One predominantly features parkinsonism (MSA-P), and the other is characterized by cerebellar symptoms (MSA-C).

Most patients are diagnosed with MSA between age 50 and 60 years. The average survival time after symptom onset of MSA is 6 to 10 years but can vary greatly from patient to patient.<sup>3,6-9</sup> MSA is an incurable disease, and available symptomatic treatments only have a modest and transient effect.<sup>10</sup> The relatively short disease course from symptom onset to death complicates targeted treatment of MSA, and therefore, there is an immediate need for improving the understanding of the general disease progression and factors affecting the disease course.

Most studies on MSA disease progression have been focusing on identifying variables affecting the survival time from diagnosis through death.<sup>6,7,11-15</sup> Common variables of interest include gender, age at symptom onset, MSA subtype, and autonomic and motor features. Several studies have found that early onset and the degree of severity of autonomic dysfunction negatively affect predicted survival time<sup>7,11,12,15</sup>; however, the effects of gender, age, and MSA subtype are not consistent across studies.<sup>6,11,13-16</sup>

Longitudinal analyses of MSA cohorts are typically based on survival analysis methodology to compensate for and investigate the large number of dropouts and deaths occurring during follow-up. As a result, the outcomes of these studies relate to survival time and the effect of covariates on the survival time. Foubert-Samier et al<sup>6</sup> took a different approach than survival analysis methods and applied linear mixed-effects models for estimating simultaneous mean trajectories for the four subscales of the Unified MSA Rating Scale (UMSARS).<sup>17</sup> The longitudinal mean trajectories were modeled to investigate the average rate of progression of a patient during the study.

Here, we propose a new method for analyzing the disease progression of MSA via multiple assessment scales. Similar to Foubert-Samier et al,<sup>6</sup> a simultaneous model is fitted to the subscales of the UMSARS and the Unified Parkinson's Disease Rating Scale<sup>18,19</sup> (UPDRS). However, in contrast to the linear mixed-effects model, we propose a model framework based on nonlinear mixed-effects models. Nonlinear methods have previously been successful for disease-progression modeling in other diseases.<sup>20,21</sup> We propose a model framework that predicts patients' progression and individual prognosis according to their disease severity in a fully data-driven manner. This continuous staging of patients makes it possible to define a disease continuum and a representative progression curve describing the evolution of assessment scales along the disease course of an individual patient (as opposed to the average rate of progression of all patients). A similar framework has been used to analyze the progression of Alzheimer's disease in several cohorts where it has been shown to make state-of-the-art predictions of individual

patient progression along the Alzheimer's disease continuum, predictions of future decline, and provide novel insights into the evolution of biomarkers with disease progression.<sup>22-24</sup>

In this paper, we present a disease-progression model framework for MSA progression and analyze progression patterns of patients in the European MSA (EMSA) natural history study.<sup>14</sup> We show how the method can predict a natural, personalized staging of patients and population-based mean progression trajectories of clinical scores along the disease continuum.

## Patients and Methods

### Participants and Data Collection

Study participants were MSA patients included in the European MSA study group (EMSA-SG) natural history study.<sup>14,25</sup> The study design and the study procedure have been described in detail elsewhere.<sup>14</sup> Briefly, 15 EMSA centers participated in this prospective natural history study, and recruitment lasted from January 2003 to July 2004. Patients with a clinical diagnosis of MSA as determined by treating neurologists were enrolled in the study. Study duration was 2 years with a follow-up every 6 months. The EMSA-SG minimal data set<sup>25</sup> was used to document basic clinical features and diagnostic procedures as well as the current medication. Validated rating instruments were applied by the investigator, patient, or caregiver, as appropriate.

Subscales of the UMSARS<sup>17</sup> and UPDRS<sup>19</sup> were considered the main outcomes of this study. The subscales included UMSARS Part I (a measure of symptoms and activity of daily living), UMSARS Part II (a motor examination scale), and UPDRS Part II (a measure of activity of daily living) and Part III (a measure of motor examination). In addition, the Hoehn and Yahr Scale<sup>26,27</sup> and Schwab and England Activities of Daily Living Scale<sup>28</sup> were included as outcomes. All subscales have higher values indicating more severe disability except the Schwab and England that relates lower values to more severe disability. Note that in this study only a subset of UPDRS Part III questions were used in the total score as some questions were not reported. The included questions were related to speech, facial expression, action or postural tremor of hands, rapid alternating movements of hands, rising from chair, posture, gait, postural stability, and body bradykinesia and hypokinesia. The total score was calculated as a sum of the included items. For the items measured on several limbs, the score of the most affected part was included. The Global Disability Scale<sup>29</sup> (GDS) was used as a discrete covariate indicator of disease severity. The GDS used in the following analyses is the UMSARS Part IV that ranges from 0 to 4, with 0 meaning no appreciable disability and 4 very severely or completely disabled.

Other variables of interest included age at symptom onset, time to death, and age at onset of autonomic

symptoms. Autonomic symptoms were assessed using the COMPASS score.<sup>30</sup>

### Statistical Analysis

A novel multivariate nonlinear mixed-effects model was used to simultaneously estimate the population-based course of disease across different outcomes and predict the individual patient’s progression and future decline along the disease continuum. For full details on the proposed method, see Kühnel et al.<sup>24</sup> R-code for the basic framework is available in the progmod package.<sup>31</sup>

Assume that subject  $i$  has been observed at  $m_i$  timepoints  $t_{i1} < \dots < t_{im_i}$ , for example, at baseline, 6, and 12 months after baseline. Note that timepoints and the number  $m_i$  of observations can vary across subjects. Let  $y_{ij} = (y_{ij1}, \dots, y_{ijK})$  be the observations of  $K$  different outcomes (subscales from UMSARS and UPDRS) for subject  $i$  at time points  $t_{ij}$ . Each observation is modeled as

$$y_{ijk} = \mu_k(t_{ij} + s_i) + u_{ik} + \varepsilon_{ijk} \text{ for } i = 1, \dots, n, j = 1, \dots, m_i, k = 1, \dots, K,$$

where  $\mu_k$  defines the population-level disease progression trajectory for the  $k$ th outcome measure.

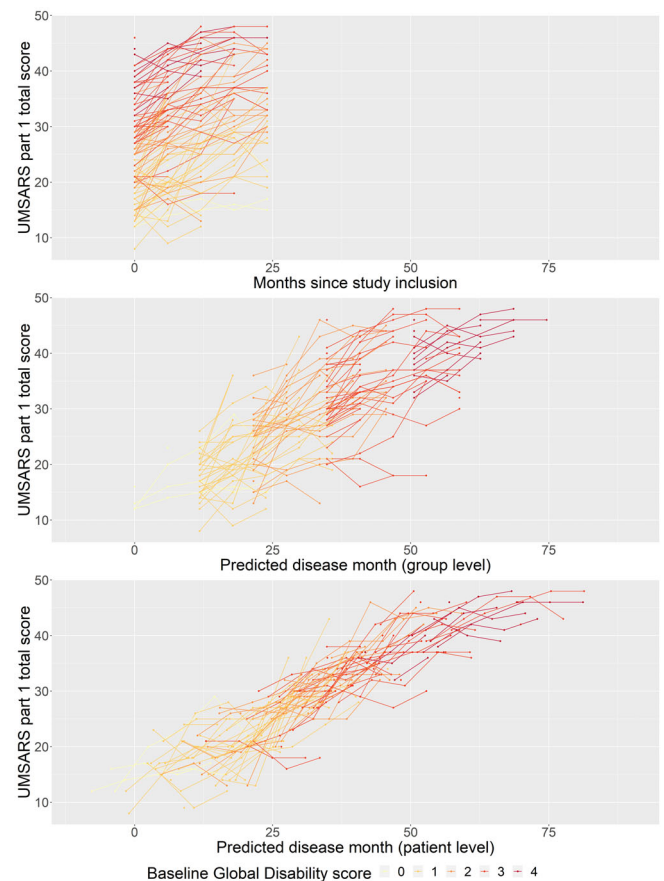
The outcome-specific population-based disease trajectory,  $\mu_k$ , is modeled as a multivariate generalized logistic function. The generalized logistic function was chosen due to its flexible nature that can describe everything between a highly exponential decay and more linear relations and can account for potential ceiling effects of clinical scores. For each individual outcome, the generalized logistic function is given by the parameterization

$$\mu(t) = A + \frac{K - A}{(1 + \exp(-B \cdot t))^v},$$

where  $A$  and  $K$  represent the lower and higher asymptotes,  $B$  is the rate of progression, and  $v$  controls the location along the disease continuum with the maximal rate of deterioration.

The variation in the population is split into a subject-specific vertical variation,  $v_i \sim N(0, \gamma^2)$   $u_{ik} \sim N(0, \gamma_k^2)$  and a subject-specific shift in time (horizontal variation)  $s_i$ . Neither of these parameters depends on time, meaning that the variation is a shift in the whole longitudinal path of each patient. The vertical variation describes a patient’s general deviation in performance on the outcome measure compared to the population, that is, whether the patient in general will perform better or worse on the outcome measure than the other individuals in the study cohort. The horizontal variation describes the individual patient’s progression on the

disease continuum relative to the other patients in the study cohort. The continuous staging of patients along the disease continuum is modeled using a latent temporal shift parameter  $s_i = x_i^T \beta + z_i$  that is shared across the  $K$  outcomes. The shift includes a contribution,  $x_i^T \beta$ , based on the patient’s baseline GDS score (fixed effect) and a contribution,  $z_i \sim N(0, \tau^2)$ ,  $z_i$  that describes the individual patient’s disease progression relative to other patients with same baseline GDS score (random effect). Figure 1 shows the effect of the two shift components on aligning longitudinal UMSARS Part I scores to produce a model-based predicted disease continuum. The fixed effect of the staging parameter  $s_i$  describes how long it takes on average for patients to progress to the next level of the GDS at group level (middle plot of Fig. 1). The random effect part of the staging parameter models the patient-level differences in progression between patients having the same GDS at baseline (bottom plot of Fig. 1). Predicted disease time is defined



**FIG. 1.** Illustration of the shift parameter in the multivariate disease-progression model. (Top) Longitudinal scores plotted against months since study inclusion. (Middle) Longitudinal scores shifted corresponding to patients’ baseline GDS (Global Disability Scale), that is, by the fixed part of the shift parameter. (Bottom) Longitudinal scores shifted according to the full patient-specific predicted disease time, that is, by both fixed and random parts of the shift parameter. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

relative to the first level of the GDS; that is, time zero defines the average progression of an MSA patient with no appreciable disability (GDS score 0).

In the following analyses, the described nonlinear mixed-effects model was fitted simultaneously on UMSARS Part I and Part II and UPDRS Parts II, III, IV, and VI. Global disability score at baseline was included as a covariate in the staging parameter as described earlier.

To investigate the appropriateness of this nonlinear progression model for analyzing the study outcomes, the model was compared to (1) a linear mixed-effects model that included random slope and intercept terms and (2) a random slope and intercept mixed-effects model quadratic in time, both models including a subscale-specific fixed effect on the baseline global

disability score. The models were compared based on the Akaike information criteria (AIC).<sup>32</sup>

To validate the meaningfulness of the predicted progression of individual patients, the ability of predicted disease time of patients to predict time since symptom onset was tested via a linear regression model. Based on the individual predicted disease time and the patient age at study inclusion, we computed age at predicted disease time zero, which should be in good correspondence with age at symptom onset if the model predicts a meaningful staging of patients. The correspondence between the two age measures and the time delay between symptom onset and predicted disease onset were investigated using linear regression and a likelihood ratio test between the linear model with both slope and intercept estimates and a model fixing the slope at 1. A similar comparison was

**TABLE 1** Baseline demographics of the included patient cohort. The mean and lower and upper quartiles are reported for the continuous measures

	All	MSA-C	MSA-P
Patients	121	53	68
Women	54 (45%)	24 (45%)	30 (44%)
Subtype			
MSA-P	68 (56.2%)	–	–
MSA-C	53 (43.8%)	–	–
Possible/probable	25/96	9/44	16/52
Age	62.1 (57.0, 67.0)	62.0 (56.0, 65.0)	62.6 (57.3, 67.0)
Age at symptom onset	56.7 (51.0, 62.0)	55.9 (50.5, 61.5)	57.3 (51.0, 62.3)
Years from symptom onset to inclusion	5.4 (3.0, 6.0)	5.9 (3.0, 8.0)	5.1 (3.0, 6.0)
Number of dropouts <sup>a</sup>	35	18	34
Number of deaths	29	12	17
Years from symptom onset to death	6.3 (5.0, 7.0)	7.2 (5.5, 8.5)	5.6 (4.0, 7.0)
Global disability score			
Level 0	5	2	3
Level 1	35	18	17
Level 2	28	11	17
Level 3	40	16	24
Level 4	13	6	7
UMSARS Part I	25.8 (15.5, 32.0)	24.5 (19.0, 29.5)	26.9 (20.0, 33.3)
UMSARS Part II	26.8 (20.0, 32.0)	25.4 (19.5, 31.0)	26.6 (21.0, 33.0)
UPDRS Part II	24.3 (17.0, 31.0)	22.9 (16.0, 29.0)	25.2 (18.0, 32.5)
UPDRS Part III	19.6 (15.0, 24.0)	18.4 (14.0, 23.8)	20.4 (16.3, 24.8)
Hoehn and Yahr	3.7 (3.0, 4.0)	3.8 (3.0, 4.3)	3.7 (3.0, 4.0)
Schwab and England	49.1 (30.0, 70.0)	52.8 (40.0, 70.0)	46.2 (03.0, 60.0)

<sup>a</sup>Number of dropouts is excluding deaths.

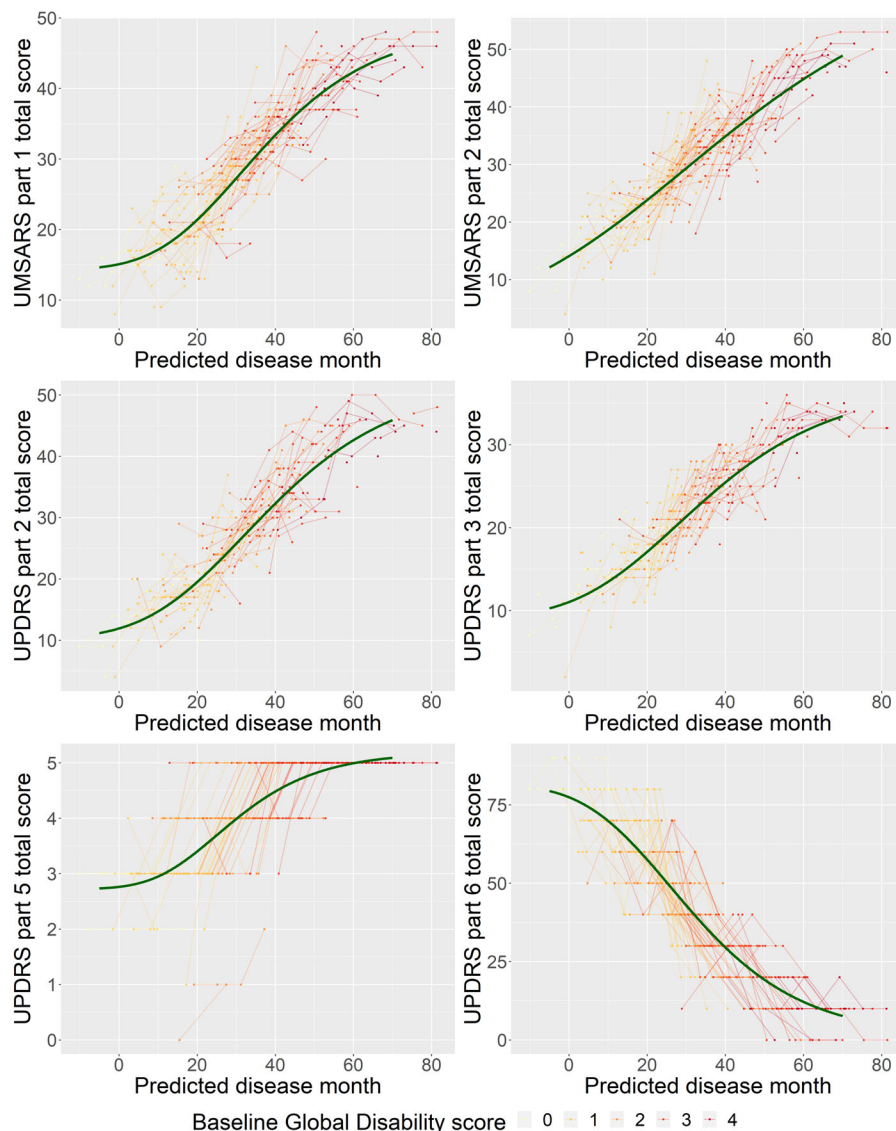
Abbreviations: MSA-C, multiple system atrophy-cerebellar symptoms; MSA-P, multiple system atrophy-parkinsonian; UMSARS, Unified Multiple System Atrophy Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

performed on the age at autonomic dysfunction onset. As final validation of the predicted disease stages of patients, two Cox proportional hazard models were fitted using time to death as the outcome. The first model adjusted for time since symptom onset and the second one for the predicted disease stages. The hazard ratios of the two models and their corresponding confidence intervals (CIs) were compared to examine the variables' ability to predict the time of survival.

To investigate the potential differences in disease progression between MSA-C and MSA-P patients, the effect of subtype diagnosis on the continuous staging and rate of decline parameters was investigated. Backward model selection was based on AIC, and the selection procedure stopped once a significant effect (tested with a likelihood ratio test) favored the more flexible model.

## Results

Of 141 MSA patients in the EMSA natural history study, 121 had an observed GDS score at baseline and at least one observation of at least one of the investigated assessment subscales UMSARS Parts I and II or UPDRS Parts II, III, IV, and VI. The patients were classified as either MSA-P or MSA-C, with 68 patients identified as probable or possible MSA-P and 53 diagnosed as probable or possible MSA-C. There were 67 men and 54 women. The distribution of patients according to their baseline GDS score was as follows: 5 patients at level 0, 35 at level 1, 28 at level 2, 40 at level 3, and 13 at level 4. The baseline demographic information for the patient cohort is provided in Table 1. The mean age at symptom onset was 56.7 years, with a



**FIG. 2.** Staging and mean curves for the outcomes resulting from the multivariate disease-progression model. The green curves represent the average population progression. The continuous ordering of patients is related to the average patient with a global disability score of 0. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

standard deviation of 8.5 years, whereas the mean age at study inclusion was 62.1, with a standard deviation of 7.9. The average time from symptom onset to inclusion was 5.4 years, with a standard deviation of 4.0 years. Of the included patients, 29 died during the study, with a median survival time from symptom onset to death of 6.0 years and an interquartile range of 2.0 (5.0, 7.0) years. The distribution of each assessment scale at study inclusion is provided in Table 1.

The multivariate model fit on each assessment scale is shown in Figure 2, with the population mean progression curve shown in green. The predicted disease continuum spans a period of approximately 6.25 years (75 months, see Fig. 2), with time zero defined as the average time when the observed patients had a GDS score of 0, which can be several years after symptom onset. The estimated fixed staging effects of the model showed that the time it took an average patient to progress from a GDS of 0 to a GDS of 1, 2, 3, and 4 was 11.7, 21.5, 34.8, and 50.6 months, respectively.

The estimated standard deviation of the subject-specific staging effect was 8.48 months, suggesting a substantial variation in disease progression between patients with similar GDS score at baseline.

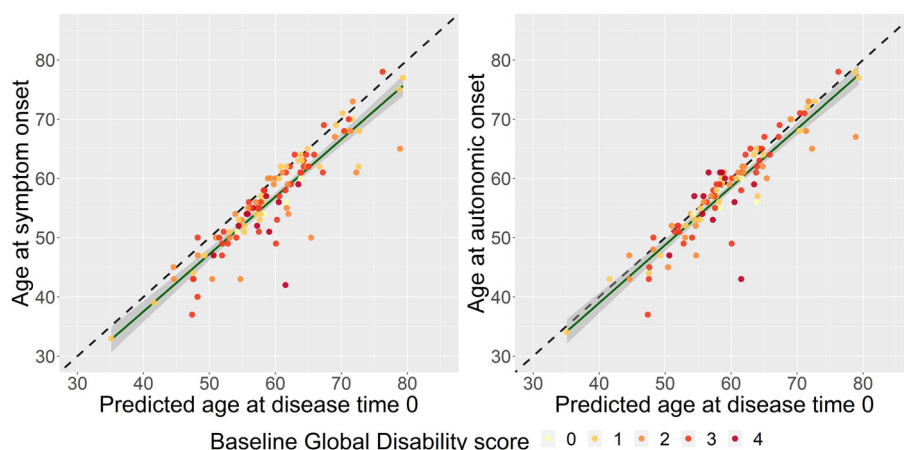
To verify the need for the nonlinear model, the AIC of the proposed model of 9672.8 was compared to the AICs of both a linear mixed-effects model and a random slope and intercept model, with quadratic time being 10,064.5 and 10,101.5, respectively. This suggests a more nonlinear progression of MSA, which the proposed model accounts better for.

Based on the estimated multivariate model, the age of the patients at predicted disease time 0 was computed and compared to the reported age at symptom onset, as shown in Figure 3. The slope was estimated to be 0.97 with a CI of (0.89, 1.05), indicating good agreement between predicted disease time and symptom onset. This model was not found significantly better than a model, with slope

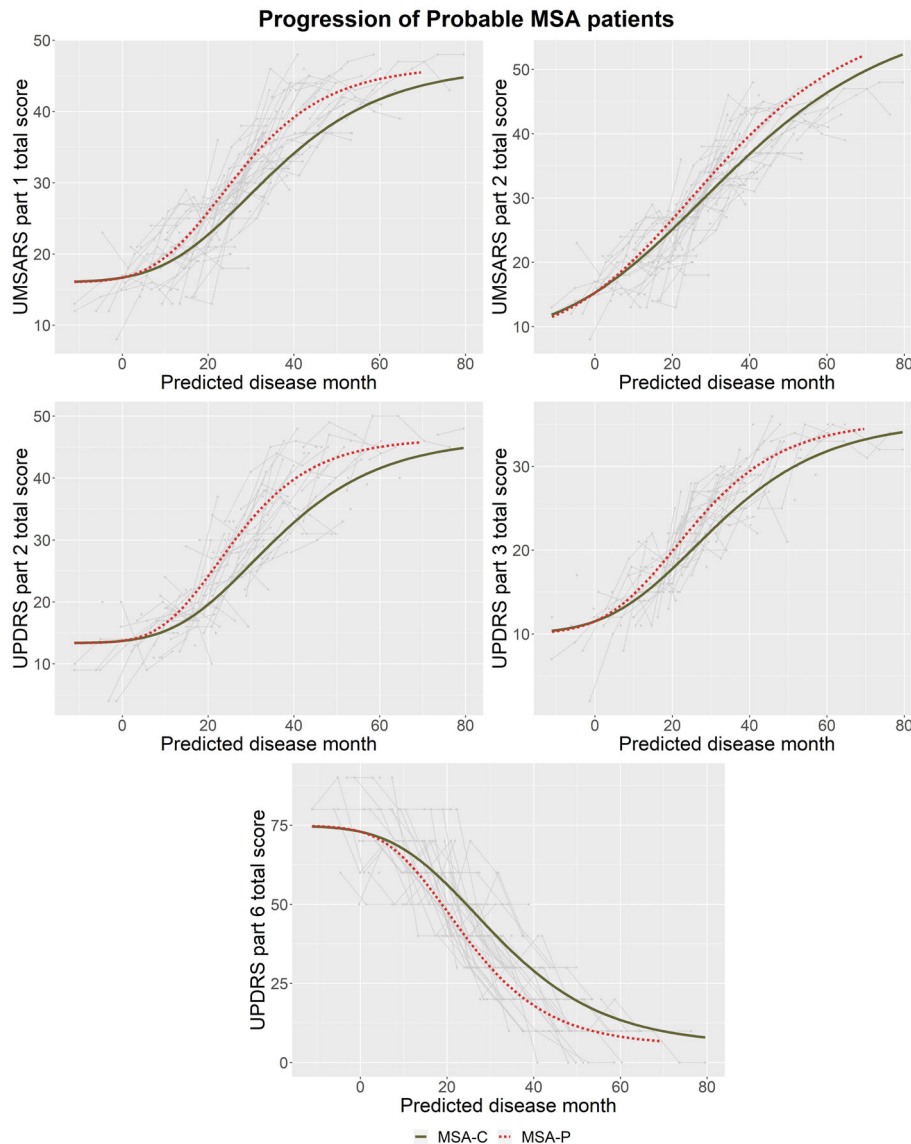
fixed at one corresponding to agreement between the two measures' assessment of disease time except for a potential delay between symptom onset and predicted disease time 0. The intercept of this regression line was  $-3.1$  years with a CI of  $(-3.7, -2.4)$ , suggesting that an average patient reached predicted disease time 0 approximately 3 years after symptom onset. Similarly, the age at onset of autonomic symptoms and the predicted age at disease time 0 were compared. The linear slope was estimated to be 0.98 with a CI of  $(0.90, 1.06)$ , indicating good agreement between predicted disease time and onset of autonomic symptoms. The intercept of the model with the slope fixed at 1 was  $-1.42$  years with a CI of  $(-2.06, -0.78)$ , implying that the average patient experienced onset of autonomic dysfunction approximately 1.5 years before disease time 0.

The association between time since symptom onset or the predicted continuous disease stage and survival time was compared by fitting two Cox proportional hazard models. Testing the proportional hazard assumption showed no indication of the assumption being violated ( $P > 0.2$  for both models). Both hazard ratios are reported in units of years and therefore describe the relative increase in hazard associated with being 1 year later in disease measured by either time since symptom onset or predicted continuous disease stage. The estimated hazard ratio of time since symptom onset was 1.07 with a 95% CI of  $(0.99, 1.15)$ , suggesting little to no effect of reported time since symptom onset on survival time. The hazard ratio of the predicted disease time on the contrary was 1.67 with a 95% CI of  $(1.27, 2.20)$ , suggesting a markedly increased hazard for patients who are predicted 1 year further along the disease continuum.

In the present study, 29 patient deaths were recorded. The majority of deaths occurred in the latter half of the predicted disease continuum. Among patients with recorded deaths, the median survival time from time 0 on the predicted disease



**FIG. 3.** Predicted age at disease time 0 associations to reported age at (left) symptom onset and (right) onset of autonomic symptoms. Given perfect correspondence, the regression fits (green lines) and  $y = x$  (black lines) would be parallel, with intercepts representing time lags. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIG. 4.** Difference in disease progression trajectories between MSA-C (multiple system atrophy-cerebellar symptoms) and MSA-P (multiple system atrophy-parkinsonian) patients. The analysis was stratified to patients with a baseline diagnosis of probable MSA. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

continuum was 3.4 years with an interquartile range of 1.4 (2.9, 4.3) years. Adding the estimated 3-year difference from first symptoms to disease time 0 results in the observed survival time of approximately 6 years.

Due to the low number of patients with an MSA subtype diagnosis classified as “possible” at baseline, the analysis of subtype effects on the disease progression trajectory was stratified to the 109 patients, with an MSA subtype diagnosis classified as “probable.” Subtype was not found to affect the continuous staging of patients but was found to have a significant effect on the rate of progression for a subset of the assessment scales ( $P < 0.0001$ ). Figure 4 shows the average difference in disease progression between MSA-C and MSA-P patients for the subset of assessment scales where the model resulted in a significant difference in progression rate between subtypes.

## Discussion

We presented a new method for modeling disease progression of MSA. The modeling framework predicted continuous staging of patients along the disease continuum and estimated a population-level disease progression trajectory of subscales of UMSARS and UPDRS. The population-level trajectories were modeled by generalized logistic functions to allow for nonlinearity in the outcome measures along the disease progression of MSA. The continuous staging of patients was based on their baseline global disability score and longitudinally observed trajectories on the clinical scales. The estimated baseline group effects showed that it took patients on average 51 months to reach the most severe level of disability relative to when they were reporting no disability. The proposed model

showed a better fit than a linear mixed-effects model and a random slope and intercept model quadratic in time. This indicates that the simpler models may overestimate and underestimate disease severity depending on the disease stage and the sample at hand. The validity of the predicted disease continuum was evaluated based on relations to reported anchor points such as registered time of symptom onset and survival time. Survival analyses showed a substantially increased hazard of dying for patients predicted to be further along the disease continuum, whereas this was not the case when measuring disease progression as reported time since symptom onset, which may be affected by significant recall bias. The finding of a largely parallel relation between age at symptom onset and age at predicted month 0 on the disease continuum further indicated validity of the predicted progression.

Analyses found the reported symptom onset to precede the predicted disease time 0 by about 3 years on average, suggesting that the patients with the mildest disability were included in the study 3 years after the initialization of symptoms. In addition, the 29 patients who died during the EMSA study survived on average 3.4 years after the predicted disease time 0 in good correspondence with an average survival time from symptom onset of 6 to 10 years.<sup>3,6-8</sup>

There have been different conclusions concerning the comparison of disease progression between MSA-C and MSA-P patients.<sup>6,13-15</sup> Including the effect of subtype in the nonlinear progression model suggested a slowed progression for the MSA-C patients compared to the MSA-P patients for five of six investigated assessment scales (UMSARS Part I and Part II and UPDRS Part II, Part III, and Part VI). The reasons for faster progression of the MSA-P patients could be different. One could be that the scales are more sensitive to change in symptoms of MSA-P patients compared to MSA-C patients or that MSA-P patients are more likely to be diagnosed at a later stage of the disease due to its similarity to Parkinson's disease.

There is an increasing focus on development of disease-modifying therapies for MSA, but this presents with challenges related to early diagnosis, heterogeneous presentation, and lack of progression markers.<sup>33</sup> Due to the improved data fit of the presented model and the natural handling of disease progression, it has the potential to increase the power to detect a treatment effect of such novel disease-modifying compounds, as the variation in clinical outcome measures due to differences in disease progression will be better explained. Furthermore, identifying which measures are most sensitive to detect disease stage can be used to develop inclusion criteria for clinical trials that ensure a more homogeneous patient population. As there are currently no treatments for MSA available, symptomatic nor disease modifying, this would be important to everyone affected by this debilitating disease.

The proposed methodology may also have further advantages that should be explored. It may inform about

sensitivity to change of subitems and could ultimately be used to enhance the clinical usefulness of the scales.

This study has some limitations. The analyses were based on a small sample size, and the predicted disease continuum was solely based on longitudinal measures of UMSARS and UPDRS subscales. These subscales might reflect the progression of only some aspects of the disease, missing out on important information for modeling the overall disease trajectory. Joint modeling, including information on different biomarker modalities such as imaging or fluid biomarkers, could increase the sensitivity to change in the early and late stages of disease and therefore refine the predicted disease continuum. Furthermore, the model performance should be externally validated to investigate how well the results generalize. Future work should focus on further investigating covariate and patient-level effects on the rate of progression and continuous staging of patients. In the current work only the difference in the rate of progression between MSA subtype for patients with a probable diagnosis was considered. The possibility of modeling patient-level differences in the rate of progression through added random model coefficients was explored but was found to be not possible due to the sparseness of longitudinal follow-up. Additional analyses should be conducted to highlight other predictors of faster progression on allowing different patient-level rates of decline. Finally, the mixed effects modeling handled missing data due to death as missing at random, which assumes that the multivariate trajectories can be estimated based on the observed data. While this can be challenged, handling death differently would require strong assumptions. ■

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## Data Availability Statement

Restrictions apply to the availability of these data, which were used under license for this study. The data that support the findings of this study are available from their respective owners upon reasonable request

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## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.