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Predictive modeling of spread in adult-onset isolated dystonia: Key properties and effect of tremor inclusion

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CONFLICT OF INTEREST

All authors report no disclosures related to the content of this research.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Abstract

Background and purpose: Several clinical and demographic factors relate to anatomic spread of adult-onset isolated dystonia, but a predictive model is still lacking. The aims of this study were: (i) to develop and validate a predictive model of anatomic spread of adult-onset isolated dystonia; and (ii) to evaluate whether presence of tremor associated with dystonia influences model predictions of spread.

Methods: Adult-onset isolated dystonia participants with focal onset from the Dystonia Coalition Natural History Project database were included. We developed two prediction models, one with dystonia as sole disease manifestation (“dystonia-only”) and one accepting dystonia OR tremor in any body part as disease manifestations (“dystonia OR tremor”). Demographic and clinical predictors were selected based on previous evidence, clinical plausibility of association with spread, or both. We used logistic regressions and evaluated model discrimination and calibration. Internal validation was carried out based on bootstrapping.

Results: Both predictive models showed an area under the curve of 0.65 (95% confidence intervals 0.62–0.70 and 0.62–0.69, respectively) and good calibration after internal validation. In both models, onset of dystonia in body regions other than the neck, older age, depression and history of neck trauma were predictors of spread.

Conclusions: This predictive modeling of spread in adult-onset isolated dystonia based on accessible predictors (demographic and clinical) can be easily implemented to inform individuals’ risk of spread. Because tremor did not influence prediction of spread, our results support the

argument that tremor is a part of the dystonia syndrome, and not an independent or coincidental disorder.

Keywords

isolated dystonia; neurological diseases; predictive models; spread; tremor

INTRODUCTION

Adult-onset isolated dystonia represents a heterogeneous clinical spectrum that includes tonic and phasic involuntary, patterned contractions commonly involving facial, cervical, upper limb and laryngeal muscles [1]. Anatomic spread of dystonia from the body region affected at onset to other regions may have a profound impact on quality of life and daily functioning. Despite this, the neural mechanisms implicated in this anatomic spread are still poorly understood. Over the past 15 years, several studies have advanced our understanding of the frequency, topography and risk-modifiers of spread in adult-onset idiopathic dystonia [2–8]. Most of these reports analyzed single- or multicenter cohorts of different size, either cross-sectionally or retrospectively [2,3,4,5,8], with the exception of two prospective studies [6,7] that also differed substantially in sample size. Overall, a higher risk of spread has been consistently demonstrated in patients with cranial onset [2,3,4,5,7], whereas a positive association between spread and alcohol responsiveness [7], family history [3,6,7] and presence of tremor as a “dominant” feature [7] were reported only by some authors. It remains unclear whether the analysis of these demographic and clinical variables might help clinicians predict the presence of spread in an individual patient. Understanding spread of adult-onset isolated dystonia could have a substantial impact on patient counseling and the design of future clinical trials. In addition, a risk prediction model based on clinical/demographic variables would help identify individuals at risk who might benefit from a targeted intervention or preventative approach.

We must take into account the contribution of coexisting tremor when tackling prediction of spread in adult-onset isolated dystonia as its frequency in this patient population is relatively high [9–14]. Neurophysiological studies suggest that coexisting tremor may be the clinical hallmark of an “oscillatory” pathophysiological subtype of adult-onset isolated dystonia, in which cerebellar outflow is more dysfunctional than in other subtypes [15–18]. Tremor may occur in a body region manifesting dystonia (labeled in the Movement Disorders Society 1998 [19] and 2018 [20] classification of tremor as “dystonic tremor”) and/or in a region not affected by dystonia (labeled in the same classifications as “tremor associated with dystonia”). The inclusion of both these tremor subtypes as a “core” feature of adult-onset isolated dystonia is supported by the observation of clinical similarities between patients with and without tremor. [9,21] If tremor is a core feature of adult-onset isolated dystonia, then its manifestation in a given body region would qualify this region as clinically affected, even when dystonia is absent in that region. However, previous studies exploring spread in this condition did not include tremor as a standalone manifestation.

The main objective of the present study was to develop and validate a prediction model of anatomic spread of adult-onset isolated dystonia employing the Dystonia Coalition cohort.

In addition, we independently developed two different predictive models, which differed on whether tremor was included as a disorder manifestation or not.

METHODS

Data

Participant data were acquired from the ongoing Natural History Project database of the Dystonia Coalition (www.dystoniacoalition.org), a multicenter, cross-sectional and prospective study of patients with adult-onset isolated dystonia. Participants were enrolled between January 12, 2011 and December 14, 2018 across 30 clinical sites in the United States, Canada, France, Germany and Italy [7,8]. The study was approved by the internal review boards of all participating clinical sites and by the Calgary Health Research Ethics Board (project # REB18–1827). Study inclusion required a diagnosis of adult-onset isolated dystonia according to international criteria [1]. Exclusion criteria were diagnosis of dystonia secondary to known causes such as medication-induced dystonia, brain structural lesions, parkinsonian syndromes and, in the case of cervical dystonia, those with orthopedic procedures that may affect neck movement. All participants gave written informed consent according to the principles of the Declaration of Helsinki.

For all participants, local physicians or coordinators completed intake forms that included documenting all body regions affected by dystonia currently or in the past, along with the age of onset of dystonia for each body region listed. All participants underwent neurological examination and were rated using the Global Dystonia Rating Scale (GDRS). Body regions of spread (defined as the appearance of dystonia in a region previously unaffected, which is not the region of onset) included in our analyses were cranial region (including upper and lower face, jaw and tongue), larynx, neck, hand, upper arm (not including shoulder), trunk, pelvis, upper leg and foot. If the presence of any tremor (regular or irregular/jerky) was documented on examination, the investigator was asked to note whether the patient's dystonia was dominated by tremor more than tonic or twisting movements. Information on age of onset, anatomic site(s) of onset, presence of a family history of dystonia, alcohol responsiveness of dystonia, and history of trauma prior to symptom onset were acquired through self-report on a history intake assessment form. Presence of depression was defined by a Beck Depression Inventory-II [22] (BDI-II) score greater than 13. All information available up to the last study visit at the time of database consultation (June 2019) was included in the analyses.

Outcome and predictors

The outcome of our study was binary, determined by whether spread to other body sites occurred after symptom onset. Two prediction models were developed, one defined by the presence of dystonia (i.e., tonic or phasic, patterned contractions as defined in Albanese et al. [1]) as the only manifestation of disease ("dystoniaonly" model), and the other defined by the presence of "dystonia OR tremor" as manifestation of disease ("dystonia OR tremor" model; this model therefore includes as affected those body sites manifesting dystonia only, body sites manifesting dystonia and tremor, and body sites manifesting tremor only). Predictors were selected on the basis of previously published studies exploring spread and

clinical plausibility of association with spread. These included age [5], sex [23–25], disease duration [26], family history [3,6], onset site (categorized as “cranial”, “cervical”, or “in other sites”; due to the small number of other individual sites of onset, the latter category combined larynx, hand, upper arm, trunk, pelvis, upper leg and foot) [2,4,5,7], presence of tremor as a prominent feature (“tremor-dominant” dystonia) [6,27], head trauma [25], limb trauma, neck trauma [28], presence of depression [29], and alcohol responsiveness of dystonia [30]; face trauma was excluded as a predictor from further analyses due to its low prevalence.

Statistical analysis

Sample characteristics were described using mean, standard deviation, median, quartiles, and frequency distributions. For each of the two models, differences between patients with and without spread were compared using the Mann–Whitney U- and χ^2 tests for continuous and categorical variables, respectively. We used logistic regression analysis to assess risk of spread. The linear relationship between continuous candidate predictors (age and disease duration) and the log of the odds of presence of spread were assessed using linear splines and restricted cubic splines. We based our selection of variables on a combination of clinical relevance and the Akaike information criterion to obtain the most parsimonious models, while retaining age and sex. All variables were included in the model prior to selection and any possible two-way interactions were tested and retained if clinically meaningful and statistically significant at an alpha level of 0.05. We evaluated predictive accuracy based on measures of discrimination (the ability to distinguish high-risk individuals from low-risk individuals) and calibration (the agreement between predicted and observed values). We assessed discriminatory performance based on area under the receiver-operating characteristic curve (AUC), while calibration was assessed by graphically comparing predicted and observed values [31,32]. An internal validation bias-corrected bootstrapping method (B = 500) was used to examine the validity of the prediction models. Analyses were performed using R studio “rms” package [33]. For statistical power considerations, a good average requirement of events per variable for clinical risk prediction models is at least 15 [34]; we had a maximum number of 13 potential predictors with a sample size of 870 (where at least 386 patients had spread), so we have more than 25 events per variable; therefore, there was sufficient power to obtain reliable estimation of variables for our prediction modeling (logistic regression).

Our predictive model reporting was based on the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines (Supplementary File 1) [35].

RESULTS

Characteristics of the study population

From the original cohort of 1,255 participants with adult-onset isolated dystonia, we excluded 247 participants who had more than one body region affected by dystonia at onset (segmental onset), to minimize misclassification of participants with respect to onset region. (Supplementary Table S1 presents descriptive statistics on the distribution of spread and

predictors in participants reporting segmental onset.) The analysis of candidate predictors for predictive modeling was therefore conducted on 1008 participants. Tables 1 and 2 present the distribution of all candidate predictors and their comparisons between patients with and without spread with respect to the “dystonia-only” and the “dystonia OR tremor” models.

To test whether or not data were missing completely at random (MCAR), we applied “MissMech” [36], which is based on testing equality of covariances between groups having identical missing data patterns [37]. Based on four different missing patterns appearing in our data, there was not sufficient evidence to reject MCAR ($p = 0.19$) and therefore we focused our analyses on patients with a complete dataset. Due to the high frequency of unavailable data on dystonia responsiveness to alcohol (Tables 1 and 2), this variable was excluded from our list of predictors. Patients with a complete dataset ($n = 870$) did not significantly differ from those with missing data ($n = 138$) for age, sex, spread characteristics, disease duration, frequency of trauma, family history of dystonia, history of depression, and proportion of patients with “tremor-dominant” dystonia (Supplementary Table S2). Patients with missing data had a slightly higher GDRS score and a slightly different distribution of onset sites (Supplementary Table S2).

Predictive models

Our “dystonia-only” predictive model yielded an AUC (based on the original cohort) of 0.67 (95% confidence interval [CI] 0.64–0.71), and an overfitting-corrected index based on bootstrapping of 0.65 (95% CI 0.62–0.70). Predictors in the models (Table 3) included age, sex, presence of depression, site of dystonia onset, history of neck trauma, disease duration, “tremor-dominant” dystonia, and family history. Irrespective of including tremor as a disease manifestation, the risk of spread was higher among patients with dystonia onset in cranial or other body sites (compared with cervical), presence of depression, older age, and presence of history of neck trauma prior to disease onset. For example, for the “dystonia-only” model, the estimate of the odds of spread in patients with cranial onset of dystonia was 3.6 times (95% CI 2.5–5.2) higher than the odds of spread in patients with cervical onset of dystonia, after controlling for other predictors.

Our “dystonia OR tremor” predictive model yielded almost identical discriminatory performance compared to the “dystonia-only” model, with an AUC (based on the original cohort) of 0.66 (95% CI 0.63–0.70), and an overfitting-corrected index based on bootstrapping of 0.65 (95% CI 0.62–0.69). The calibration curves of the two models, obtained using bootstrapping validation, were similar, and both indicated an overall good calibration (Figure 1).

Finally, for each of the two predictive models, Figure 2 displays nomograms built to measure a cumulative index that is calculated by adding all the points assigned to each predictive variable within that model in an individual patient. This index is then transformed into the individual’s predicted risk of spread (higher index score indicating higher predicted risk of spread). For example, applying the “dystonia-only” model (Figure 2a), a 70-year old woman with depression, cranial dystonia onset, no history of neck trauma, with family history, 10 years of disease duration, and no history of dystonia dominated by tremor will score as follows: 58 (on age) + 7 (on sex), + 33 (on depression), + 32 (on family history), + 0 (no on

history of neck trauma) + 100 (on site of onset) + 8 (on disease duration) + 0 (on dystonia dominated by tremor) = 238, which will correspond to an 80% risk of spread. Using the nomogram related to the “dystonia OR tremor” model (Figure 2b), the same patient (without neck trauma) will score a cumulative predictive index of (71 + 0 + 28 + 57 + 11 + 0 + 0 + 0) =167, which will correspond to approximately 75% risk of spread.

DISCUSSION

The novelty of the present study is the development and validation of risk prediction models for the anatomic spread of adult-onset isolated dystonia, using widely available predictors based on a clinical dataset from the Dystonia Coalition cohort. Overall, our models predict a higher risk of spread in patients with the following characteristics: dystonia onset in a region other than the neck, older age, depression, and a reported history of neck trauma prior to disease onset. At the same time, the discriminatory and calibration performance of our models shows that demographic and clinical variables have, at best, only a moderate prediction ability to diagnose anatomic spread.

Most of the previous studies have focused on the prevalence, anatomic distribution and risk-modifying variables of spread in adult-onset isolated dystonia, based on retrospective datasets of different size and number of recruitment centers [2,5,6]. Two reports adopted a prospective design [6,7], including a recent study of 487 patients from the Dystonia Coalition cohort (a different subset of this cohort compared to ours) with median disease duration ranging between 3.6 and 4 years across different onset regions [7]. None of these studies used a predictive modeling approach to assess the ability to discriminate between presence and absence of spread while taking into account selected demographic and clinical factors.

Our predictive models confirmed that dystonia onset in the neck carries a lower risk of spread when compared to other onset regions. The prevalence of spread observed in our cohort in patients with neck onset (36%) and cranial onset (62%) is consistent with the upper range of prevalence estimates reported in previous studies (8%–38% and 50%–64%, respectively [2,5,7]). We observed a greater prevalence of spread than Berman et al. [7], who investigated this phenomenon in the Dystonia Coalition cohort and reported a frequency of spread in 8.4% of patients with neck onset and 50% of those with cranial onset. However, Berman et al. conducted a prospective study in a smaller subset of the Dystonia Coalition cohort, after excluding patients with disease duration longer than 5 years. Compared to their prospective investigation, the present study detected larger estimates of spread due to the inclusion of patients with longer disease durations. Whereas the design of this earlier prospective study minimizes recall bias concerning onset by restricting disease duration to 5 years or less, it also carries a higher risk of misclassifying as “non-spreading” those individuals who might develop spread later in the disease course. We also observed a slightly higher prevalence of spread compared to the previous literature in patients with upper limb onset [38,39] (52%) and laryngeal onset [40] (41%), which, as mentioned above, might be attributable to small differences in recall bias across studies. As expected, spread was more prevalent for all onset region subgroups when tremor was included as a standalone manifestation of disease.

The observation of older age and longer disease duration as predictors of a diagnosis of spread is not surprising, given that spread events build up over time and are therefore detectable in greater numbers cross-sectionally in older patients or patients with a longer duration of illness. Disease duration was a weaker predictor than age in both of our models, which is in line with a previous retrospective study from an Italian multicenter cohort that identified an age window of vulnerability to spread [5]. Of note, Berman et al. [7] did not observe an effect of age at onset on the risk of spread in their prospective analysis in the Dystonia Coalition cohort, but the mean age of their population was approximately 5 years younger than the population in the present study, which may also have influenced their ability to detect an age effect.

Unlike previous reports, our models included depression as a relevant predictor of the presence of spread. Depression is a well-established non-motor feature in adult-onset isolated dystonia, as confirmed by large service-based [41] and population-based [29] investigations, as well as by study meta-analyses [42]. Given the uncertainty around the relative timing of depression onset and spread in the Dystonia Coalition cohort, its effect as a predictor of spread could be explained by reverse causality, that is, patients with spread are more likely to develop depression. The lack of information on the subjective perception of dystonia severity and of its impact on social fitness and other areas of functioning do not allow us to evaluate in more depth whether reverse causality is the best explanation for a predictive effect of depression on spread. Of note, clinic-based studies do not consistently report an association between depression and focal versus non-focal distribution of adult-onset isolated dystonia [43]. Overall, our observation suggests that this association should be investigated in future prospective studies, given the finding that depression onset can predate dystonia onset in approximately 60% of cases [44], and the recent finding of familial co-aggregation of depression and adult-onset isolated dystonia from population-based registries [29].

The identification of neck trauma and, with weaker influence, head trauma as predictors of spread is novel and potentially interesting. Trauma, including car accidents, with need for hospitalization and surgical intervention has been reported in association with cervical dystonia in a case–control study [28]. Nevertheless, conflicting evidence persists across studies on the existence of an association between trauma and dystonia onset [45], and pathophysiological mechanisms explaining this association remain elusive. Our results are based on a relatively small number of trauma self-reports; therefore, they are prone to recall bias and should be verified by future prospective investigations. Moreover, because of the low prevalence of history of neck trauma, the present study was not sufficiently powered to evaluate whether its predictive effect is greater in subgroups of patients with a specific site of onset or site of spread.

Our analysis showed that family history of dystonia is a weak predictor of spread. This variable was included in our “dystonia-only” model, but was not included in the most parsimonious model obtained applying the Akaike information criterion to the “dystonia OR tremor” dataset. In the prospective study by Berman et al. [8] a stronger association was observed between family history and spread. The difference in demographic features between the cohort subsets included in these two studies might, in part, explain this

difference in predictive effect of family history. The future application of our predictive models to prospective cohorts is necessary to clarify this aspect.

We did not confirm a predictive effect of dystonia responsiveness to alcohol on spread, as previously reported [7]. Of note, we highlight the high frequency (37%–42%) of participants who were unable to report alcohol responsiveness in the Dystonia Coalition cohort [7], likely due to insufficient exposure to alcohol in a substantial proportion of cohort participants. Because of this difficulty in ascertaining dystonia responsiveness to alcohol and its exclusion from predictive models in the present study, the role of this variable in predicting spread of adult-onset isolated dystonia appears limited.

Another key new finding of the present study is that the discriminatory performance, reliability, goodness-of-fit and most contributing predictors of the predictive model do not change if we include tremor in a non-dystonic body region as an expression of adult-onset isolated dystonia. Overall, discrimination and calibration performance of the two models indicates a similar ability of clinical/demographic variables to predict spread regardless of whether tremor in a nondystonic region is treated as a core feature of this condition. Even if the prevalence of spread in our cohort increased only by approximately 8% after including tremor as a standalone feature, these results support the concept that tremor in a body region not affected by tonic or phasic, patterned contractions is an intrinsic manifestation of adult-onset isolated dystonia. These results and the existing evidence of high coprevalence rates for tremor and dystonia [13] support the existence of overlapping biological mechanisms [46]. At the same time, the ability of our models to predict dystonia spread exclusively based on putatively relevant demographic and clinical variables is clearly sub-optimal. Although other, not yet investigated clinical variables might have predictive value, our findings suggest that subclinical, physiological or genetic markers need to be explored to predict the anatomic progression of dystonia.

The present study has some noteworthy limitations. The date of spread was not available for all participants in whom spread had already occurred before database entry, which hindered a longitudinal retrospective analysis of predictors of spread. We also acknowledge the possibility of differences across sites in the ascertainment of milder forms of dystonia or tremor within the multi-center Dystonia Coalition cohort. In this respect, a recent study, focused on the characterization of tremor in this cohort, has highlighted the impact of recruitment center on both prevalence and type of tremor, implying potential differences in tremor ascertainment among experts [13]. Kinematic tools or electromyography might be more sensitive and specific than direct clinical observation in detecting tremor and differentiating it from nonrhythmic contractions. This notwithstanding, our findings are based on a large cohort systematically evaluated by multiple investigators, and therefore less likely to be influenced by small, non-representative groups of patients with very irregular tremor that may be misdiagnosed as dystonia, or by idiosyncratic investigator habits in evaluating tremor. Finally, we opted not to include sensory tricks amongst predictors [8] as these were collected as a binary variable (present/absent) despite their large phenomenological heterogeneity and their greater association with specific locations of adult-onset isolated dystonia.

In conclusion, we present here the key properties of predictive models of anatomic spread of adult-onset isolated dystonia based on demographic and clinical features which demonstrate moderate discriminatory performance and good calibration properties. Other tools (e.g. kinematic), physiological or neuroimaging markers should be explored to increase our ability to predict the progression of this condition. External validation of our models is needed for future studies. Incorporating tremor in nondystonic body regions as a clinical manifestation of dystonia does not decrease the goodness-of-fit of this model, which suggests that tremor can be considered as part of the dystonia syndrome, and not as an independent comorbid disorder. This finding can inform the design of new observational studies exploring risk prediction, prognostication and basic mechanisms of spread, as well as clinical trials of new interventions to prevent spread [7] in adult-onset isolated dystonia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Data of this study are available from the corresponding authors upon reasonable request.

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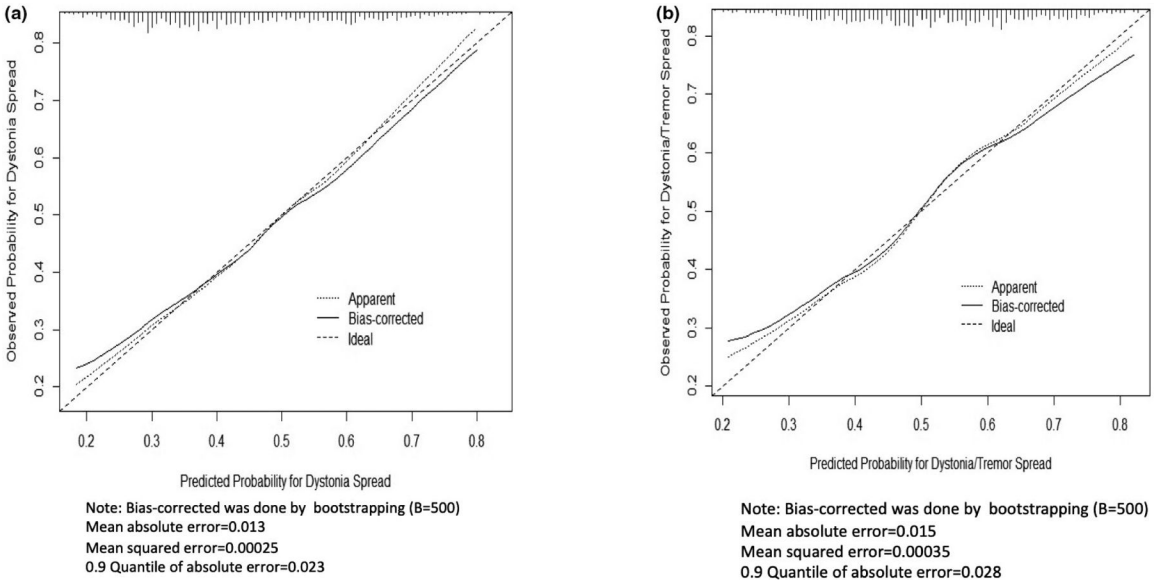

FIGURE 1.

Calibration plots from the internal validation procedure (bootstrapping-corrected overfitting)

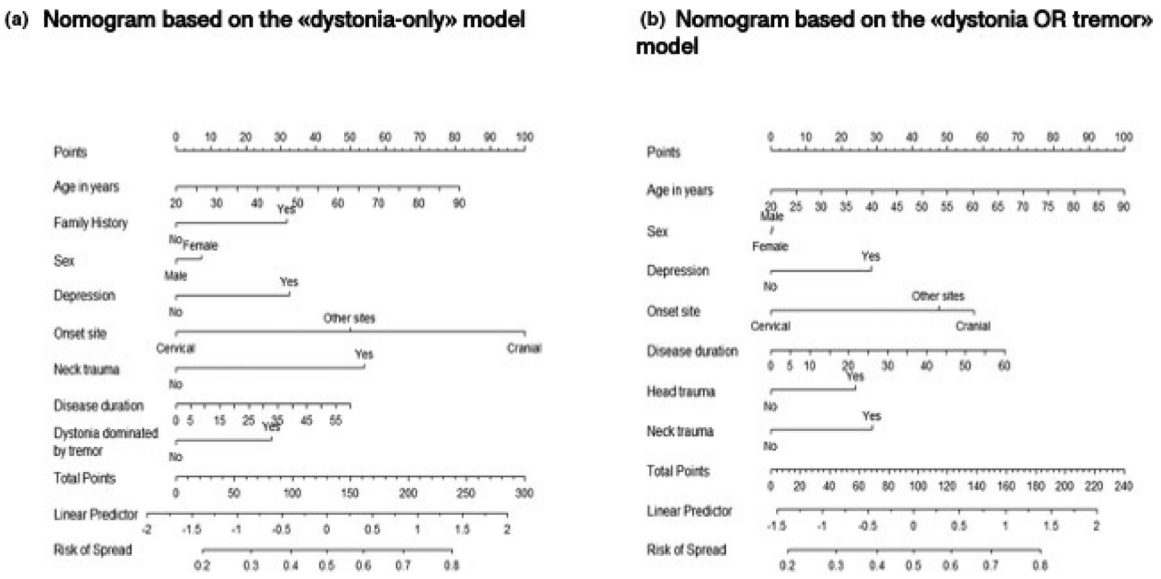

FIGURE 2.

(a) Nomogram that allows calculation of the value of a cumulative predictive index ("Total Points") of spread for each individual, based on the "dystonia-only" predictive model. The index score ("Total Points") is calculated summing the points for each of the predictive variable, which can be measured graphically connecting through a perpendicular line the point on the metric scale for each variable to the metric scale for Points. A higher index score indicates higher predicted risk of spread. For example, a 70-year-old female with depression, cranial dystonia onset, no history of neck trauma, with family history, 10 years of disease duration, and no history of dystonia dominated by tremor will score as follows: 58 (on age) + 7 (on sex) + 33 (on depression) + 32 (on family history) + 0 (no on history of neck trauma) + 100 (on site of onset) + 8 (on disease duration) + 0 (on dystonia dominated by tremor) = 238, which will correspond to a 80% risk of spread. (b) Similar nomogram, but based on the "dystonia OR tremor" predictive model. Using this second nomogram, the same patient (without neck trauma) will score a cumulative predictive index of (71 + 0 + 28 + 57 + 11 + 0 + 0 + 0) =167, which will correspond to approximately 75% risk of spread

TABLE 1

Descriptive statistics of demographic and clinical variables of interest in the overall sample and in the two subgroups (no spread and spread) within the "dystonia-only" model

	Overall sample ***N*** **= 1008**	**No spread** ***N*** **= 568**	**Spread**[a] ***N*** **= 440**	***p***
Mean (SD) age, years	60.7 (12.2)	59.4 (12.8)	62.5 (11.2)	<0.001
Median (Q1–Q3) disease duration, years	8 (4–17)	7 (4–16)	9 (4–19)	0.03
Female, *n* (%)	729 (72.3)	403 (71.0)	326 (74.1)	0.27
Race:White, *n* (%)	924 (92.6)	520 (92.4)	404 (92.9)	0.76
Usage of botulinum toxin[b], *n* (%)	791 (78.5)	432 (76.1)	359 (81.6)	0.03
Family history, *n* (%)	127 (13.6)	64 (12.2)	63 (15.4)	0.16
Head trauma before onset, *n* (%)	78 (7.8)	39 (6.9)	40 (9.1)	0.19
Limb trauma before onset, *n* (%)	111 (11.0)	65 (11.4)	46 (10.5)	0.62
Neck trauma before onset, *n* (%)	53 (5.3)	25 (4.4)	28 (6.4)	0.17
Face trauma before onset, *n* (%)	43 (4.3)	24 (4.2)	19 (4.3)	0.94
Initial sites, *n* (%)				
Cervical	620 (61.5)	397 (69.9)	223 (50.7)	<0.001
Cranial	223 (22.1)	84 (14.8)	139 (31.6)	<0.001
Upper limb	83 (8.2)	40 (7.0)	43 (9.8)	0.12
Larynx	64 (6.4)	38 (6.7)	26 (5.9)	0.61
Other sites	18 (1.8)	9 (1.6)	9 (2.1)	0.58
Depression, *n* (%)	217 (22.8)	107 (20.0)	110 (26.3)	0.02
Alcohol responsiveness of dystonia, *n* (%)				0.10
No	459 (45.5)	260 (45.8)	199 (45.2)	
Yes	158 (15.7)	100 (17.6)	58 (13.2)	
Unknown	391 (38.8)	208 (36.6)	183 (41.6)	
Dystonia dominated by tremor, *n* (%)	113 (11.4)	56 (10.8)	57 (13.1)	0.14

Abbreviations: Q1, the first quartile; Q3, the third quartile; SD, standard deviation.

[a]Distribution of sites of spread for the four most common sites of onset (total number of absolute values of site of spread representation is higher than the number of patients with spread for that site of onset, due to the possibility of multiple sites of spread):

Cervical onset (*n* = 223): spread to cranial sites, 106; spread to upper limb, 96; spread to larynx, 60; spread to trunk, 26; spread to pelvis, 3; spread to lower limb, 16.

Cranial onset (n = 139): spread to neck, 89; spread to upper limb, 25; spread to larynx, 31; spread to trunk, 6; spread to pelvis, 0; spread to lower limb, 1.

Upper limb onset (n = 43): spread to cranial sites, 10; spread to neck, 23; spread to larynx, 9; spread to trunk, 3; spread to pelvis, 1; spread to lower limb, 2.

Laryngeal onset (n = 26): spread to cranial sites, 14; spread to neck, 19; spread to upper limb, 10; spread to trunk, 1; spread to pelvis, 0; spread to lower limb, 1.

[b] The addition of "usage of botulinum toxin" to the predictive model detailed in Table 3 did not change its discriminatory performance or its calibration.

TABLE 2

Descriptive statistics of demographic and clinical variables of interest in the two subgroups (no spread and spread) within the “dystonia or tremor” model

	No spread ***N*** **= 490**	**Spread** ***N*** **= 518**	***p***
Mean (SD) age, years	58.6 (12.5)	62.7 (11.6)	<0.001
Median (Q1–Q3) disease duration, years	7 (4–16)	9 (4–19)	0.01
Female, *n* (%)	350 (71.4)	379 (73.1)	0.54
Race, *n* (%)			
White/Caucasian	447 (92.2)	477 (93.0)	0.62
Usage of botulinum toxin[a], *n* (%)	369 (75.3)	422 (81.5)	0.02
Family history, *n* (%)	59 (13.1)	68 (14.1)	0.64
Head trauma before onset, *n* (%)	31 (6.3)	48 (9.3)	0.08
Limb trauma before onset, *n* (%)	58 (11.8)	53 (10.2)	0.42
Neck trauma before onset, *n* (%)	22 (4.5)	31 (6.0)	0.29
Face trauma before onset, *n* (%)	23 (4.7)	20 (3.9)	0.51
Initial sites, *n* (%)			
Cervical	346 (70.6)	274 (52.9)	<0.001
Cranial	77 (15.7)	146 (28.2)	<0.001
Upper limb	30 (6.1)	53 (10.2)	0.02
Larynx	28 (5.7)	36 (7.0)	0.42
The rest	9 (1.8)	9 (1.7)	0.91
Depression, *n* (%)	89 (19.3)	128 (26.0)	0.01
Alcohol responsiveness of dystonia, *n* (%)			0.05
No	226 (46.1)	233 (45.0)	
Yes	89 (18.2)	69 (13.3)	
Unknown	175 (35.7)	216 (41.7)	
Dystonia dominated by tremor, *n* (%)	48 (10.0)	65 (12.7)	0.20

Abbreviations: Q1, the first quartile; Q3, the third quartile; SD, standard deviation.

[a]The addition of “usage of botulinum toxin” to the predictive model detailed in Table 3 did not change its discriminatory performance or its calibration.

TABLE 3

Odds ratio and related 95% confidence intervals expressing the association between individual predictive variables and the anatomic spread of adult-onset isolated dystonia in the two predictive models

	Dystonia-only		Dystonia or tremor	
AUC (95% CI)				
Original cohort	0.67 (0.64–0.71)		0.66 (0.63–0.70)	
Index-corrected	0.65 [0.62–0.70)		0.65 [0.62–0.69)	
	Estimate (SE)	**OR (95% CI)**	**Estimate (SE)**	**OR (95% CI)**
Age[a]	0.23 (0.10)	1.26 (1.04–1.54)	0.36 (0.09)	1.43 (1.19–1.72)
Female vs. male	0.09 (0.16)	1.10 (0.79–1.51)	−0.01 (0.15)	0.99 (0.73–1.34)
Depressed	0.42 (0.17)	1.52 (1.09–2.13)	0.46 (0.17)	1.58 (1.14–2.19)
Onset sites				
Cranial vs. cervical	1.29 (0.19)	3.63 (2.52–5.23)	0.93 (0.17)	2.52 (1.79–3.55)
Other onset sites vs. cervical	0.65 (0.19)	1.91 (1.31–2.78)	0.77 (0.19)	2.15 (1.49–3.11)
Neck trauma	0.70 (0.32)	2.01 (1.08–3.72)	0.70 (0.32)	2.01 (1.08–3.72)
Disease duration[a]	0.14 (0.10)	1.15 (0.95–1.39)	0.46 (0.31)	1.59 (0.87–2.90)
“Tremor-dominant” dystonia	0.35 (0.23)	1.42 (0.52–2.22)		
Family history	0.41 (0.21)	1.51 (0.99–2.28)		
Head trauma			0.38 (0.25)	1.47 (0.89–2.42)

Abbreviation: AUC, area under the receiver-operating characteristic curve; CI, confidence interval; OR, odds ratio.

[a]Age interquartile range = 15.5 years, with the first quartile (Q1) = 53.5 years old and the third quartile (Q3) = 69 years old; disease duration interquartile range = 13 years, with Q1 = 4 years and Q3 = 17 years.