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Survival analysis and prognostic nomogram model for multiple system atrophy

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A B S T R A C T

Objective: The purpose of our study was to explore the factors associated with the survival of multiple system atrophy (MSA) patients and to produce a prognostic nomogram to predict survival in an individual MSA patient.
Methods: 220 *probable* MSA patients were included from 2009 to 2013. Disease severity was measured by the Unified Multiple System Atrophy Rating Scale (UMSARS). The univariate and multivariable Cox regression analyses were used to identify factors associated with survival in MSA patients. A nomogram model predicting the probability of survival was formulated based on the results of the multivariate Cox analysis. The results were validated using bootstrap resampling and a prospective study on 80 patients included from January 2014 to August 2015 at the same institution.
Results: Median survival from symptom onset to death was 6.4 years (95%CI = 6.1–6.7). The multivariate Cox survival model suggested that autonomic onset, higher UMSARS score, frequent falls, orthostatic hypotension (OH) and shorter diagnostic delay were associated with poor survival. The nomogram model for the multivariate Cox survival model had a concordance index of 0.677 in primary cohort, which showed a concordance index of 0.721 in validation cohort.
Conclusion: Autonomic onset, higher UMSARS score, frequent falls, OH and shorter diagnostic delay at baseline were independent markers for poor survival in MSA. The prognostic nomogram model created by the significant independent factors for longer survival provided an effective way to predict the probability of longer survival in an individual MSA patient.

1. Introduction

Multiple system atrophy (MSA) is a fatal α-synucleinopathy characterized by parkinsonism, cerebellar ataxia, autonomic dysfunction and pyramidal tract dysfunction at any combination [1,2]. The etiology of MSA remains unknown. To date, no effective treatment for MSA is available. MSA has considerable variability in outcome, with a mean survival time for MSA being 6–10 years [3–6]. Better understanding of the prognostic factors of MSA may guide therapeutic interventions and the design of clinical trials, prolong the survival of patients with MSA and improve their living quality.

Although there were some studies focusing on the survival factors for MSA, the findings were not consistent among different studies. For example, older age at onset was identified to be associated with poor survival in most studies [3,7–10], but Low et al. failed to observe such association [5]. Some studies found that MSA-P subtype predicted worse survival [3,6,11], while two recent studies with large sample sizes noted that the disease subtype was not associated with survival in MSA [5,9]. Autonomic system involvement is particularly essential for the diagnosis of MSA. The early autonomic system involvement [7,9,10] and autonomic symptoms as initial symptoms [8] have been reported to predict poor survival. However, other study found that the life-span was not affected by initial or involvement of autonomic system [4].

Some limitations of the aforementioned studies may contribute to such inconsistent findings. First, the second consensus statement on the diagnosis of MSA was published in 2008 [12] and is thought to be the most highly valid diagnostic criteria at present. However, some studies did not use the consensus diagnostic criteria for MSA [3,11], which may affect the inclusion criteria of patients. Second, the Unified Multiple System Atrophy Rating Scale (UMSARS) has been considered to be a multidimensional, reliable, and valid scale for clinical assessments of

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MSA patients [13], but only two of those studies included in enough samples [5,6] applied the UMSARS to measure the disease severity of MSA patients. Furthermore, some serum biomarkers, such as uric acid [14], lipids [15] and creatinine [16], were thought to be associated with the prevalence or disease severity of MSA; however, there was no available study of the role of these serum biomarkers for survival in MSA.

Therefore, it is worthy to comprehensively explore survival factors for MSA, including demographic information, clinical characters and serum biomarkers, by using a large patient population sample that meets the consensus diagnostic criteria for MSA and by measuring the disease severity with UMSARS.

Additionally, a nomogram has been developed in the majority of cancers [17,18], which was thought to be an ocular and effective tool for multifactor survival analysis but has never been applied in the MSA study. Nomogram provides a graphical representation of the factors that can be applied to calculate the probability of survival for an individual patient by the points associated with each associated factor. Thus, we attempted to establish a prognostic nomogram for MSA based on the independent survival factors identified in our study, which can predict the probability of longer survival in an individual MSA patient.

1.1. Patients and methods

A total of 220 MSA patients admitted to the Department of Neurology, West China Hospital, Sichuan University (Tertiary Referral Center of South-west China) from July 2009 to December 2013 were enrolled and followed up by using telephone or face-to-face interview in one-year interval by our neurologists until 31st December 2017. From January 2014 to August 2015, an independent cohort of 80 consecutive patients with MSA also was prospectively studied until 31st December 2017, using the same inclusion and exclusion criteria. These patients formed the validation cohort of this study.

For each patient, a diagnosis was established based on the probable MSA clinical diagnostic criteria [12]. Each patient was independently examined by two neurologists. The patients were categorized as the MSA-C subtype when cerebellar ataxia symptoms and signs were observed predominately and categorized as the MSA-P subtype when parkinsonism symptoms and signs were observed predominated at baseline. At baseline evaluation, all patients were evaluated by face-to-face interviews. Patients were subjected to brain MRI scan to exclude other neurological disorders at baseline evaluation. Fasting serum uric acid (UC), creatinine (CR), lipid concentration, which consists of total cholesterol, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) of all MSA patients were measured at the baseline visit. Clinical information regarding sex, age at onset, clinical information of motor symptoms (parkinsonism and cerebellar ataxia) and autonomic symptoms and neurological examination were recorded. Symptom onset was defined as the initial presentation of any motor symptoms (i.e., parkinsonism or cerebellar ataxia) or selected autonomic features including orthostatic hypotension or neurogenic bladder disturbances. Parkinsonism was defined as bradykinesia plus at least one of the following signs: resting tremor, rigidity, postural instability and gait changes. Cerebellar ataxia was defined as gait ataxia, ataxic dysarthria and limb ataxia [12]. Autonomic symptoms consisted of orthostatic hypotension(OH), bowel bladder symptoms, sexual impairment and erectile dysfunction in males. OH symptoms were defined as symptoms of light-headedness, altered vision, nausea, weakness, fatigue and a coat-hanger distribution of pain only while standing. Urinary urgency, frequency, incontinence and incomplete bladder emptying were considered bladder symptoms when these are not attributable to non-neurological cause. In males, erectile dysfunction was only recorded as the presenting symptom if the onset occurred with motor symptoms or within 1 year of bladder symptoms. We considered the patients involved in sexual impairment when the item “Sexual function” in UMSARS I was “Moderate impairment compared to healthy days”. Rapid-eye-movement sleep behavior disorder (RBD) was diagnosed according to the international classification of sleep disorders. Stridor was recorded according to documentation in the clinical history. Frequent falls were diagnosed as falls occurring more than once per month. All the participants underwent blood pressure testing to evaluate whether they had OH at the baseline visit, defined as a reduction of systolic blood pressure of at least 30 mm Hg or a reduction of diastolic blood pressure of at least 15 mm Hg after 3 min of standing from a previous 10-min interval in the supine position. The severity of MSA was assessed using UMSARS, which was assessed for each patient at the baseline visit. Higher scores indicate greater disease severity.

Diagnostic delay is defined as the time from symptom onset to the baseline evaluation in the present study. For the deceased patient, survival time was defined as the interval time from the date of onset to the date of death. Additionally, survival time is defined as time from disease onset to the present for surviving patients and the time from disease onset to the last contact for patients lost to follow-up. Loss to follow-up was due to a change in the telephone number or refusal to participate in more than three follow-up evaluations. Censored data included alive patients and loss to follow-up. Uncensored data only included patients with a known date of death.

All MSA patients gave informed written consent prior to being enrolled. This study was approved by the Ethics Committee of West China Hospital of Sichuan University.

1.2. Statistical analysis

Continuous variables were categorized into adequate forms according to the quartile to fit the proportional hazards. Kaplan-Meier curves were used to graphically analyze the overall death (or related death), and the log-rank test was performed to compare survival between patient subgroups. To identify variables associated with survival in MSA, univariate and multivariable Cox regression analyses were performed. We analyzed the following factors to determine which of them were related to disease outcome by using a Cox regression: age at onset, sex, sub-type, onset form, UMSARS score, diagnostic delay, presence with RBD, snore, stridor, orthostatic hypotension, bladder symptoms, erectile dysfunction, sexual impairment, parkinsonism symptoms, cerebellar symptoms, frequent falls, OH and levels of UC, CR, TG, total cholesterol, HDL-C and LDL-C. All predictors of interest were added in the starting full models before model selection. Stepdown method was used in model selection to choose predictive variables. Of the multiple variable combinations assessed, factors with the highest predictive value were parsimoniously selected for the scale, limited by the number of events. For the final models, predictive accuracy was assessed by discrimination (the ability of a model to separate patients with different outcomes) and calibration (how far predictions are from actual outcomes). Discrimination was measured with the concordance index (C-index), the larger the C-indexes were, the more accurate the prognostic prediction was. Calibration was measured by graphically plotting the predicted against the actual probability for tertiles of the predicted probability of recurrence. Bootstraps with 1000 resamples were used for internal validations for cox models. During the external validation of the nomogram, the total points of each patient in the validation cohort were calculated according to the established nomogram, then Cox regression in this cohort was per-formed using the total points as a factor, and finally, the C-index and calibration curve were derived based on the regression analysis.

2. Results

2.1. Clinical characteristics of patients

In the primary cohort, among the 220 enrolled patients with MSA, including 113 males and 107 females, 6 (2.7%) patients were lost to