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Trends in Invasive Interventions and Risk Factors for Early Critical Events in Multiple System Atrophy

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Abstract

Objectives: Multiple system atrophy (MSA) is a progressive, adult-onset neurodegenerative disorder involving autonomic failure, cerebellar ataxia, and parkinsonism. Patients often require invasive interventions, such as gastrostomy or tracheostomy, and sudden death is common. This study aimed to elucidate patterns of invasive treatment and identify risk factors for tracheostomy or sudden death within 5 years of onset.

Methods: In total, 214 patients diagnosed with MSA between November 2014 and October 2024 across 66 institutions in Hokkaido were enrolled in the Hokkaido Rare Disease Consortium for MSA (HoRC-MSA). Patients were grouped by clinical course and interventions. We analyzed use of invasive procedures, including enteral nutrition via gastrostomy, enterostomy, esophagostomy, nasogastric tube insertion, central venous nutrition, tracheostomy, and ventilator support. Multivariable analyses were performed to compare patients with and without early critical events, defined as tracheostomy or sudden death within 5 years of disease onset.

Results: Invasive procedures were performed in 63.1% of patients. Patients receiving enteral nutrition and tracheostomy had prolonged survival. Early events correlated with older onset age (mean, 65.9 years), orthostatic hypotension, stridor, and an elevated apnea–hypopnea index (median, 32.45). Patients with preserved activities of daily living (ADL) in the Unified MSA Rating Scale part IV also had an increased risk of early critical events.

Conclusion: Autonomic dysfunction, sleep-disordered breathing, and vocal cord impairment predict key risk factors for early mortality in patients with MSA. Monitoring is necessary, regardless of preserved ADL. The impact of invasive interventions on quality of life should be further explored.

Keywords: multiple system atrophy, MSA, HoRC-MSA, risk factors, care level, mRS

24 **Introduction**

25 Multiple system atrophy (MSA) is an adult-onset, intractable, and progressive neurodegenerative
26 disorder characterized by cerebellar ataxia, parkinsonism, and autonomic dysfunction. Patients
27 generally require a cane or wheelchair within 5 years and often die within 6–10 years after disease
28 onset, with few surviving beyond 15 years [1]. The defining pathological feature of MSA is the
29 accumulation of alpha-synuclein in oligodendrocytes, which form glial cytoplasmic inclusions.
30 Potential mechanisms include p25 α overexpression in oligodendrocytes and the uptake of alpha-
31 synuclein aggregates by oligodendrocytes, leading to neurodegeneration through disruptions in tubulin
32 polymerization, inflammation with activation of microglia and astrocytes, mitochondrial dysfunction,
33 and abnormal brain insulin signaling [1, 2]. Genetic risk factors, such as the COQ2 V393A mutation
34 in Japanese families and mutations in C9orf72, LRRK2, and MAPT, have been reported, contributing
35 to ongoing research on the pathogenesis of MSA [2, 3]. However, many aspects of its pathophysiology
36 remain poorly understood, and no effective treatment has been established to date.

37 Given this background, MSA is now recognized as an intractable disease in Japan. The
38 Designated Intractable Disease System of Japan is a framework that provides various forms of support
39 aimed at reducing the financial burden of medical expenses and improving the quality of life (QOL)
40 of patients diagnosed with severe and chronic diseases requiring long-term treatment or diseases for
41 which no fundamental cure has been established. This system, based on strict diagnostic criteria,
42 promotes early diagnosis and appropriate therapeutic interventions while helping alleviate the
43 economic and psychological burden on patients and their families [4]. Additionally, patients who
44 require long-term care in daily life, including those with MSA, can receive certifications under the
45 Long-Term Care Insurance System of Japan. This system evaluates individuals aged ≥ 65 years as well
46 as those aged ≥ 40 years with designated diseases based on a comprehensive assessment of their
47 physical and cognitive function, along with their living environment. Based on this evaluation,
48 individuals are assigned one of seven care levels, ranging from Support Level 1 to Care Level 5,

49 allowing personalized care services based on an individual's needs (Table 1) [4]. Although the
50 modified Rankin Scale (mRS) is a simple measure of physical disability, it does not fully capture the
51 multifaceted aspects of care needs and living conditions. Therefore, a comprehensive classification
52 system under the Long-Term Care Insurance System would be more useful for accurately assessing
53 the diverse care requirements of patients with MSA.

54 As MSA progresses, many patients require percutaneous endoscopic gastrostomy due to
55 dysphagia or tracheostomy because of increased sputum production and respiratory failure. Sudden
56 death is also common; therefore, determining the appropriate timing for invasive interventions is
57 challenging. One primary cause of sudden death in patients with MSA is vocal cord abductor paralysis,
58 which occurs predominantly during sleep and may be associated with weakened posterior
59 cricoarytenoid muscle function or dystonia-like involuntary movements [5]. Central sleep apnea,
60 orthostatic hypotension, and arrhythmias have also been implicated in sudden death [6, 7]. Previous
61 studies have explored prognostic factors in MSA, identifying parkinsonism and autonomic symptom
62 onset, older age at onset, early falls, and lack of levodopa responsiveness as poor prognostic indicators
63 [8–12], and a nomogram has been developed to estimate prognosis at seven years after onset [13].
64 However, sudden death can occur within a few years of disease onset, even in patients with mild
65 neurological symptoms. Elucidating the risk factors for early sudden death and developing reliable
66 indicators to guide the timing of therapeutic interventions remain critical challenges. However, these
67 issues have been largely underexplored. No previous studies have systematically analyzed real-world
68 data on invasive interventions and early critical events in patients with MSA using a large-scale
69 regional registry.

70 At the Department of Neurology at Hokkaido University, we established the Hokkaido Rare
71 Disease Consortium for MSA (HoRC-MSA) to create an MSA patient registry using the Designated
72 Intractable Disease System of Japan [14]. This initiative aims to facilitate natural history research and
73 the development of clinical trial infrastructure. Low population mobility and a high level of

74 cooperation among neurologists in Hokkaido provide an advantage for conducting large-scale
75 epidemiological studies. Currently, our registry includes 274 MSA cases from 66 facilities across
76 Hokkaido, with an observation period of up to 10 years, which is comparable in both case numbers
77 and follow-up duration to other research projects.

78 In this study, we analyzed the data from patients registered in the HoRC-MSA to examine their
79 clinical course, trends in invasive therapeutic interventions, and risk factors for early tracheostomy or
80 sudden death.

81

82 **Patients and Methods**

83 Between November 2014 and October 2024, patients with MSA diagnosed by neurologists at 66
84 institutions, including Hokkaido University Hospital, and who provided consent, were registered in
85 the HoRC-MSA. Among them, we extracted patients whose registered data and clinical survey forms
86 from their designated intractable disease applications were available and analyzed their clinical course
87 and treatment details. Additionally, for patients with more detailed clinical records, such as laboratory
88 test results and clinical scores, we examined the risk factors for early events including tracheostomy
89 or sudden death. The early phase was defined as within 5 years of disease onset, based on the typical
90 progression of MSA, in which patients become bedridden approximately 6 years after onset and have
91 an average survival of 6–10 years [1]. Patients were categorized into those who had early events and
92 those who had no early events for risk factor analysis. Patients diagnosed with other diseases (e.g.,
93 hereditary spinocerebellar ataxia) after HoRC-MSA registration and those whose causes of death were
94 clearly unrelated (e.g., myocardial infarction or malignancy) were excluded.

95 • *Patient Evaluation*

96 As the HoRC-MSA project was initiated in 2014, the diagnostic criteria used at the time of patient
97 registration were based on the Second Consensus Statement. For patients with sufficiently detailed
98 medical records, a retrospective re-evaluation using the Movement Disorder Society (MDS) criteria

was conducted when analyzing risk factors for early critical events [15, 16]. Patients were classified as MSA-C (cerebellar ataxia dominant), MSA-P (parkinsonism dominant), or as unclassified if the differentiation was unclear. The patients underwent detailed evaluations at registration or when a neurodegenerative disease was strongly suspected. For those with continued follow-up, periodic examinations including interviews, neurological assessments, blood tests, and imaging evaluations were conducted. This study evaluated patient information, such as age, sex, onset date, and date of death, as well as neurological symptoms, including parkinsonism and cerebellar ataxia, assessed using the Unified Multiple System Atrophy Rating Scale (UMSARS), Scale for the Assessment and Rating of Ataxia (SARA), and Barthel index (BI). Interviews on urinary incontinence and constipation, blood pressure measurements, post-void residual urine assessments, and brain magnetic resonance imaging (MRI) findings were also included. Regarding neurological assessments and brain MRI findings, we applied the evaluation items from the MDS criteria to the findings assessed at the time of diagnosis and examined features observed in at least 10 patients at the time of diagnosis to ensure statistical stability and avoid overfitting. This threshold was based on the conventional recommendation concerning the minimum number of events per variable [17]. In hospitalized patients, apnea was monitored, and vocal cord abduction insufficiency (both during wakefulness and sleep) was evaluated by otolaryngologists. Clinical survey forms provided data on invasive interventions, including gastrostomy, enterostomy, esophagostomy, nasogastric tube insertion, central venous nutrition, tracheostomy, and mechanical ventilation, along with implementation dates. Patients with available designated intractable disease registrations and updated forms were assessed for mRS scores and long-term care certification changes over time.

• *Statistical Methods*

Descriptive statistics were used to summarize patient characteristics and clinical parameters. Continuous variables with normal distributions (e.g., age, disease duration) are presented as means with standard deviations (SD), whereas variables with skewed distributions (e.g., apnea–hypopnea

index [AHI], UMSARS scores) are presented as medians with interquartile ranges (IQR) to account for data dispersion and the influence of potential outliers. Categorical variables were summarized as frequencies and percentages. The survival period after disease onset was compared between patients who underwent gastrostomy, enterostomy, esophagostomy, or tracheostomy using the log-rank test. For the multivariable analyses of risk factors associated with early events, logistic regression was employed. For the multivariable logistic regression analysis of early events risk factors, missing values in explanatory variables were imputed using the multivariate imputation by chained equations method. To enhance the reliability of the results, both univariate analyses and multivariable regression analyses following variable selection using a stepwise method based on the Akaike Information Criterion (AIC) were conducted. To prevent overfitting, multicollinearity, and computational errors, explanatory variables were categorized into three domains—patient background and examination findings, clinical symptoms, and MRI features—and analyzed separately within each domain. Furthermore, variables with a limited number of evaluable cases, such as age at death, vocal cord abduction impairment during the awake and sleep phases, and erectile dysfunction (which is not applicable to female patients), were excluded from the multivariable analyses. Statistical significance was set at $p < 0.05$, with a confidence level (CI) of 0.95. All statistical analyses were performed using Python and Statcel5 (Microsoft, Redmond, WA, USA).

Results

A total of 274 patients with MSA were registered in the HoRC-MSA, of whom 214 were included in this study (Figure 1). The cohort comprised 96 men (44.9%) and 118 women (55.1%). The subtypes were MSA-C ($n = 145$, 67.8%), MSA-P ($n = 51$, 23.8%), and unclassified MSA ($n = 18$, 8.4%). According to the diagnostic categories of the Second Consensus Statement at the time of registration in the HoRC-MSA database, 136 patients were classified as having probable MSA, 37 as possible MSA, and 41 could not be classified due to insufficient diagnostic information. At the time of the study,

149 110 patients had died. The mean age of disease onset was 61.41 ± 10.18 years, whereas the mean age
150 at death was 72.03 ± 9.28 years. The average disease duration from disease onset to death was $8.65 \pm$
151 4.11 years. Among the 112 patients whose clinical assessment forms from their designated intractable
152 disease applications were available, the median duration from disease onset to initial application was
153 2.00 years (IQR: 0.88–3.71 years), from disease onset to the most recent update was 5.83 years (IQR:
154 3.88–8.46 years), and from initial application to the most recent update was 3.13 years (IQR: 1.42–
155 5.54 years) (Table 2).

156 • *Long-term Care Certification and mRS*

157 In total, 112 patients with designated intractable disease registration forms were evaluated. At the time
158 of initial application, the largest group comprised 76 patients who did not receive care certification.
159 The distribution of care levels was as follows: nine patients were classified as requiring support, five
160 as requiring care level 1, nine as level 2, four as level 3, and two as level 4; whereas, zero patients were
161 classified as level 5 and seven patients had unknown details. In the most recent update, the distribution
162 changed; 13 patients had no care certification, 14 required support, 16 required care level 1, 15 required
163 level 2, 7 required level 3, 13 required level 4, 18 required level 5, and 16 patients had unknown details
164 (Figure 2). Regarding mRS, at the time of the initial application, no patients had an mRS of 1, 24
165 patients had an mRS of 2, 46 patients had an mRS of 3, 38 patients had an mRS of 4, 3 patients had an
166 mRS of 5 and 1 patient had unknown details. In the most recent update, no patients had an mRS 1, 2
167 had an mRS of 2, 18 had an mRS of 3, 55 had an mRS of 4, 36 had an mRS of 5, and one had unknown
168 details (Figure 3). The rate of obtaining care certification increased from 27.6% at the time of initial
169 application to 86.5% at the most recent update. Additionally, the mean mRS worsened from 3.18 to
170 4.14, and the median mRS deteriorated from 3 to 4.

171 • *Invasive Procedures*

172 Among the 214 patients evaluated, 60 underwent gastrostomy, enterostomy, or esophagostomy; 11
173 underwent nasogastric tube feeding; 11 received central venous nutrition; 41 underwent tracheostomy;

174 and 21 received ventilatory support (excluding biphasic positive airway pressure). The mean duration
175 from onset to each intervention was 6.73 ± 2.89 years for gastrostomy, enterostomy, or esophagostomy,
176 8.03 ± 3.45 years for nasogastric tube feeding, 7.85 ± 3.53 years for central venous nutrition, $6.97 \pm$
177 3.59 years for tracheostomy, and 10.85 ± 4.44 years for ventilatory support (Figure 4). Patients who
178 underwent both enteral nutrition (including gastrostomy, enterostomy, esophagostomy or received
179 nasogastric tube feeding) and tracheostomy (including ventilatory support) had a significantly longer
180 survival duration than those who did not undergo either intervention (12.50 ± 5.15 years vs. $7.19 \pm$
181 5.04 years, Table 3). In contrast, no significant prolongation of survival was observed in patients who
182 underwent either enteral nutrition or tracheostomy alone (enteral nutrition only vs. none: $p = 0.96$;
183 tracheostomy only vs. none: $p = 0.95$).

184 • *Risk Factors for Early Events*

185 Among the patients with detailed clinical information, 68 (including 19 patients who had an early event
186 and 49 patients who had no early event) were analyzed using multivariable logistic regression to
187 investigate early event risk factors (Figure 1). The patient backgrounds are shown in Table 4. Patients
188 who experienced early events had a significantly higher mean age at onset (mean: 65.10 ± 10.14 years)
189 than patients who had no early event (mean: 59.24 ± 8.96 years) (odds ratio [OR]: 1.17, 95% CI: 1.03–
190 1.33, $p=0.017$). In terms of clinical symptoms, orthostatic hypotension (OR: 5.45, 95% CI: 1.02–29.15,
191 $p=0.047$) and stridor (OR: 8.50, 95% CI: 1.32–54.92, $p=0.025$) at diagnosis were significantly more
192 common in patients who experienced early event. By contrast, no significant differences in urinary
193 dysfunction, cerebellar ataxia, or parkinsonism at diagnosis were observed (Table 5). Regarding
194 examination findings, the apnea monitoring test performed at the time of diagnosis (on average 2.86
195 years after symptom onset) showed a significantly higher mean AHI in patients who experienced early
196 events (median: 32.45, IQR: 22.1–44.2) than those without early events (median: 11.25; IQR: 4.6–
197 27.3). The difference between groups was 21.2 (OR: 1.18, 95% CI: 1.04–1.34, $p = 0.009$). Among the
198 clinical severity scales, UMSARS part IV was significantly associated with early events in the

multivariable regression analysis, with an odds ratio below 1 (OR: 0.01, 95% CI: 0.00–0.30, $p = 0.010$), suggesting that better activities of daily living (ADL) may paradoxically be linked to a higher risk of early events. No significant associations were observed for other clinical rating scales or MRI findings (Tables 4 and 6). In the univariate analysis, UMSARS part IV did not reach statistical significance, despite being a significant predictor in the multivariable model. In contrast, vocal cord abduction insufficiency within 5 years of disease onset—during both the awake and sleep phases, and during the awake phase alone—showed significant associations with early events, whereas no association was found for the sleep phase alone. Additionally, dysphagia within 3 years of onset was also significantly associated with early events. In the final multivariable model following stepwise variable selection, the variables that were initially significant remained so, confirming the robustness of the findings. Notably, none of the MRI findings were selected as variables in the stepwise selection process.

Discussion

In this study, we analyzed data from patients with MSA registered in the HoRC-MSA to examine their clinical course, trends in invasive therapeutic interventions, and risk factors for early tracheostomy or death. To the best of our knowledge, this is the first study in Japan to integrate data from designated intractable disease application forms, including the mRS, long-term care certification levels, and invasive interventions, with a large regional registry to investigate the impact of invasive interventions and early risk factors for MSA. As disability levels, such as mRS and long-term care certification, worsened over time, invasive interventions contributed to prolonged survival. Furthermore, among patients who experienced early medical interventions, older age at onset, orthostatic hypotension, stridor, relatively severe sleep apnea at the time of diagnosis, and better ADL—as indicated by lower UMSARS part IV scores—were identified as significant risk factors.

Moreover, many patients with MSA experienced progressive worsening of symptoms, leading to increased caregiving needs and deterioration in mRS scores. Notably, the proportion of

224 patients certified for long-term care increased from 27.6% at the time of initial application to 86.5%
225 at the most recent update, over an average period of approximately 3.8 years, highlighting the
226 substantial and increasing caregiving burden associated with disease progression. Although no
227 previous studies have directly compared mRS scores and QOL in patients with MSA, the progression
228 of symptoms has been shown to be associated with reduced QOL in patients, as well as increased
229 caregiver burden and psychological stress [18, 19]. These findings underscore the importance of
230 introducing public welfare services and home-based support systems at an early stage to help reduce
231 both physical and emotional burden for patients and their families.

232 Additionally, 63.1% of patients underwent some form of invasive intervention, and our
233 findings suggest that undergoing both gastrostomy and tracheostomy may be associated with
234 prolonged survival. Although this study did not demonstrate a significant survival benefit from either
235 enteral nutrition or tracheostomy alone compared with the non-intervention group, previous studies
236 have reported extended survival in patients with parkinsonian syndromes who underwent
237 gastrostomy (median survival after recommendation or placement of gastrostomy: 24 months in the
238 gastrostomy group vs. 12 months in the non-gastrostomy group) [20], as well as in patients with
239 stridor who received tracheostomy (survival from disease onset: 5.9 ± 2.9 years in the tracheostomy
240 group vs. 2.6 ± 2.1 years in the non-tracheostomy group) [21]. In addition, a study demonstrated that
241 tracheostomy was beneficial for survival in patients with stridor, worsening oxygenation, or vocal
242 cord abduction insufficiency, regardless of whether other invasive interventions were performed
243 (survival from disease onset: 10.1 years in the tracheostomy group vs. 7.5 years in the non-
244 tracheostomy group, $p = 0.001$) [22]. The absence of significant differences in our study may be
245 partly due to the small number of patients in each individual intervention group. Notably, no prior
246 studies have specifically compared outcomes in patients who received enteral nutrition alone,
247 tracheostomy alone, or both interventions. Our results suggest that the combination of multiple
248 invasive procedures may contribute more substantially to prolonged survival than either intervention

alone. These findings provide important evidence to support the proposal of multiple treatment options in the advanced stages of MSA and may facilitate appropriate, individualized communication with patients and their families when considering invasive interventions.

The underlying pathophysiology of sudden death in MSA remains unclear; however, one known cause is vocal cord abduction insufficiency, which is associated with significant degeneration of serotonergic neurons in the medullary raphe nuclei [5, 23, 24]. This pathology may also contribute to central sleep apnea. Although autonomic dysfunction has been implicated in MSA prognosis, patients with severe autonomic dysfunction also exhibit a significant loss of medullary serotonergic neurons [25], suggesting that autonomic failure may be linked to the risk of sudden death associated with respiratory causes [6]. Our study identified older age at onset, orthostatic hypotension, stridor, and high AHI as significant risk factors for early events. In addition, univariate analysis revealed that vocal cord abduction insufficiency and early-onset dysphagia were also significantly associated with early events. These findings already recognized as poor prognostic factors [2, 7, 8, 10, 26–28], were reaffirmed; stridor indicated upper airway narrowing, whereas a high AHI suggested obstructive or central apnea. Because these factors suggest an increased risk of sudden death, early identification of these risk factors is crucial. Neurological symptoms such as cerebellar ataxia and parkinsonism, as well as MRI findings, were not significantly associated with early events in the present study; however, these outcomes may vary depending on the timing of evaluation. Furthermore, the finding that good ADL in the UMSARS part IV was a risk factor of early events is notable and requires further validation. On the other hand, variable selection using the stepwise method identified a high UMSARS part I score as a risk factor for early events, which appears contradictory to the finding that lower UMSARS part IV scores were associated with increased risk. These results should be interpreted with caution, as they may be influenced by multicollinearity between UMSARS parts I and IV or by the variable selection process inherent in the stepwise method. Nevertheless, clinicians should remain aware that

even patients who appear functionally independent may still be at risk of sudden death. Comprehensive assessments, including polysomnography, apnea monitoring, and vocal cord evaluation, are essential for proper risk management and patient education.

This study has some limitations. First, the study population was limited to patients registered in the HoRC-MSA in Hokkaido, and thus, generalizability should be interpreted cautiously. Hokkaido has a relatively high population mobility since its development in the 19th century and is a demographically representative population of Japan; therefore, studies involving nationwide or global cohorts are needed. Second, the diagnosis of MSA was based on the Second Consensus Statement, rather than the latest MDS criteria, and pathological confirmation was not available for all cases; therefore, the inclusion of patients with different underlying conditions cannot be ruled out. Third, electrocardiogram analysis was not conducted, making it difficult to assess the risk of sudden death from the perspective of arrhythmias such as QT prolongation [29–31]. In addition, obstructive and central sleep apnea could not be analyzed separately in the evaluation of sleep-disordered breathing. Fourth, the sample size was not sufficiently large, and some variables had missing values. Although imputation methods were used to address these, their influence on the results cannot be entirely excluded. Furthermore, because the timing of assessment varied among patients in this study, the results may be subject to fluctuation in future analyses. Therefore, prospective studies with evaluations conducted at standardized time points are needed to clarify causality. Finally, this study did not assess changes in QOL, psychological burden, or economic impact related to invasive procedures, which should be addressed in future studies.

Conclusion

This multicenter, registry-based study was conducted as part of an investigation into the natural history and risk factors of patients with MSA using data from institutions across Japan. It provides practical insights into disease progression and therapeutic decision-making. Our findings revealed that

deterioration in ADL and increased caregiving needs accompany disease progression. Moreover, invasive interventions such as enteral nutrition and tracheostomy may contribute to reducing the risk of sudden death and extending survival. Furthermore, our results suggest that patients with older age at onset and respiratory symptoms may be at increased risk for early critical events. Therefore, even in patients with relatively preserved ADL, it is important to conduct early screening and provide timely information and support to patients and their families to facilitate shared decision-making regarding future care.

305

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309

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315

Authors Contributions

Monami Tarisawa contributed to data analysis, drafting, and writing. Masaaki Matsushima contributed to patient enrollment in the HoRC-MSA, data acquisition, and medical treatment. Akihiko Kudo, Taichi Nomura, Hisashi Uwatoko, Shinichi Shirai, Ikuko Takahashi-Iwata, Ken Sakushima, Hiroaki Yaguchi, Isao Yokota, Naoki Nishimoto, Jun Sawada, Takeshi Matsuoka, Haruo Uesugi, Naoya Minami, Kazuya Sako, Asako Takei, Shin Hisahara, Yasuhiro Kanatani, Akiko Tamakoshi, and Norihiro Sato contributed to medical treatment and data acquisition, and critically

reviewed the manuscript. Ichiro Yabe supervised the study and approved the final draft.

Compliance with Ethical Standards

• Ethical Approval

All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the Institutional Review Board of Hokkaido University Hospital (013-0208). Written informed consent was obtained from all the participants. Clinical trial number is not applicable.

• Declaration of Competing Interest

The authors declare no competing interests.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding authors.

References

1. Fanciulli A, Wenning GK. Multiple-system atrophy. *N Engl J Med*. 2015;372:249–63. <https://doi.org/10.1056/NEJMra1311488>
2. Krismer F, Fanciulli A, Meissner WG, Coon EA, Wenning GK. Multiple system atrophy: advances in pathophysiology, diagnosis, and treatment. *Lancet Neurol*. 2024;23:1252–66. [https://doi.org/10.1016/S1474-4422\(24\)00396-X](https://doi.org/10.1016/S1474-4422(24)00396-X)
3. Liu M, Wang Z, Shang H. Multiple system atrophy: an update and emerging directions of biomarkers and clinical trials. *J Neurol*. 2024;271:2324–44. <https://doi.org/10.1007/s00415-024-12269-5>
4. Ministry of Health, Labour and Welfare. Title of the webpage; n.d. Accessed Feb 23, 2025, <https://www.mhlw.go.jp/english/>
5. Ozawa T, Sekiya K, Aizawa N, Terajima K, Nishizawa M. Laryngeal stridor in multiple system atrophy: clinicopathological features and causal hypotheses. *J Neurol Sci*. 2016;361:243–9. <https://doi.org/10.1016/j.jns.2016.01.007>
6. Watanabe H, Riku Y, Nakamura T, Hara K, Ito M, Hirayama M, et al. [Expanding concept of clinical conditions and symptoms in multiple system atrophy]. *Rinsho Shinkeigaku*. 2016;56:457–64. Japanese. <https://doi.org/10.5692/clinicalneurology.cn-000903>
7. Ralls F, Cutchen L. Respiratory and sleep-related complications of multiple system atrophy. *Curr Opin Pulm Med*. 2020;26:615–22. <https://doi.org/10.1097/MCP.0000000000000725>
8. Sakushima K, Nishimoto N, Nojima M, Matsushima M, Yabe I, Sato N, et al. Epidemiology of multiple system atrophy in Hokkaido, the Northernmost Island of Japan. *Cerebellum*. 2015;14:682–7. <https://doi.org/10.1007/s12311-015-0668-6>
9. Wenning GK, Geser F, Krismer F, Seppi K, Duerr S, Boesch S, et al. The natural history of multiple system atrophy: a prospective European cohort study. *Lancet Neurol*. 2013;12:264–74. [https://doi.org/10.1016/S1474-4422\(12\)70327-7](https://doi.org/10.1016/S1474-4422(12)70327-7)

- 364 10. Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, et al. Progression and prognosis in
365 multiple system atrophy: an analysis of 230 Japanese patients. *Brain*. 2002;125:1070–83.
366 <https://doi.org/10.1093/brain/awf117>
- 367 11. Coon EA, Sletten DM, Suarez MD, Mandrekar JN, Ahlskog JE, Bower JH, et al. Clinical features
368 and autonomic testing predict survival in multiple system atrophy. . *Brain*. 2015;138:3623–31.
369 <https://doi.org/10.1093/brain/awv274>
- 370 12. Wenning GK, Ben Shlomo Y, Magalhães M, Daniel SE, Quinn NP. Clinical features and natural
371 history of multiple system atrophy. An analysis of 100 cases. *Brain*. 1994;117:835–45.
372 <https://doi.org/10.1093/brain/117.4.835>
- 373 13. Eschlboeck S, Goebel G, Eckhardt C, Fanciulli A, Raccagni C, Boesch S, et al. Development and
374 validation of a prognostic model to predict overall survival in multiple system atrophy. *Mov Disord*
375 *Clin Pract*. 2023;10:1368–76. <https://doi.org/10.1002/mdc3.13822>
- 376 14. Matsushima M, Yabe I, Sakushima K, Kanatani Y, Nishimoto N, Matsuoka T, et al. Multiple system
377 atrophy in Hokkaido, Japan: a prospective registry study of natural history and symptom
378 assessment scales followed for 5 years. *BMJ Open*. 2021;11:e045100.
379 <https://doi.org/10.1136/bmjopen-2020-045100>
- 380 15. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus
381 statement on the diagnosis of multiple system atrophy. *Neurology*. 2008;71:670–6.
382 <https://doi.org/10.1212/01.wnl.0000324625.00404.15>
- 383 16. Wenning GK, Stankovic I, Vignatelli L, Fanciulli A, Calandra-Buonaura G, Seppi K, et al. The
384 Movement Disorder Society criteria for the diagnosis of multiple system atrophy. *Mov Disord*.
385 2022;37:1131–48. <https://doi.org/10.1002/mds.29005>
- 386 17. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of
387 events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49:1373–9.
388 [https://doi.org/10.1016/s0895-4356\(96\)00236-3](https://doi.org/10.1016/s0895-4356(96)00236-3)

- 389 18. Langford B, Zhou Y, Miyasaki JM. Multiple system atrophy caregivers' experience: A mixed
390 methods study. *Can J Neurol Sci.* 2023;50:49–59. <https://doi.org/10.1017/cjn.2021.252>
- 391 19. Ali N, Nesspor V, Bang J, Scholz SW, Pantelyat A. Factors impacting quality of life in multiple
392 system atrophy. *Front Neurol.* 2023;14:1111605. <https://doi.org/10.3389/fneur.2023.1111605>
- 393 20. Kobylecki C, Chelban V, Goh YY, Michou E, Fumi R, Theilmann Jensen M, et al. Frequency and
394 outcomes of gastrostomy insertion in a longitudinal cohort study of atypical parkinsonism. *Eur J*
395 *Neurol.* 2024;31:e16258. <https://doi.org/10.1111/ene.16258>
- 396 21. Giannini G, Provini F, Cani I, Cecere A, Mignani F, Guaraldi P, et al. Tracheostomy is associated
397 with increased survival in multiple system atrophy patients with stridor. *Eur J Neurol.*
398 2022;29:2232–40. <https://doi.org/10.1111/ene.15347>
- 399 22. Nishida K, Sakashita K, Yamasaki H, Futamura N. Impact of tracheostomy invasive ventilation
400 on survival in Japanese patients with multiple system atrophy. *Parkinsonism Relat Disord.* 2022
401 Apr;97:107-111. doi: 10.1016/j.parkreldis.2022.01.008.
- 402 23. Benarroch EE. The clinical approach to autonomic failure in neurological disorders. *Nat Rev*
403 *Neurol.* 2014;10:396–407. <https://doi.org/10.1038/nrneurol.2014.88>
- 404 24. Cersosimo MG, Benarroch EE. Central control of autonomic function and involvement in
405 neurodegenerative disorders. *Handb Clin Neurol.* 2013;117:45–57. [https://doi.org/10.1016/B978-](https://doi.org/10.1016/B978-0-444-53491-0.00005-5)
406 [0-444-53491-0.00005-5](https://doi.org/10.1016/B978-0-444-53491-0.00005-5)
- 407 25. Benarroch EE, Schmeichel AM, Low PA, Parisi JE. Involvement of medullary serotonergic groups
408 in multiple system atrophy. *Ann Neurol.* 2004;55:418–22. <https://doi.org/10.1002/ana.20021>
- 409 26. Jo S, Kim TY, Lee YS, Lee EJ, Lee S, Lee J, et al. Severity of sleep apnea as a prognostic factor
410 for mortality in patients with multiple system atrophy. *Parkinsonism Relat Disord.*
411 2024;124:106994. <https://doi.org/10.1016/j.parkreldis.2024.106994>
- 412 27. Ohshima Y, Nakayama H, Matsuyama N, Hokari S, Sakagami T, Sato T, et al. Natural course and
413 potential prognostic factors for sleep-disordered breathing in multiple system atrophy. *Sleep Med.*

- 2017;34:13–7. <https://doi.org/10.1016/j.sleep.2017.01.020>
28. Wada T, Shimizu T, Asano Y, et al. Early-onset dysphagia predicts short survival in multiple system atrophy. *J Neurol*. 2024 Oct;271(10):6715–6723. doi: 10.1007/s00415-024-12623-7.
29. Lo SS, Mathias CJ, Sutton MS. QT interval and dispersion in primary autonomic failure. *Heart*. 1996;75:498–501. <https://doi.org/10.1136/hrt.75.5.498>
30. Deguchi K, Sasaki I, Tsukaguchi M, Kamoda M, Touge T, Takeuchi H, et al. Abnormalities of rate-corrected QT intervals in Parkinson’s disease-a comparison with multiple system atrophy and progressive supranuclear palsy. *J Neurol Sci*. 2002;199:31–7. [https://doi.org/10.1016/s0022-510x\(02\)00079-5](https://doi.org/10.1016/s0022-510x(02)00079-5)
31. Choy AMJ, Lang CC, Roden DM, Robertson D, Wood AJ, Robertson RM, et al. Abnormalities of the QT interval in primary disorders of autonomic failure. *Am Heart J*. 1998;136:664–71. [https://doi.org/10.1016/s0002-8703\(98\)70014-6](https://doi.org/10.1016/s0002-8703(98)70014-6)

426 **Figure Legends**

427 **Fig. 1** Study flowchart

428 MSA, multiple system atrophy; HoRC-MSA, Hokkaido Rare Disease Consortium for MSA.

429 **Fig. 2** Number of patients who received long-term care certification at the initial and recent
430 applications

431 **Fig. 3** Number of patients who received modified Rankin Scale certification at the initial and recent
432 applications

433 **Fig. 4** Number of patients who underwent invasive procedures and duration from disease onset

HoRC-MSA registered patients: 274 patients



Patients meeting inclusion criteria: 214 patients



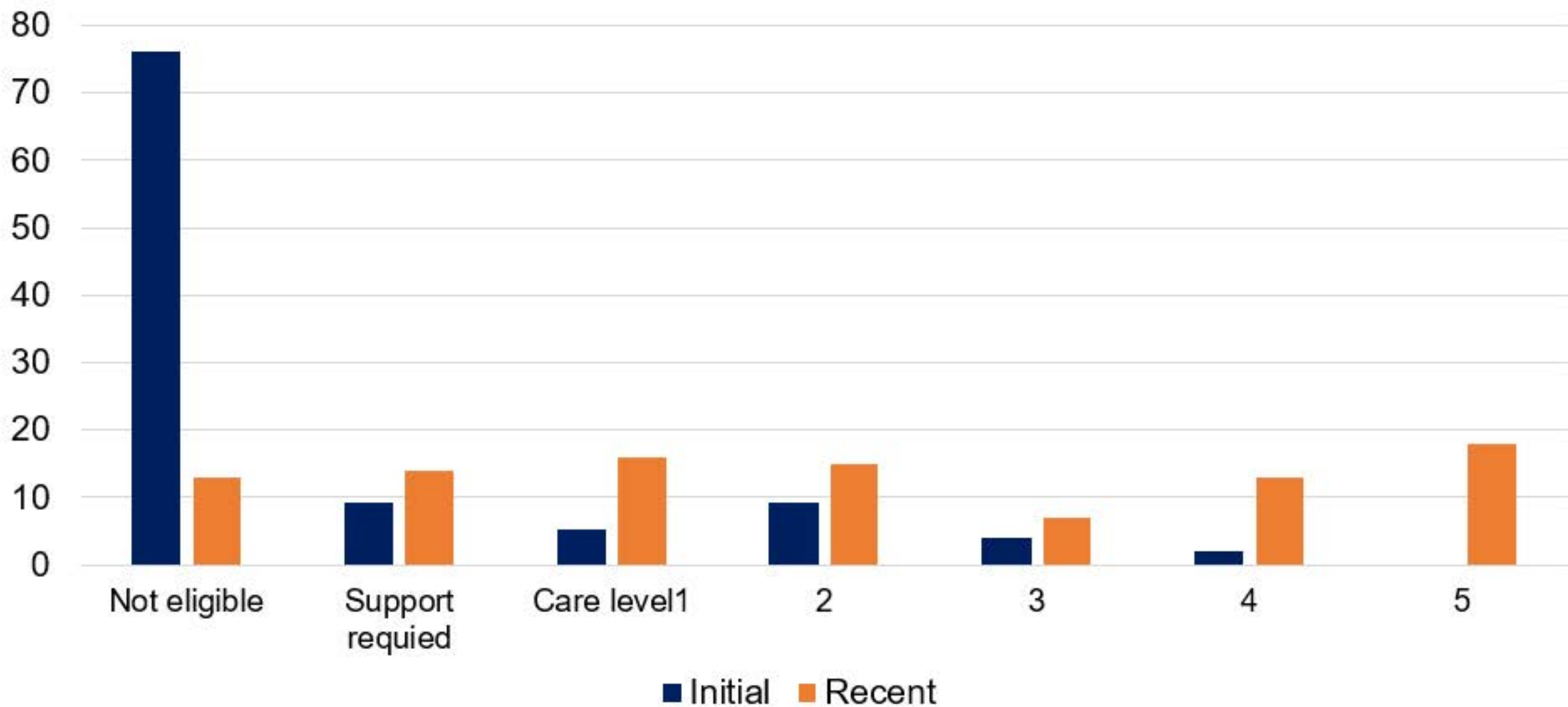
Patients with more detailed clinical records:
68 patients

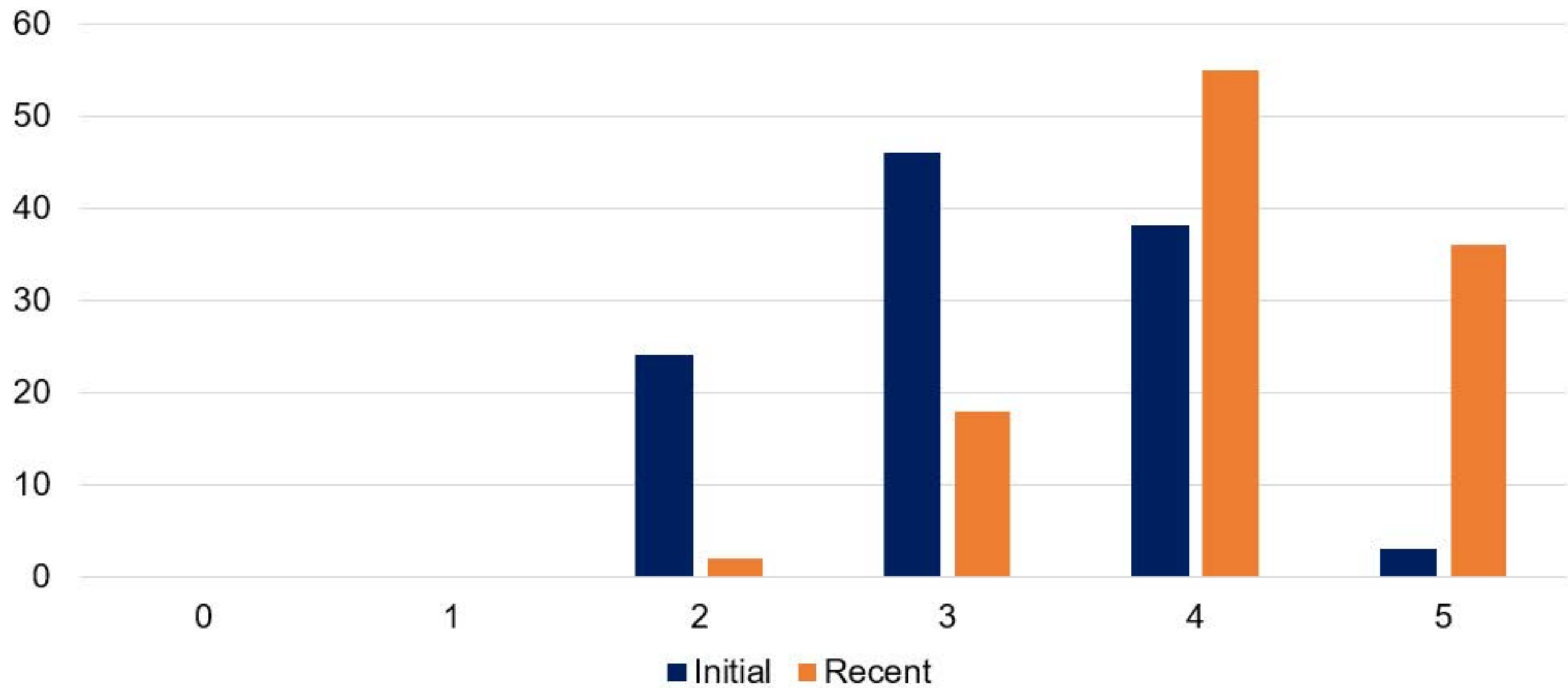


No event occurred: 49 patients



Early event occurred: 19 patients





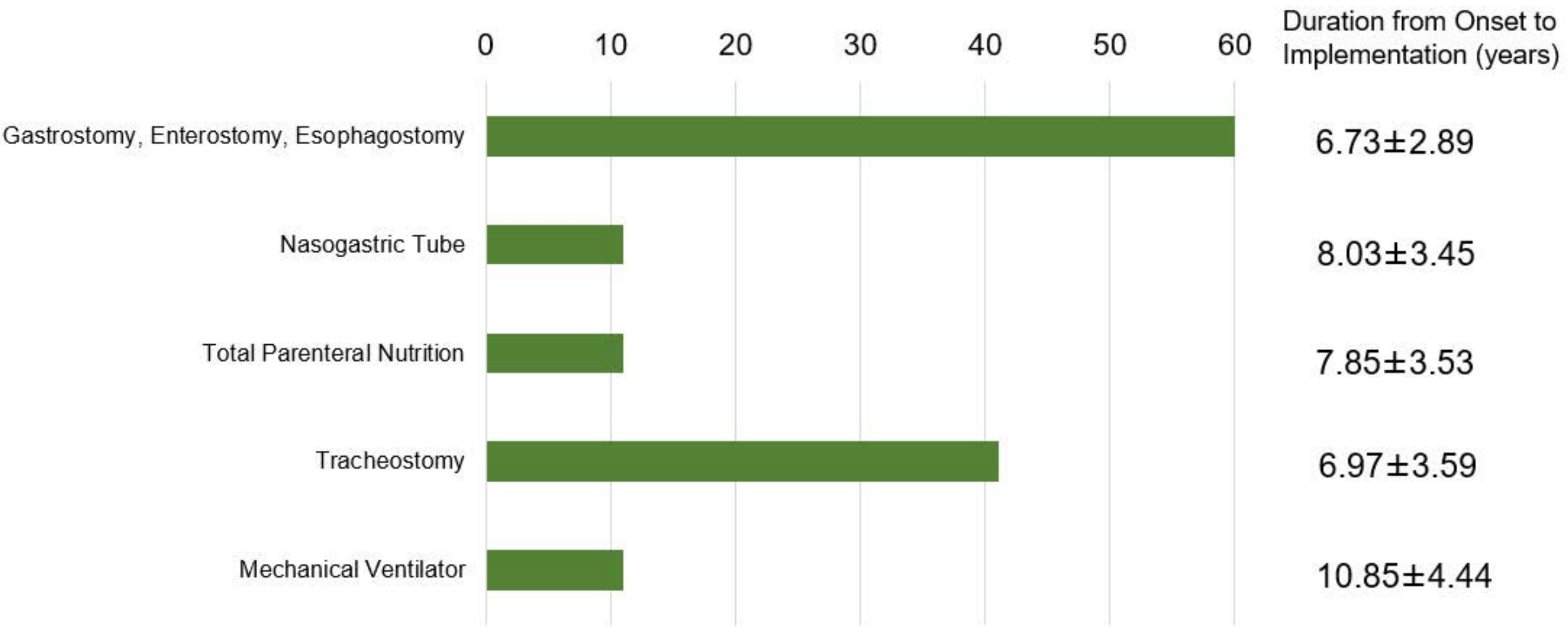


Table 1. Long-Term Care Classification in Japan [4].

Category / Level	Description
Support-Required (1-2)	Individuals can generally perform basic ADL independently but require some assistance with IADL, such as shopping, cooking, or medication management. This level is intended to prevent further decline that may lead to more severe care needs.
Care Required	Individuals have difficulty performing basic ADL independently and require varying levels of nursing care or assistance in daily life. This category is subdivided into five care levels as follows:
Care Level 1	Partial assistance is required for IADL due to a decline in functional abilities compared to the support-required level.
Care Level 2	In addition to the need for help with IADL, partial assistance is also necessary for basic ADL.
Care Level 3	Marked decline in both ADL and IADL abilities, with a need for substantial and frequent assistance in daily life.
Care Level 4	Further deterioration in physical and functional status, making it difficult to maintain daily life without consistent caregiving support.
Care Level 5	The most severe level of dependency, where the individual is almost entirely unable to live independently and requires constant care for virtually all aspects of daily living.

ADL, activities of daily living; IADL, instrumental activities of daily living;

Table 2. Patient characteristics.

Age at onset (years)	61.40±10.18
Sex (M:F)	96:118
Phenotype (MSA-C : P : unclassified)	145:51:18
Age at death (years)	72.03±9.28
Duration from onset to death (years)	8.65±4.11
Duration from onset to the first application (years)	2.00 (IQR: 0.88–3.71)
Duration from onset to the most recent update (years)	2.83 (IQR: 3.88–8.46)
Duration from the first application to the most recent update (years)	3.13 (IQR: 1.42–5.54)

MSA, multiple system atrophy; M, male; F, female; MSA-C, MSA cerebellar ataxia-dominant ; P, parkinsonism-dominant; Interquartile Range, IQR

Table 3. Differences in survival period based on the invasive treatment using log-rank test.

Procedure	None (n=134)	Enteral nutrition only (n=39)	Tracheostomy only (n=10)	Both (n=31)	p-value
Survival period (years)	7.19 ± 5.04	8.92 ± 3.54	6.68 ± 3.32	12.50 ± 5.15	0.036

Table 4. Analysis of patient data and risk factors for early events between the two groups.

	No event occurred	Early event occurred	OR(95% CI)*	p-value*	OR(95% CI)**	p-value**	OR(95% CI)***	p-value***
n	49	19						
Sex (M:F)	25:24	8:11	6.54(0.69–62.00)	0.102	1.43(0.49-4.12)	0.510	5.43 (0.85-34.5)	0.073
Phenotype (MSA-C: P: unclassified)	33:14:2	13:5:1	1.97 (0.44–8.69)	0.373	1.00(0.39-2.56)	0.994		
Age at onset (years)	59.24±8.96	65.10±10.14	1.17 (1.03-1.33)	0.017	1.07(1.01-1.14)	0.028	3.77 (1.32-10.8)	0.013
Age of death (years)	69.0±8.10	70.53±8.57			0.12(0.94-1.12)	0.584		
AHI	11.25 [IQR:4.6–27.3]	32.45 [IQR:22.1–44.2]	1.18(1.04–1.34)	0.009	1.07(1.01-1.13)	0.014	9.40 (2.71-32.60)	<0.001
Vocal cord abduction insufficiency within 5 years of disease onset	7 (36) [#]	11 (17) [#]	1.61 (0.09–28.27)	0.747	7.60(2.09-27.66)	0.002		
During awake phase	3 (33) [#]	9 (16) [#]	-	-	13.28(2.84-62.14)	0.001		
During sleep	5 (13) [#]	6 (9) [#]	-	-	3.20(0.54-18.98)	0.200		
Reported snoring within 5 years from onset	20	10	0.86 (0.14–5.40)	0.869	3.06(0.96-9.72)	0.058		
UMSARS at diagnosis								
Part I	15 [IQR:10–18]	16 [IQR:11.5–20.75]	1.35(0.98–1.85)	0.063	1.04(0.96.14)	0.388	8.50 (1.40-51.7)	0.020
Part II	14.5 [IQR:10.75–17.25]	17 [IQR:11.0–16.25]	1.25 (0.89–1.74)	0.200	1.05(0.98-1.13)	0.300	7.16 (0.83-61.4)	0.073
Part IV	2 [IQR:1–3]	1.5 [IQR:1–2]	0.01 (0.00–0.30)	0.010	0.85(0.50-1.46)	0.249	0.007 (0.00-0.22)	0.005
SARA at diagnosis	13 [IQR:10.13-17.25]	13.5 [IQR:12.88–17.25]	1.21 (0.86–1.70)	0.271	1.06(0.96-1.18)	0.348		

* Multivariable analysis

** Univariable analysis

*** Multivariable analysis following stepwise variable selection

[#]Number of patients who reviewed the findings

OR, Odds ratio; 95% CI, 95% confidence interval; M, male; F, female; MSA-C, MSA cerebellar ataxia-dominant; P, parkinsonism-dominant; AHI, apnea–hypopnea index; UMSARS, Unified Multiple System Atrophy Rating Scale; SARA, Scale for the Assessment and Rating of Ataxia

Table 5. Analysis of neurological findings in the MDS criteria.

Neurological findings	No event occurred	Early event occurred	OR (95% CI) *	p-value *	OR (95% CI) **	p-value **	OR(95% CI) ***	p-value ***
Unexplained urinary urge incontinence	23	10	0.94 (0.21–4.20)	0.933	1.26(0.44-3.63)	0.673		
Unexplained voiding difficulties with post-void urinary residual volume > 100 mL	9	3	1.19 (0.10–13.51)	0.890	0.833(0.20-3.48)	0.802		
Post-void urinary residual of any volume	25	15	1.24 (0.21–7.36)	0.812	1.65(0.56-4.88)	0.389		
Neurogenic OH	24	15	5.45 (1.02–29.15)	0.047	3.91(1.13-13.46)	0.031	3.18(0.85-11.96)	0.086
Cerebellar dysarthria	33	13	1.21 (0.23–6.47)	0.827	1.05(0.34-3.27)	0.932		
Limb ataxia	45	16	0.43 (0.02–11.10)	0.608	0.47(0.10-2.35)	0.361		
Oculomotor dysfunction	34	11	0.50 (0.08–3.15)	0.457	0.61(0.20-1.81)	0.371		
Gait ataxia	38	14	1.70 (0.15–19.56)	0.671	0.81(0.24-2.75)	0.736		
Poor levodopa responsiveness	16	8	1.55 (0.21–11.45)	0.670	1.50(0.51-4.46)	0.466		
Rapid progression within 3 years of motor onset	28	14	0.82 (0.09–7.67)	0.864	2.10(0.65-6.75)	0.213		
Moderate to severe postural instability within 3 years of motor onset	28	14	1.91 (0.22–16.29)	0.556	2.10(0.65-6.75)	0.213		
Severe speech impairment within 3 years of motor onset	15	9	0.74 (0.09–6.10)	0.781	2.04(0.69-6.05)	0.198		
Severe dysphagia within 3 years of motor onset	5	6	3.00 (0.39–23.03)	0.292	4.06(1.07-15.49)	0.040		
Unexplained Babinski sign	23	10	1.08 (0.21–5.61)	0.930	1.26(0.44-3.63)	0.674		
Postural deformities	6	2	0.44 (0.03–7.19)	0.565	0.84(0.16-4.60)	0.844		
Stridor	6	10	8.50 (1.32–54.92)	0.025	7.96(2.30-27.55)	0.001	6.93(1.93-24.87)	0.003
Inspiratory sighs	3	2	0.10 (0.00–2.50)	0.158	1.80(0.28-11.75)	0.537		
Erectile dysfunction	11	5	-	-	3.18(0.51-19.91)	0.220		

* Multivariable analysis

** Univariable analysis

*** Multivariable analysis following stepwise variable selection

MDS, Movement Disorder Society, OR, Odds ratio; 95% CI, 95% confidence interval; OH, orthostatic hypotension

Table 6. Analysis of MRI findings in MDS criteria.

MRI findings	No event occurred	Early event occurred	OR (95% CI) [*]	p-value [*]	OR (95% CI) ^{**}	p-value ^{**}
Atrophy of putamen	14	5	0.60 (0.11–3.16)	0.547	0.89(0.27-2.95)	0.853
Atrophy of pons	35	16	3.60 (0.64–20.22)	0.146	2.13(0.54-8.48)	0.282
Atrophy of middle cerebellar peduncle	38	14	0.37 (0.06–2.47)	0.307	0.81(0.24-2.75)	0.736
Atrophy of cerebellum	43	17	1.39 (0.14–14.23)	0.782	1.19(0.22-6.47)	0.844
“Hot cross bun” sign	37	13	0.35 (0.08–1.61)	0.178	0.70(0.22-2.26)	0.553
Increased diffusivity of putamen	15	6	1.11 (0.22–5.65)	0.903	1.05(0.33-3.28)	0.938
Increased diffusivity middle cerebellar peduncle	26	11	1.87 (0.44–8.00)	0.401	1.22(0.42-3.55)	0.720

^{*} Multivariable analysis

^{**} Univariable analysis

MDS, Movement Disorder Society, OR, Odds ratio; 95% CI: 95% confidence interval; MRI, magnetic resonance imaging