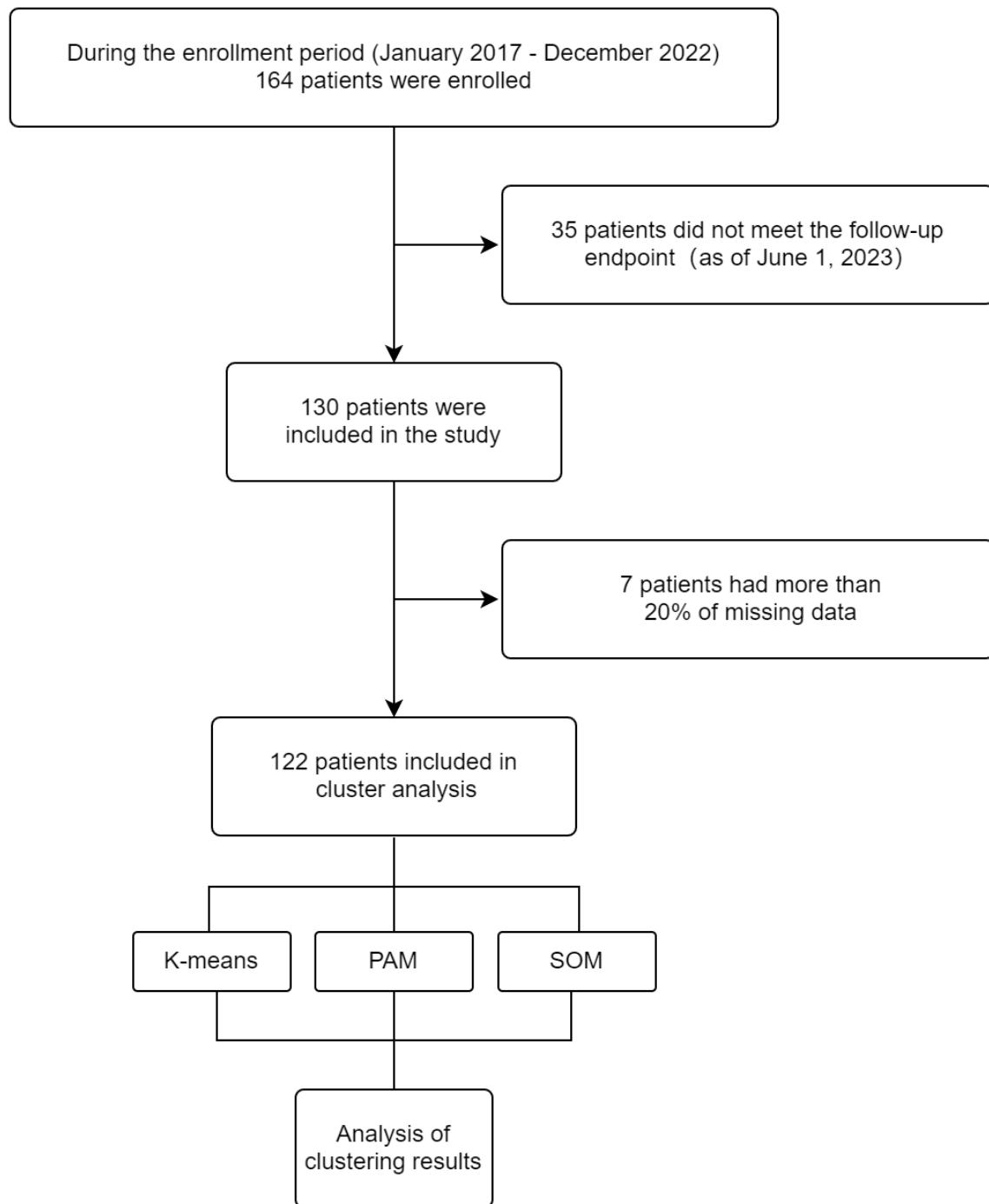


# Supplementary Material

## Identifying New Subtypes of Multiple System Atrophy Using Cluster Analysis

Supplementary Figure 1. Study Flow Chart



**Supplementary Table 2. Classification of diagnostic reliability (n=122)**

	2008		2022		
Levels of certainty	Clinically possible	Clinically probable	Clinically established	Clinically probable	Clinically possible prodromal
Essential features	A sporadic, progressive adult (>30 years) onset disease				
Core clinical features	<ul style="list-style-type: none"> <li>• Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or</li> <li>• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and</li> <li>• At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA)</li> </ul>	<ul style="list-style-type: none"> <li>• Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic and</li> <li>• Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or</li> <li>• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)</li> </ul>	Autonomic dysfunction defined as (at least one is required) <ul style="list-style-type: none"> <li>- Unexplained voiding difficulties with post-void urinary residual volume <math>\geq 100</math> mL</li> <li>- Unexplained urinary urge incontinence</li> <li>- Neurogenic OH (<math>\geq 20/10</math> mmHg blood pressure drop) within 3 minutes of standing or head-up tilt test and at least one of               <ol style="list-style-type: none"> <li>1. Poorly L-dopa-responsive parkinsonism</li> <li>2. Cerebellar syndrome (at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features)</li> </ol> </li> </ul>	At least two of the following: <ol style="list-style-type: none"> <li>1. Autonomic dysfunction defined as (at least one is required):               <ul style="list-style-type: none"> <li>- Unexplained voiding difficulties with post-void urinary residual volume</li> <li>- Unexplained urinary urge incontinence</li> <li>- Neurogenic OH (<math>\geq 20/10</math> mmHg blood pressure drop) within 10 min of standing or head-up tilt test</li> </ul> </li> <li>2. Parkinsonism</li> <li>3. Cerebellar syndrome (at least one of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features)</li> </ol>	At least one of the following: <ul style="list-style-type: none"> <li>• RBD (polysomnography proven)</li> <li>• Neurogenic OH (<math>\geq 20/10</math> mmHg blood pressure drop) within 10 min of standing or head-up tilt</li> <li>• Urogenital failure (erectile dysfunction in males below age of 60 years combined with at least one of unexplained voiding difficulties with post-void urinary residual volume <math>&gt;100</math> mL and unexplained urinary urge incontinence)</li> </ul> At least one of the following: <ul style="list-style-type: none"> <li>• Subtle parkinsonian signs</li> <li>• Subtle cerebellar signs</li> </ul>
Supportive clinical (motor or non-motor) features	At least one	Not required	At least two	At least one	Not required
MRI marker	Not required	Not required	At least one	Not required	Not required
Exclusion criteria	Absence				
Number of cases	68 (55.7)	54 (44.3)	34 (27.9)	79 (64.8)	9 (7.3)
Total	122		122		

**Supplementary Table 2. Definition of Clinical Symptoms**

	Symptoms	Definition
Motor symptoms	Abnormal gait	Loss of speed, stability, symmetry, or balance as assessed by a Parkinson's disease specialist
	Limb ataxia	Ataxia as determined by neurologist examination
	Bradykinesia	Slowness, stagnation, and a decrease in the amplitude or speed of motion during sustained motion
	Muscle rigidity	Confirmed by neurologist physical examination.
	Cerebellar dysarthria	Dysarthria identified after the exclusion of other diseases
	Static tremor	Confirmed by neurologist physical examination.
	Postural tremor	Confirmed by neurologist physical examination.
Nonmotor symptoms	Unexplained voiding difficulties with postvoid	Exclude serious prostate-related conditions
	Urinary residual volume	Residual urine volume $\geq 100$ ml on urinary tract ultrasound after voiding
	Unexplained urinary urge incontinence	Urge and Stress Incontinence Exclude Pelvic Floor Relaxation and Prostate Disease
	Erectile dysfunction	Erectile dysfunction reported by the patient or a family member before the age of 60
	Abnormal sweating	Description of hyperhidrosis or hypohidrosis provided by the patient or family member.
	Neurogenic orthostatic hypotension	$\geq 30/15$ mmHg blood pressure drop within 3 min of standing or head-up tilt test
	Sleep apnea	Polysomnosis monitoring prompts

**Supplementary Table 3.** Difference between groups of red flag sign**K-means**

	cluster1	cluster2	cluster3	p	Multiple comparisons
moderate to severe postural instability within 3 years of motor onset	31 (86.1)	26 (55.3)	9 (23.1)	<0.001	All comparisons
rapid progression within 3 years of motor onset	21 (58.3)	10 (21.3)	3 (7.7)	<0.001	I vs. II, I vs. III
craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia	2 (5.6)	7 (14.9)	3 (7.7)	0.349	/
postural deformities	0 (0.0)	4 (8.5)	1 (2.6)	0.187	/
jerky myoclonic postural or kinetic tremor	0 (0.0)	0 (0.0)	0 (0.0)	/	/
stridor	6 (16.7)	3 (6.4)	2 (5.1)	0.196	/
inspiratory sighs	0 (0.0)	0 (0.0)	1 (2.6)	0.615	/
severe speech impairment within 3 years of motor onset	10 (27.8)	19 (40.4)	3 (7.7)	0.003	I vs. III, II vs. III
severe dysphagia within 3 years of motor onset	6 (16.7)	16 (34.0)	15 (38.5)	0.103	/
cold discolored hands and feet	1 (2.8)	7 (14.9)	2 (5.1)	0.146	/
pathologic laughter or crying	0 (0.0)	3 (6.4)	0 (0.0)	0.110	/
unexplained Babinski sign	17 (47.2)	25 (53.2)	21 (53.8)	0.828	/
erectile dysfunction (below age of 60 years)	12 (70.6)	11 (39.3)	16 (66.7)	0.216	/

**PAM**

	cluster1	cluster2	cluster3	p	Multiple comparisons
moderate to severe postural instability within 3 years of motor onset	23 (88.5)	34 (60.7)	9 (22.5)	<0.001	All comparisons
rapid progression within 3 years of motor onset	13 (50.0)	18 (32.1)	3 (7.5)	<0.001	I vs. III, II vs. III
craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia	2 (7.7)	7 (12.5)	3 (7.5)	0.729	/
postural deformities	0 (0.0)	4 (7.1)	1 (2.5)	0.436	/
jerky myoclonic postural or kinetic tremor	0 (0.0)	0 (0.0)	0 (0.0)	/	/
stridor	5 (19.2)	4 (7.1)	2 (5)	0.160	/
inspiratory sighs	0 (0.0)	0 (0.0)	1 (2.5)	0.541	/
severe speech impairment within 3 years of motor onset	5 (19.2)	24 (42.9)	3 (7.5)	<0.001	I vs. II, II vs. III
severe dysphagia within 3 years of motor onset	5 (19.2)	17 (30.4)	15 (37.5)	0.315	/
cold discolored hands and feet	1 (3.8)	7 (12.5)	2 (5.0)	0.385	/
pathologic laughter or crying	0 (0.0)	3 (5.4)	0 (0.0)	0.311	/
unexplained Babinski sign	10 (38.5)	32 (57.1)	21 (52.5)	0.291	/
erectile dysfunction (below age of 60 years)	10 (38.5)	13 (23.2)	16 (40.0)	0.165	/

## SOM

	cluster1	cluster2	cluster3	p	Multiple comparisons
moderate to severe postural instability within 3 years of motor onset	29 (87.9)	33 (42.3)	4 (36.4)	<0.001	I vs. II, I vs. III
rapid progression within 3 years of motor onset	19 (57.6)	14 (17.9)	1 (9.1)	<0.001	I vs. II, I vs. III
craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia	2 (6.1)	9 (11.5)	1 (9.1)	0.800	/
postural deformities	0 (0.0)	3 (3.8)	2 (18.2)	0.056	/
jerky myoclonic postural or kinetic tremor	0 (0.0)	0 (0.0)	0 (0.0)	/	/
stridor	5 (15.2)	5 (6.4)	1 (9.1)	0.271	/
inspiratory sighs	0 (0.0)	0 (0.0)	1 (9.1)	0.090	/
severe speech impairment within 3 years of motor onset	8 (24.2)	22 (28.2)	2 (18.2)	0.855	/
severe dysphagia within 3 years of motor onset	6 (18.2)	28 (35.9)	3 (27.3)	0.173	/
cold discolored hands and feet	1 (3.0)	5 (6.4)	3 (36.4)	0.008	I vs. III, II vs. III
pathologic laughter or crying	0 (0.0)	2 (2.6)	1 (9.1)	0.267	/
unexplained Babinski sign	15 (45.5)	44 (56.4)	4 (36.4)	0.330	/
erectile dysfunction (below age of 60 years)	12 (36.4)	24 (30.8)	3 (27.3)	0.829	/