

Supplemental Appendix

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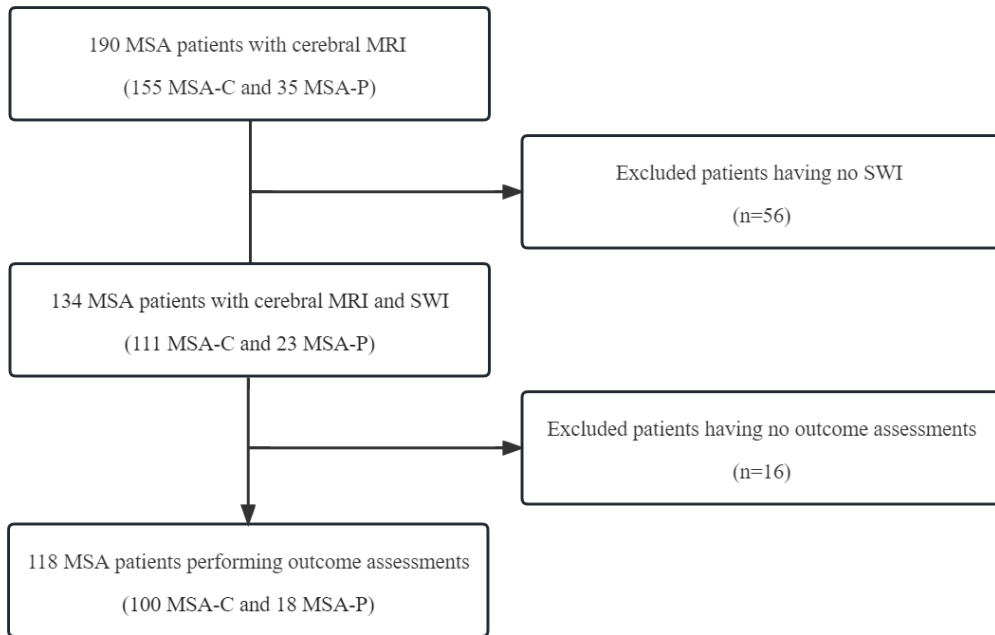
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Supplementary Methods

Specific parameter information for Neuroimaging Assessment

MSA patients received MRI examinations on a GE 3.0-T scanner (Discovery MR750, GE Healthcare, Milwaukee, WI, USA) with a standard 8-channel HRBRAIN coil. The full sequence of cranial MRI included axial T2-weighted sequences, fluid-attenuated inversion recovery (FLAIR), T1-weighted sequences, diffusion-weighted imaging (DWI), and axial susceptibility-weighted imaging (SWI). The MRI protocol included the following: (1) an axial T1-FLAIR-weighted sequence [repetition time (TR)=1,878 ms, echo time (TE)=23 ms, matrix=288×192, field of view (FOV)=240 mm, slice thickness=6 mm, spacing=2, number of excitations (NEX)=1], (2) an axial T2-PROPELLER-weighted [fast recovery fast spin echo (FRFSE)] sequence (TR=4,526 ms, TE=96 ms, matrix=416×416, FOV=240 mm, slice thickness=6 mm, spacing=2, NEX=1), (3) a T2-FLAIR sequence [TR=8,800 ms, TE=147 ms, inversion time (TI)=2,100 ms, matrix=256×224, FOV=240 mm, slice thickness=6 mm, spacing=2, NEX=1], (4) an SWI sequence (TR=76 ms; TE=43 ms; FOV=24 cm; matrix=320×256, slice thickness=3 mm, spacing=1.5, NEX=0.69); and (V) a DWI sequence (TR=3,000 ms; TE=65 ms; matrix=320×256, FOV=240 mm, slice thickness=6 mm, spacing=8, NEX=1).

Figure S1: Flow diagram of the inclusion process



Note: A total of 190 MSA patients had complete imaging data of WMH, lacunes, and EPVS, of whom 134 patients underwent susceptibility-weighted imaging (SWI) examinations and had additional complete imaging data of microbleeds and overall CSVD burden. Among 134 patients with complete data on overall CSVD burden and four imaging markers (microbleeds, WMH, lacunes, and EPVS), 16 patients without outcome assessments were excluded. The remaining 118 patients had complete data on overall CSVD burden and four imaging markers (microbleeds, WMH, lacunes, and EPVS), as well as data on outcome assessments were used to explore whether CSVD has a relationship with motor, cognitive, and emotional dysfunction in patients with MSA.

Table S1. Demographic characteristics and CSVD neuroimaging features of 118 MSA**patients and healthy controls**

Demographic characteristics	MSA patients	Healthy Controls	p value
Age (years)	58.25 ± 7.67	59.01 ± 9.51	0.494
Male (n, %)	77 (65.25)	75 (63.56)	0.786
Vascular risk factors			
Smoking (n, %)	23 (19.66)	40 (33.90)	0.018
Drinking (n, %)	24 (20.34)	10 (8.47)	0.015
Hypertension (n, %)	94 (79.66)	87 (73.73)	0.281
Diabetes (n, %)	98 (83.05)	90 (76.27)	0.196
Blood tests			
Total cholesterol (mmol/L)	4.39 (3.68,4.89)	4.38 (3.80,5.20)	0.697
HDL (mmol/L)	1.15 (0.97,1.42)	1.09 (0.93,1.29)	0.035
LDL (mmol/L)	2.72 ± 0.80	2.87 ± 0.84	0.155
Triglyceride (mmol/L)	1.21 (0.88,1.70)	1.37 (0.98,1.90)	0.036
Homocysteine (μ mol/L)	10.40 (8.40,12.80)	11.05 (9.68, 14.61)	0.008
MRI findings			
Lacunae (n, %)	100 (84.74)	78 (66.10)	0.001
BG-EPVS (n, %)			0.572
1 grade (count≤10)	95 (80.51)	101 (85.59)	
2 grade(count=11 - 25)	18 (15.25)	13 (11.02)	
3 grade (count≥25)	5 (4.24)	4 (3.39)	

CS-EPVS (n, %)			0.185
1 grade (count \leq 10)	70 (59.32)	80 (67.80)	
2 grade (count=11 - 25)	35 (29.66)	32 (27.12)	
3 grade (count \geq 25)	13 (11.02)	6 (5.08)	
H-EPVS (n, %)			0.004
0 score (non-extensive burden)	68 (57.63)	89 (76.07)	
1 score (extensive burden)	50 (42.37)	28 (23.93)	
M-EPVS (n, %)			0.1
0 score (absence)	71 (60.17)	84 (71.19)	
1 score (presence)	47 (39.83)	34 (28.81)	
WMH score (n, %)			
Periventricular-WMH			<0.001
0 score	22 (18.64)	50 (42.37)	
1 score	63 (53.39)	35 (29.66)	
2 score	25 (21.19)	25 (21.19)	
3 score	8 (6.78)	8 (6.78)	
Deep-WMH			<0.001
0 score	44 (37.29)	77 (65.25)	
1 score	43 (36.44)	28 (23.73)	
2 score	21 (17.80)	89 (6.78)	
3 score	10 (8.47)	5 (4.24)	
Microbleeds (n, %)	36 (30.51)	35 (31.25)	0.903

Severity of CSVD burden (n, %)			0.004
None-to-mild (CSVD score 0 - 1)	58 (49.15)	83 (70.34)	
Moderate (CSVD score 2)	39 (33.05)	23 (19.49)	
Severe (CSVD score 3 - 4)	21 (17.80)	12 (10.17)	

Note: 118 MSA patients are those who were used to explore associations between CSVD neuroimaging makers and multi-dimensional outcomes. For continuous variables, Student t-test for normally distributed parameters (Age and LDL) and Wilcoxon test for non-normally distributed parametric variables (the remaining continuous variables other than Age and LDL) were used. For categorical variables, χ^2 test or Fisher exact test was used.

Table S2: Group comparisons of demographic profiles and CSVD burden between MSA subtypes and healthy controls

	MSA-C	MSA-P	HC	MSA-C vs MSA-P	MSA-C vs HC	MSA-P vs HC
	n = 155	n = 35	n = 190	P value	P value	P value
Demographic characteristics						
Age (years)	57.75 ± 7.52	62.00 ± 7.44	59.59 ± 9.78	0.003	0.056	0.167
Male (n, %)	92 (59.35%)	22 (62.86%)	114 (60.00%)	0.702	0.903	0.860
Vascular risk factors						
Smoking (n, %)	24 (15.58%)	3 (8.57%)	41 (21.58%)	0.285	0.158	0.075
Drinking (n, %)	23 (14.94%)	5 (14.29%)	19 (10.00%)	0.922	0.164	0.450
Supine hypertension (n, %)	33 (21.29%)	5 (14.29%)	40 (21.05%)	0.349	0.957	0.358
Diabetes (n, %)	21 (13.55%)	5 (14.29%)	35 (18.42%)	0.909	0.222	0.557
Blood tests						

Total cholesterol (mmol/L)	4.39 (3.66, 4.88)	4.41 (3.96, 5.13)	4.35 (3.70, 5.20)	0.527	0.757	0.656
HDL (mmol/L)	1.17 (0.99, 1.45)	1.17 (0.94, 1.42)	1.11 (0.96, 1.32)	0.622	0.045	0.492
LDL (mmol/L)	2.73 ± 0.79	2.80 ± 0.78	2.86 ± 0.87	0.610	0.145	0.718
Triglyceride (mmol/L)	1.26 (0.91, 1.62)	1.34 (0.84, 1.85)	1.31 (0.96, 1.89)	0.774	0.070	0.452
Homocysteine (μmol/L)	10.30 (8.40, 12.70)	10.94 (9.00, 12.30)	11.30 (9.80, 14.40)	0.423	<0.001	0.084
MRI findings						
Lacunae (n, %)	122 (78.71%)	27 (77.14%)	133 (70.00%)	0.839	0.067	0.392
BG-EPVS (n, %)				0.505	0.184	0.556
1 grade (count≤10)	128 (82.58%)	28 (80.00%)	165 (86.84%)			
2 grade (count=11–25)	23 (14.84%)	5 (14.29%)	17 (8.94%)			
3 grade (count≥25)	4 (2.58%)	2 (5.71%)	8 (4.21%)			
CS-EPVS (n, %)				0.033	0.316	<0.001
1 grade (count≤10)	101 (65.16%)	17 (48.57%)	134 (70.53%)			

2 grade (count=11–25)	42 (27.10%)	10 (28.57%)	48 (25.26%)			
3 grade (count≥25)	12 (7.74%)	8 (22.86%)	8 (4.21%)			
H-EPVS (n, %)				0.403	0.016	0.018
0 score (non-extensive burden)	96 (61.94%)	19 (54.29%)	140 (74.07%)			
1 score (extensive burden)	59 (38.06%)	16 (45.71%)	49 (25.93%)			
M-EPVS (n, %)				0.167	0.025	0.005
0 score (absence)	95 (61.29%)	17 (48.57%)	138 (72.63%)			
1 score (presence)	60 (38.71%)	18 (51.43%)	52 (27.37%)			
WMH score (n, %)						
Periventricular-WMH				0.494	0.001	0.355
0 score	40 (25.81%)	9 (25.71%)	78 (41.05%)			
1 score	78 (50.32%)	14 (40.00%)	60 (31.58%)			
2 score	30 (19.35%)	9 (25.71%)	35 (18.42%)			

3 score	7 (4.52%)	3 (8.57%)	17 (8.95%)			
Deep-WMH				0.223	0.195	0.016
0 score	75 (48.39%)	12 (34.29%)	114 (60.00%)			
1 score	48 (30.97%)	14 (40.00%)	47 (24.74%)			
2 score	22 (14.19%)	4 (11.43%)	20 (10.53%)			
3 score	10 (6.45%)	5 (14.29%)	9 (4.74%)			
Patients with SWI	n = 111	n = 23	n = 134			
Microbleeds (n, %)	26 (23.42%)	12 (52.17%)	45 (33.58%)	0.005	0.082	0.092
Severity of CSVD burden (n, %)	n = 111	n = 23	n = 134	0.275	0.048	0.006
None-to-mild (CSVD score 0–1)	58 (52.25%)	8 (34.78%)	90 (67.16%)			
Moderate (CSVD score 2)	34 (30.63%)	9 (39.13%)	31 (23.13%)			
Severe (CSVD score 3–4)	19 (17.12%)	6 (26.09%)	13 (9.70%)			
MSA outcomes	n = 100	n = 18				

UMSARS-II	12.00 (9.00, 16.75)	14.28 (9.96, 18.39)	0.264
SARA	11.06 (8.63, 15.15)	12.13 (9.92, 15.10)	0.582
ICARS	25.57 (16.70, 34.95)	33.85 (24.45, 38.75)	0.140
COMPASS31	29.44 ± 18.35	31.81 ± 14.80	0.607
MMSE	25.39 (22.00, 27.00)	20.50 (13.97, 25.00)	0.001
MoCA	17.00 (13.99, 21.00)	12.00 (8.86, 20.50)	0.072
HAMA	7.00 (3.41, 13.00)	11.00 (6.25, 16.22)	0.156
HAMD	5.81 (2.00, 9.00)	6.50 (4.00, 13.25)	0.297

Note: For continuous variables, ANOVA for normally distributed parameters (Age, LDL, and COMPASS31) and Kruskal–Wallis test for non-normally distributed parametric variables (Total cholesterol, HDL, Triglyceride, Homocysteine, UMSARS-II, SARA, ICARS, MMSE, HAMA, MoCA, and HAMD) were used. For categorical variables, χ^2 test or Fisher exact test was used. Based on Bonferroni correction, the p-value $< 0.05/3$ was considered to be statistically significant.

Table S3: Group comparisons of demographic profiles and outcomes stratified by the severity of CSVD burden in 100 MSA-C patients

Characteristics	None-to-mild (CSVD score 0–1)	Moderate (CSVD score 2)	Severe (CSVD score 3–4)	P value
	n = 53	n = 31	n = 16	
Demographic characteristics				
Age (years)	54.08 ± 6.36	59.87 ± 6.93	64.00 ± 6.07	< 0.001
Motor dysfunction duration (months)	16.00 (12.00, 24.00)	24.00 (12.00, 30.00)	24.00 (13.50, 30.00)	0.123
Male (n, %)	31 (58.49%)	21 (67.74%)	13 (81.25%)	0.229
Education (years)	9.00 (7.50, 12.00)	9.00 (5.00, 10.00)	9.00 (6.38, 12.00)	0.382
Smoking (n, %)	11 (20.75%)	4 (12.90%)	6 (37.50%)	0.152
Drinking (n, %)	9 (16.98%)	6 (19.35%)	7 (43.75%)	0.079
Supine hypertension (n, %)	6 (11.32%)	8 (25.81%)	9 (56.25%)	0.001
Diabetes (n, %)	4 (7.55%)	10 (32.26%)	5 (31.25%)	0.006
Orthostatic hypotension (n, %)	26 (49.06%)	23 (74.19%)	10 (62.50%)	0.074

RBD (n, %)	41 (77.36%)	25 (80.65%)	14 (87.50%)	0.747
Sleep-related breathing disorders (n, %)	27 (50.94%)	19 (61.29%)	12 (75.00%)	0.231
Blood tests				
Total cholesterol (mmol/L)	4.48 ± 0.95	4.56 ± 0.94	3.94 ± 0.90	0.079
HDL (mmol/L)	1.29 ± 0.40	1.18 ± 0.26	1.11 ± 0.28	0.130
LDL (mmol/L)	2.77 ± 0.80	2.88 ± 0.84	2.40 ± 0.73	0.143
Triglyceride (mmol/L)	1.12 (0.89, 1.64)	1.50 (1.02, 1.80)	1.19 (0.89, 1.64)	0.168
Homocysteine (µmol/L)	10.10 (8.10, 12.70)	10.70 (8.60, 12.80)	11.35 (9.08, 15.45)	0.246
MSA outcomes				
UMSARS-II	11.00 (6.99, 13.82)	14.00 (10.00, 18.00)	15.13 (13.00, 20.50)	< 0.001
SARA	10.00 (7.50, 12.31)	15.00 (10.24, 17.00)	14.10 (10.75, 19.88)	< 0.001
ICARS	20.00 (15.75, 29.00)	29.00 (20.56, 39.00)	30.86 (17.20, 43.35)	0.037
COMPASS31	28.17 (10.77, 42.56)	38.44 (15.78, 47.25)	23.63 (13.35, 50.81)	0.233

MMSE	26.00 (22.50, 27.00)	25.00 (22.00, 27.00)	24.59 (19.77, 27.00)	0.542
MoCA	18.26 ± 6.08	16.15 ± 4.75	15.70 ± 6.97	0.158
HAMA	6.00 (2.61,13.00)	8.00 (5.00, 19.00)	8.00 (3.25, 11.45)	0.091
HAMD	4.66 (2.00, 8.27)	7.00 (3.00, 11.00)	3.50 (2.00, 8.75)	0.142

Note: For continuous variables, ANOVA for normally distributed parameters (Age, Total cholesterol, HDL, LDL, and MoCA) and Kruskal–Wallis test for non-normally distributed parametric variables (Motor dysfunction duration, Triglyceride, Homocysteine, UMSARS-II, SARA, ICARS, MMSE, HAMA, and HAMD) were used. For categorical variables, χ^2 test or Fisher exact test was used.

Table S4: Group comparisons of demographic profiles and outcomes stratified by the severity of CSVD burden in 18 MSA-P patients

Characteristics	None-to-mild (CSVD score 0–1)	Moderate (CSVD score 2)	Severe (CSVD score 3–4)	P value
	n = 5	n = 8	n = 5	
Demographic characteristics				
Age (years)	58 ± 8.60	61.13 ± 5.54	69.6 ± 2.70	0.020
Motor dysfunction duration (months)	29.60 ± 15.13	23.38 ± 17.25	22.6 ± 13.81	0.738
Male (n, %)	2 (40.00%)	5 (62.50%)	5 (40.00%)	0.141
Education (years)	12.00 (3.00, 14.00)	5.00 (0.25, 9.00)	1.43 (0.00, 7.00)	0.230
Smoking (n, %)	0 (0.00%)	1 (12.50%)	1 (20.00%)	1.000
Drinking (n, %)	0 (0.00%)	1 (12.50%)	1 (20.00%)	1.000
Supine hypertension (n, %)	0 (0.00%)	1 (12.50%)	0 (0.00%)	1.000
Diabetes (n, %)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0.556
Orthostatic hypotension (n, %)	2 (40.00%)	6 (75.00%)	2 (40.00%)	0.424

RBD (n, %)	5 (100.00%)	7 (87.50%)	5 (100.00%)	1.000
Sleep-related breathing disorders (n, %)	1 (20.00%)	4 (50.00%)	5 (100.00%)	0.044
Blood tests				
Total cholesterol (mmol/L)	4.91 ± 0.59	4.08 ± 0.93	4.10 ± 0.62	0.164
HDL (mmol/L)	1.19 ± 0.38	1.38 ± 0.34	0.98 ± 0.16	0.123
LDL (mmol/L)	3.25 ± 0.74	2.35 ± 0.77	2.43 ± 0.47	0.089
Triglyceride (mmol/L)	0.86 (0.79, 2.76)	0.87 (0.74, 1.34)	1.94 (1.00, 2.90)	0.354
Homocysteine (µmol/L)	8.88 ± 1.46	10.59 ± 2.16	13.16 ± 2.21	0.014
MSA outcomes				
UMSARS-II	10.00 (9.00, 12.00)	15.00 (11.02, 21.46)	16.00 (12.40, 40.50)	0.070
SARA	7.00 (6.00, 14.45)	12.13 (11.16, 13.40)	15.39 (13.50, 22.00)	0.039
ICARS	20.39 ± 11.38	30.81 ± 9.97	40.34 ± 5.62	0.015
COMPASS31	23.10 (16.90, 39.41)	33.04 (23.68, 46.87)	25.78 (17.05, 45.41)	0.454

MMSE	17.80 ± 10.76	21.50 ± 5.63	16.38 ± 6.03	0.457
MoCA	17.20 ± 6.76	14.00 ± 8.43	10.88 ± 5.58	0.417
HAMA	7.80 ± 4.87	14.63 ± 7.86	10.19 ± 8.01	0.258
HAMD	4.20 ± 2.05	9.88 ± 4.55	7.03 ± 5.45	0.100

Note: For continuous variables, ANOVA for normally distributed parameters (Age, Motor dysfunction duration, Total cholesterol, HDL, LDL, Homocysteine, ICARS, MMSE,

MoCA, HAMA, and HAMD) and Kruskal–Wallis test for non-normally distributed parametric variables (Triglyceride, UMSARS-II, SARA, and COMPASS31) were used.

For categorical variables, χ^2 test or Fisher exact test was used.

Table S5. Linear regression for the association between the severity of CSVD burden and outcomes in 118 MSA patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II ¹	3.432 (1.387, 5.478)	0.001	2.430 (0.130, 4.731)	0.039
SARA ²	2.682 (1.357, 4.007)	< 0.001	1.882 (0.377, 3.388)	0.015
ICARS ³	5.046 (1.571, 8.521)	0.005	3.082 (-0.986, 7.150)	0.136
COMPASS31	2.976 (-1.307, 7.258)	0.171	-	-
MMSE	-1.246 (-2.526, 0.035)	0.056	-	-
MoCA ⁴	-1.923 (-3.386, -0.460)	0.01	-0.460 (-1.774, 0.853)	0.489
HAMA	1.444 (-0.523, 3.412)	0.149	-	-
HAMD	0.479 (-0.807, 1.764)	0.462	-	-

¹ The multivariable regression model was adjusted for age, motor dysfunction duration (months), high-density lipoprotein, and diabetes.

² The multivariable regression model was adjusted for age, motor dysfunction duration (months), and diabetes.

³ The multivariable regression model adjusted for age, motor dysfunction duration (months), high-density lipoprotein, and diabetes.

⁴ The multivariable regression model was adjusted for age and education.

Table S6: Linear regression for the association between the severity of CSVD burden and outcomes in 100 MSA-C patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II ¹	2.616 (0.458, 4.773)	0.018	1.163 (-0.554, 4.064)	0.135
SARA ²	2.546 (1.024, 4.067)	0.001	0.246 (0.484, 3.449)	0.010
ICARS ³	4.003 (-0.030, 8.036)	0.052	0.097 (-2.565, 6.564)	0.387
COMPASS31	3.114 (-1.768, 7.996)	0.209	-	-
MMSE	-0.863 (-2.070, 0.343)	0.159	-	-
MoCA ⁴	-1.448 (-3.006, 0.110)	0.068	-	-
HAMA	1.345 (-0.871, 3.561)	0.231	-	-
HAMD	0.223 (-1.231, 1.677)	0.761	-	-

¹ The multivariable regression model was adjusted for age, motor dysfunction duration (months), total cholesterol, and diabetes.

² The multivariable regression model was adjusted for age, motor dysfunction duration (months), diabetes, and HDL.

³The multivariable regression model was adjusted for age, motor dysfunction duration (months), diabetes, and HDL.

Table S7: Linear regression for the association between the severity of CSVD burden and outcomes in 18 MSA-P patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II ¹	6.980 (0.020, 13.940)	0.049	0.469 (0.021, 13.940)	0.049
SARA ²	3.849 (0.995, 6.702)	0.011	0.167 (-3.727, 5.949)	0.630
ICARS ³	9.976 (3.839, 16.112)	0.003	0.674 (3.219, 17.372)	0.008
COMPASS31	1.499 (-8.697, 11.695)	0.759	-	-
MMSE	-0.710 (-5.785, 4.365)	0.770	-	-
MoCA ⁴	-3.158 (-7.9144, 1.599)	0.178	-	-
HAMA	1.196 (-3.898, 6.289)	0.626	-	-
HAMD	1.413 (-1.772, 4.598)	0.361	-	-

¹ The multivariable regression model was adjusted for age and homocysteine.

² The multivariable regression model was adjusted for age and homocysteine.

³The multivariable regression model was adjusted for age and hypertension.

Table S8: Linear regression for the association between the CS-EPVS burden and outcomes in 118 MSA patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II ¹	3.560 (1.293, 5.827)	0.002	2.181 (-0.098, 4.460)	0.061
SARA ²	2.619 (1.136, 4.101)	0.001	1.558 (0.030, 3.086)	0.046
ICARS	2.336 (-1.605, 6.278)	0.243	-	-
COMPASS31	0.485 (-4.273, 5.243)	0.840	-	-
MMSE ³	-1.821 (-3.216, -0.427)	0.011	-0.378 (-1.680, 0.924)	0.567
MoCA ⁴	-1.680 (-3.310, -0.050)	0.043	-0.009 (-1.333, 1.314)	0.989
HAMA	0.298 (-1.890, 2.486)	0.788	-	-
HAMD	0.729 (-0.685, 2.143)	0.310	-	-

¹ The multivariable regression model was adjusted for age, motor dysfunction duration (months), high-density lipoprotein, and diabetes.

² The multivariable regression model was adjusted for age, motor dysfunction duration (months), and diabetes.

³ The multivariable regression model was adjusted for age and education.

⁴ The multivariable regression model was adjusted for age and education.

Table S9: Linear regression for the association between the BG-EPVS burden and outcomes in 118 MSA patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II	0.546 (-2.591, 3.682)	0.731	-	-
SARA ¹	2.592 (0.575, 4.609)	0.012	1.721 (-0.275, 3.716)	0.090
ICARS	2.526 (-2.726, 7.779)	0.342	-	-
COMPASS31	0.348 (-5.982, 6.677)	0.914	-	-
MMSE	-0.814 (-2.715, 1.088)	0.398	-	-
MoCA	-1.011 (-3.210, 1.188)	0.364	-	-
HAMA ²	3.286 (0.439, 6.133)	0.024	3.275 (0.469, 6.081)	0.023
HAMD	0.495 (-1.392, 2.382)	0.604	-	-

¹ The multivariable regression model was adjusted for age, motor dysfunction duration (months), and diabetes.

² The multivariable regression model was adjusted for homocysteine.

Table S10: Linear regression for the association between the H-EPVS burden and outcomes in 118 MSA patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II	1.297 (-1.968, 4.562)	0.433	-	-
SARA	1.777 (-0.360, 3.915)	0.102	-	-
ICARS	5.197 (-0.220, 10.615)	0.060	-	-
COMPASS31	2.483 (-4.105, 9.070)	0.457	-	-
MMSE ¹	-3.528 (-5.409, -1.648)	< 0.001	-1.963 (-3.655, -0.271)	0.023
MoCA ²	-4.646 (-6.783, -2.508)	< 0.001	-2.530 (-4.222, -0.838)	0.004
HAMA	1.014 (-2.016, 4.046)	0.508	-	-
HAMD	-0.866 (-2.830, 1.098)	0.384	-	-

¹ The multivariable regression model was adjusted for age and education.

² The multivariable regression model was adjusted for age and education.

Table S11: Linear regression for the association between the M-EPVS burden and outcomes in 118 MSA patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II	0.451 (-2.435, 3.336)	0.758	-	-
SARA	0.288 (-1.785, 2.361)	0.783	-	-
ICARS	0.189 (-5.167, 5.545)	0.944	-	-
COMPASS31	-2.999 (-9.461, 3.464)	0.360	-	-
MMSE	-0.431 (-2.380, 1.519)	0.663	-	-
MoCA	0.073 (-2.187, 2.334)	0.949	-	-
HAMA	2.861 (-0.068, 5.791)	0.055	-	-
HAMD	0.238 (-1.696, 2.173)	0.808	-	-

Table S12: Linear regression for the association between the whole-brain WMH burden and outcomes in 118 MSA patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II ¹	1.957 (0.989, 2.924)	< 0.001	1.600 (0.550, 2.649)	0.003
SARA ²	1.150 (0.502, 1.798)	0.001	0.713 (0.005, 1.421)	0.049
ICARS ³	2.390 (0.712, 4.067)	0.006	1.395 (-0.499, 3.289)	0.147
COMPASS31	1.694 (-0.364, 3.752)	0.106	-	-
MMSE ⁴	-0.919 (-1.523, -0.315)	0.003	-0.231 (-0.832, 0.369)	0.447
MoCA ⁵	-1.272 (-1.959, -0.585)	< 0.001	-0.676 (-1.275, -0.078)	0.027
HAMA ⁶	1.096 (0.160, 2.032)	0.022	1.177 (0.255, 2.099)	0.013
HAMD	0.471 (-0.144, 1.086)	0.133	-	-

¹ The multivariable regression model was adjusted for age, motor dysfunction duration (months), high-density lipoprotein, and diabetes.

² The multivariable regression model was adjusted for age, motor dysfunction duration (months), and diabetes.

³ The multivariable regression model was adjusted for age, motor dysfunction duration (months), high-density lipoprotein, and diabetes.

⁴ The multivariable regression model was adjusted for age and education;

⁵ The multivariable regression model was adjusted for age and education.

⁶ The multivariable regression model was adjusted for homocysteine.

Table S13: Linear regression for the association between the presence of lacunes and outcomes in 118 MSA patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II	1.783 (-2.704, 6.271)	0.433	-	-
SARA	2.069 (-0.879, 5.016)	0.167	-	-
ICARS	7.229 (-0.214, 14.672)	0.057	-	-
COMPASS31	-0.075 (-9.150, 9.000)	0.987	-	-
MMSE	-2.536 (-5.231, 0.158)	0.065	-	-
MoCA	-1.788 (-4.935, 1.359)	0.263	-	-
HAMA	3.328 (-0.800, 7.456)	0.113	-	-
HAMD	0.187 (-2.521, 2.895)	0.892	-	-

Table S14: Linear regression for the association between the presence of microbleeds and outcomes in 118 MSA patients

MSA outcomes	Univariate regression model		Multivariable regression model	
	Unstandardized B coefficient (95% CI)	p value	Standardized β coefficient (95% CI)	p value
UMSARS-II ¹	3.516 (0.062, 6.969)	0.046	2.626 (-0.666, 5.918)	0.117
SARA	1.946 (-0.347, 4.239)	0.095	-	-
ICARS	4.411 (-1.436, 10.259)	0.138	-	-
COMPASS31	0.708 (-6.377, 7.794)	0.843	-	-
MMSE	-0.752 (-2.883, 1.378)	0.486	-	-
MoCA	-0.512 (-2.981, 1.956)	0.682	-	-
HAMA	-2.035 (-5.272, 1.202)	0.216	-	-
HAMD	-0.981 (-3.088, 1.126)	0.358	-	-

¹ The multivariable regression model was adjusted for age, motor dysfunction duration (months), high-density lipoprotein, and diabetes.

Table S15: The Spearman's correlation between the CSVD neuroimaging and MSA outcomes stratified by

		age			
MSA		≤ 60 years		> 60 years	
outcomes	CSVD Neuroimaging	Spearman r	p value	Spearman r	p value
UMSARSII	Overall CSVD burden	0.147	0.218	0.273	0.066
	CS-EPVS	0.268	0.023	0.167	0.268
	BG-EPVS	0.063	0.601	-0.145	0.337
	H-EPVS	0.062	0.604	-0.061	0.687
	M-EPVS	-0.015	0.899	0.084	0.585
	WMH burden	0.206	0.083	0.360	0.014
	Lacunes	0.042	0.728	0.027	0.859
	Microbleeds	0.087	0.468	0.188	0.210
SARA	Overall CSVD burden	0.112	0.349	0.396	0.006
	CS-EPVS	0.335	0.004	0.126	0.405
	BG-EPVS	0.160	0.180	0.148	0.327
	H-EPVS	0.112	0.347	0.037	0.805
	M-EPVS	0.011	0.926	0.007	0.962
	WMH burden	0.168	0.159	0.250	0.094
	Lacunes	0.074	0.538	0.114	0.451
	Microbleeds	-0.005	0.967	0.204	0.174
ICARS	Overall CSVD burden	0.105	0.382	0.269	0.070
	CS-EPVS	0.200	0.092	-0.157	0.299

	BG-EPVS	0.207	0.081	-0.129	0.394
	H-EPVS	0.073	0.545	0.209	0.163
	M-EPVS	0.034	0.779	-0.059	0.699
	WMH burden	0.148	0.216	0.216	0.150
	Lacunes	0.198	0.095	0.030	0.842
	Microbleeds	0.000	0.999	0.212	0.158
COMPASS31	Overall CSVD burden	0.147	0.217	0.080	0.597
	CS-EPVS	0.000	0.998	0.012	0.937
	BG-EPVS	0.138	0.248	-0.113	0.455
	H-EPVS	0.053	0.656	0.070	0.646
	M-EPVS	-0.122	0.309	-0.059	0.701
	WMH burden	0.061	0.608	0.255	0.088
	Lacunes	0.003	0.982	-0.035	0.816
	Microbleeds	0.075	0.533	-0.084	0.580
MMSE	Overall CSVD burden	-0.011	0.928	-0.079	0.602
	CS-EPVS	-0.083	0.487	-0.227	0.129
	BG-EPVS	0.083	0.489	-0.016	0.918
	H-EPVS	-0.093	0.437	-0.476	0.001
	M-EPVS	0.104	0.382	-0.125	0.413
	WMH burden	-0.148	0.215	-0.183	0.223
	Lacunes	-0.168	0.158	-0.096	0.524
	Microbleeds	-0.029	0.808	0.036	0.810

MOCA	Overall CSVD burden	-0.165	0.165	-0.114	0.449
	CS-EPVS	-0.190	0.109	-0.047	0.759
	BG-EPVS	-0.061	0.612	0.028	0.852
	H-EPVS	-0.219	0.064	-0.500	0.000
	M-EPVS	0.098	0.415	-0.093	0.543
	WMH burden	-0.215	0.070	-0.295	0.047
	Lacunes	-0.085	0.478	-0.042	0.783
	Microbleeds	-0.036	0.763	0.091	0.546
HAMA	Overall CSVD burden	0.240	0.043	-0.006	0.969
	CS-EPVS	0.043	0.720	-0.024	0.873
	BG-EPVS	0.240	0.043	0.199	0.186
	H-EPVS	0.117	0.328	-0.041	0.785
	M-EPVS	0.091	0.448	0.338	0.023
	WMH6	0.163	0.170	0.263	0.077
	Lacunes	0.148	0.213	0.130	0.389
	Microbleeds	0.015	0.900	-0.298	0.044
HAMD	Overall CSVD burden	0.157	0.188	0.014	0.927
	CS-EPVS	0.090	0.451	0.145	0.338
	BG-EPVS	0.250	0.034	-0.075	0.618
	H-EPVS	-0.028	0.813	-0.148	0.326
	M-EPVS	-0.050	0.678	0.222	0.142
	WMH burden	0.070	0.560	0.327	0.027

Lacunes	0.018	0.880	0.021	0.892
Microbleeds	-0.028	0.818	-0.148	0.325

Note: Based on Bonferroni correction, the p-value $< 0.05/8$ was considered to be statistically significant.

Table S16: The Spearman's correlation between the CSVD neuroimaging and MSA motor dysfunction

duration (months)		
CSVD Neuroimaging	Spearman r	p value
Overall CSVD burden	0.053	0.572
CS-EPVS	0.141	0.127
BG-EPVS	0.003	0.973
H-EPVS	0.098	0.290
M-EPVS	0.175	0.059
WMH burden	0.042	0.651
Lacunae	0.017	0.858
Microbleeds	-0.022	0.814

Note: Based on Bonferroni correction, the p-value $< 0.05/8$ was considered to be statistically significant.

Table S17: Association of orthostatic hypotension and other cardiovascular risk factors with increasing severity of CSVD burden in MSA patients

	OR value (95% CI)	p value
Age	1.21 (1.13, 1.30)	<0.001
Male	0.52 (0.19, 1.41)	0.200
Diabetes	0.54 (0.17, 1.72)	0.302
Supine Hypertension	4.67 (1.59, 13.71)	0.005
Orthostatic hypotension	2.89 (1.19, 7.01)	0.019
Sleep-related breathing disorders	3.00 (1.20, 7.48)	0.018
Homocysteine	0.98 (0.90, 1.07)	0.646
Total cholesterol	0.93 (0.58, 1.50)	0.764

Abbreviations:

BG-EPVS, enlarged perivascular spaces in the basal ganglia; COMPASS31, Composite Autonomic Symptom Score 31; CS-EPVS, enlarged perivascular spaces in the centrum semiovale; CSVD, cerebral small vessel disease; FOV, field of view; FRFSE, fast recovery fast spin echo; HC, healthy controls; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; HDL, high-density lipoprotein; H-EPVS, enlarged perivascular spaces in the hippocampus; ICARS, International Cooperative Ataxia Rating Scale; LDL, low-density lipoprotein; M-EPVS, enlarged perivascular spaces in the midbrain; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MSA, multiple system atrophy; MSA-P, MSA-parkinsonian type; MSA-C, MSA-cerebellar type; NEX, number of excitations; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder; SARA, Scale for the Assessment and Rating of Ataxia; TE, echo time; TI, inversion time; TR, repetition time; UMSARS-II, Unified Multiple System Atrophy Rating Scale-II; WMH, white matter hyperintensities.