# The Diagnostic Utility of the New MDS Criteria for Multiple System Atrophy: A Retrospective Autopsy Cohort Study

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## ABSTRACT

### OBJECTIVE
This study aimed to validate the clinical utility of the newly proposed criteria for multiple system atrophy (MSA) by the International Parkinson and Movement Disorder Society (MDS).

### BACKGROUND
The second consensus statement has been widely used to diagnose MSA; however, it has been pointed out that the diagnostic accuracy is suboptimal. The new MDS criteria developed 4 categories: neuropathologically established MSA, clinically established MSA, clinically probable MSA, and possible prodromal MSA. Clinically established MSA was designed to have maximum specificity with acceptable sensitivity and clinically probable MSA was then aimed to balance sensitivity and specificity. The sensitivity and specificity of the new diagnostic criteria have not been fully examined.

### METHODS
We identified consecutive patients with a clinical or pathological diagnosis of MSA from the Mayo Clinic Brain Bank between 1998 and 2021. We restricted the cohort to **352 patients** with medical charts by neurologists or movement disorder specialists. Clinical signs and symptoms were extracted by systematic medical chart review. The MDS criteria and the second consensus criteria were applied to the cohort. The sensitivity, specificity, and area under the curve (AUC) of receiver operating characteristic curves were compared between these criteria. Comparison was conducted between clinical subtypes and among clinically challenging cases (those with different clinical diagnoses or those with suspected but undiagnosed MSA before death).

### RESULTS
The sensitivity and specificity of clinically established MSA and clinically probable MSA by the MDS criteria were 16% and 99% and 64% and 74%, respectively. The sensitivity and specificity of probable MSA and possible MSA by the second consensus criteria were 72% and 52% and 93% and 21%, respectively. Clinically established MSA exhibited the highest specificity and clinically probable MSA demonstrated the greatest AUC. The diagnostic performance did not differ between clinical subtypes. In clinically challenging cases, clinically established MSA kept high specificity and clinically probable MSA demonstrated the highest AUC.

### CONCLUSIONS
In this retrospective autopsy cohort study, the MDS criteria showed high specificity with clinically established MSA and moderate sensitivity and specificity with clinically probable MSA.

## BACKGROUND & OBJECTIVES

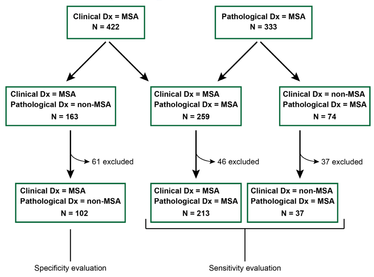
- The second consensus statement has been widely used to diagnose Multiple system atrophy (MSA)[1]. The International Parkinson and Movement Disorder Society (MDS) has recently published new diagnostic criteria[2].
- In the new MDS criteria, 4 diagnostic criteria were created: neuropathologically established MSA, clinically established MSA, clinically probable MSA, and possible prodromal MSA[2].
- This study aimed to compare the diagnostic accuracy between the two criteria and validate the clinical utility of the newly proposed criteria for MSA.

## METHODS

- We identified consecutive cases in the Mayo Clinic brain bank between 1998 and 2021 of 422 clinically diagnosed MSA (including cases in which MSA was included in the differential disease) and 333 pathologically confirmed MSA.
- After excluding cases with inadequate medical records, this study included 102 cases with a clinical diagnosis of MSA but a pathological diagnosis other than MSA, 213 cases with a clinical and pathological diagnosis of MSA, and 37 cases with a pathological diagnosis of MSA and clinical diagnosis other than MSA (Figure 1).
- Clinical information was collected through the systematical review of the medical records and brain bank questionnaire.
- We applied MDS criteria (clinically established MSA and clinically probable MSA) and the second consensus criteria (probable MSA and possible MSA) to our cohort and compared sensitivity, specificity, and area under the curve (AUC) of receiver operating characteristics (ROC) curves between these criteria.
- We also compared the two criteria in each clinical subtype (MSA-P and MSA-C).
- We defined clinically challenging cases as those with different clinical diagnoses or those with suspected but undiagnosed MSA before their death. Comparison of the two criteria were conducted between clinical subtypes and among clinically challenging cases.

## RESULTS

### FIGURE 1: Study design

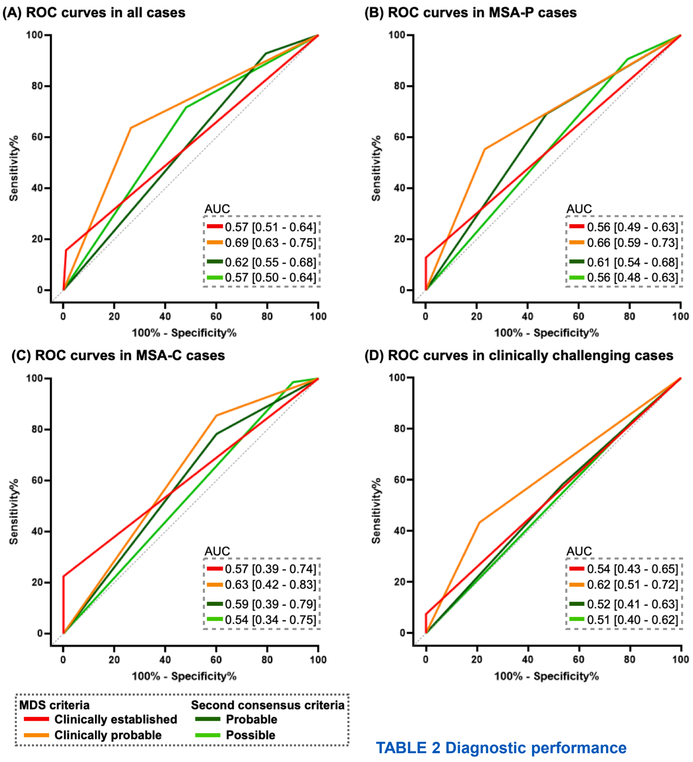



### TABLE 1 Characteristics of patients

| | All | C-Dx: MSA P-Dx: non-MSA | C-Dx: MSA P-Dx: MSA | C-Dx: non-MSA P-Dx: MSA |
|---|---|---|---|---|
| **Sex, Male** | 58% (205) | 72% (73) | 53% (112) | 54% (20) |
| **Age at onset (y)** | 61 ± 10 | 65 ± 9 | 58 ± 9 | 64 ± 11 |
| **Age at death (y)** | 69 ± 9 | 75 ± 9 | 65 ± 8 | 72 ± 10 |
| **Disease duration (y)** | 8 ± 4 | 10 ± 6 | 8 ± 3 | 8 ± 5 |
| **Clinical subtypes** | | | | |
| **MSA-P** | 77% (272) | 89% (91) | 69% (147) | 92% (34) |
| **MSA-C** | 22% (79) | 10% (10) | 31% (66) | 8% (3) |
| **MSA-A** | 0.3% (1) | 0.1% (1) | 0% (0) | 0% (0) |

*C-Dx*, clinical diagnosis; *P-Dx*, pathological diagnosis; *y*, years; *P*, parkinsonian type; *C*, cerebellar type; A, autonomic dysfunction type

### FIGURE 2 ROC curves of each criterion




### TABLE 2 Diagnostic performance

| Patients | Criteria | Sensitivity (%) | Specificity (%) | Accuracy (%) |
|---|---|---|---|---|
| **All (N = 352)** | (1) | 16 | 99 | 40 |
| | (2) | 64 | 74 | 67 |
| | (3) | 72 | 52 | 66 |
| | (4) | 93 | 21 | 72 |
| **MSA-P (N = 272)** | (1) | 13 | 100 | 42 |
| | (2) | 55 | 77 | 63 |
| | (3) | 69 | 53 | 64 |
| | (4) | 91 | 21 | 67 |
| **MSA-C (N = 79)** | (1) | 23 | 90 | 32 |
| | (2) | 86 | 40 | 80 |
| | (3) | 78 | 40 | 73 |
| | (4) | 99 | 10 | 87 |
| **Clinically Challenging (N = 110)** | (1) | 8 | 100 | 44 |
| | (2) | 43 | 79 | 57 |
| | (3) | 58 | 47 | 54 |
| | (4) | 84 | 19 | 58 |

MDS criteria: (1) clinically established MSA, (2) clinically probable MSA
Second consensus criteria (3) probable MSA, (4) possible MSA

*P*, parkinsonian type; *C*, cerebellar type; A, autonomic dysfunction type

## DISCUSSION

- Clinically established MSA with the MDS criteria showed excellent specificity (99%) and fulfilled the purpose of its creation. Future trials of disease-modifying therapies in MSA can be expected to include only genuine MSA patients by adapting these stringent criteria.
- Clinically probable MSA with the MDS criteria had moderate sensitivity (64%) and specificity (74%). These criteria also showed the highest AUC (0.69).
- The AUC of clinically probable MSA was significantly higher than that of probable and possible MSA with the second consensus criteria in MSA-P (P = 0.046 and P = 0.0011). The AUC of clinically probable MSA was significantly higher than that of probable MSA with the second consensus criteria in MSA-C (P = 0.021).
- It is notable that clinically established MSA with the MDS criteria exhibited high specificity (100%) in clinically challenging cases, although the second consensus criteria classified many non-MSA cases as probable or possible MSA, resulting in a low specificity (47% and 19%).
- To meet the criteria for clinically established MSA, two or more supportive features, MRI findings suggestive of MSA, and absence of exclusion criteria are required in addition to clinical core features. The combination of these requirements was considered to be the reason why clinically established MSA could achieve a high specificity.
- The present results are consistent with those of the recent report from the Queen Square Brain Bank in that clinically established MSA had the highest specificity[3]. The sensitivity of clinically established MSA and clinically probable MSA of the MDS criteria in the present study were lower than those in the previous study. The reasons for this may be as follows: the Queen Square Brain Bank cohort consisted of cases with parkinsonism or cerebellar symptoms, whereas ours consisted of cases with clinically diagnosed and pathologically confirmed MSA.

## CONCLUSIONS

- We validated the diagnostic utility of new diagnostic criteria for MSA by MDS using a large autopsy cohort from the Mayo Clinic brain bank.
- The new category, clinically established MSA, showed high specificity, while clinically probable MSA showed moderate sensitivity and specificity.
- The present study demonstrated the validity of the new diagnostic criteria for MSA proposed by the MDS.

## REFERENCES

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