




## ORIGINAL ARTICLE

# Tracheostomy is associated with increased survival in Multiple System Atrophy patients with stridor

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## Abstract

**Background and purpose:** Stridor treatment in multiple system atrophy (MSA) mainly comprises tracheostomy or continuous positive airway pressure (CPAP), but guidelines for the use of these treatments are lacking. The aim of the study was to evaluate the predictive value of stridor treatment in an MSA cohort.

**Methods:** This is a retrospective and prospective monocentric cohort study including MSA patients evaluated at least once a year during the disease course. Stridor was video-polysomnography confirmed. The time of stridor treatment (CPAP or tracheostomy) and latency from stridor onset were collected. Survival and predictors of survival were calculated.

**Results:** A total of 182 (107 males, mean age at disease onset  $57.3 \pm 8.4$  years) MSA patients were included in the study; 141 were deceased at the time of study. Of the total sample, 75 patients were diagnosed with stridor: 22 patients were treated with tracheostomy and 29 with CPAP, whilst 24 patients did not receive treatment. Treatment with tracheostomy showed longer survival compared with both treatment with CPAP or no treatment (incidence rate of death 12 vs. 21 vs. 23 per 100 person-years, respectively). Tracheostomy remained an independent factor associated with longer survival (hazard ratio 0.38,  $p = 0.029$ ), also after adjustment for other confounders and latency for stridor treatment.

**Conclusions:** This is the largest monocentric and long-term follow-up study comparing survival between tracheostomy and CPAP in MSA patients with stridor. Treatment with tracheostomy showed longer survival compared with both treatment with CPAP or no treatment. A careful multidisciplinary approach is required for the management of MSA patients with stridor.

## KEYWORDS

cohort study, movement disorders, multiple system atrophy, prognosis, stridor

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## INTRODUCTION

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by a combination of autonomic failure, cerebellar syndrome and poorly levodopa responsive parkinsonism [1]. The diagnostic criteria define three degrees of certainty for diagnosis (possible, probable and definite) and two phenotypes—parkinsonian (MSA-P) or cerebellar (MSA-C)—according to the predominant feature at the time of evaluation [1]. Mean survival in MSA ranges from 6.2 to 10 years [2–4]. Causes of death in MSA commonly include bronchopneumonia, urosepsis or sudden death that often occurs at night and has been attributed to either bilateral vocal cord paralysis or disruption of the brain-stem cardiorespiratory drive [5–7].

Respiratory abnormalities and different sleep-related breathing disorders are frequently reported in MSA and include snoring, obstructive sleep apnoea/hypopnoea syndrome, central sleep apnoea, stridor, paradoxical breathing, nocturnal tachypnoea, dysrhythmic breathing or irregular patterns and Cheyne–Stokes respiration [8–13].

Stridor in MSA is a strained, high-pitched, harsh respiratory sound, mainly inspiratory, caused by laryngeal dysfunction leading to narrowing of the rima glottidis. It may occur only during sleep or it may be present during both sleep and wakefulness [14,15]. The prevalence of stridor in MSA ranges from 12% to 42%, and it might develop at any time point in the disease process [4,16–22].

Few studies have investigated the role of stridor on survival in MSA and, because of the heterogeneity in design, method, study population, MSA diagnostic certainty (clinical vs. autopsy based) and stridor diagnosis across studies, results on this topic remain controversial [14].

Stridor treatment is based mainly on tracheostomy or continuous positive airway pressure (CPAP), but guidelines for the use of these treatments in patients with MSA have yet to be established and few studies with small sample sizes have analysed the role of treatment type as a predictor of survival [14]. CPAP as a non-invasive therapy can be used for mild stridor and initially eliminated this symptom in almost all patients [14]. One follow-up study reported high CPAP tolerance and low complication rate [19], but the long-term symptomatic effect remains unknown [14]. Tracheostomy bypasses upper airway obstruction at laryngeal level and relieves distressing stridor [23,24]. This treatment option is effective in the symptomatic control of stridor and is required when this symptom becomes persistent and severe [14]. The international consensus on stridor in MSA declared that tracheostomy might improve survival in patients with stridor and that CPAP can be useful in the symptomatic control of stridor but it is uncertain if this treatment improves survival [14]. Therefore, findings on stridor treatment remain inconclusive.

The aim of the present study was to evaluate the predictive value of stridor treatment in a cohort of patients with MSA comparing tracheostomy and CPAP.

## METHODS

This is a retrospective and prospective cohort study including 182 patients with a final diagnosis of MSA, according to international criteria [1].

In this study 56 patients were recruited from prospective studies of our department and followed up during the disease course (BoProPark Study, RFPS2006-7-336374, CE 09070; Natural History of Multiple System Atrophy, CE 17083; Prognostic predictive value of autonomic markers during sleep and wakefulness in multiple system atrophy, RF-2016-02361597, CE 18056).

Further, 126 individuals attending the Movement and Autonomic Disorders Clinic of the University of Bologna between 1991 and October 2017 with a clinical diagnosis of MSA were retrospectively selected. Only patients evaluated at least once a year during the disease course were included. Three neurologists expert in movement disorders (PC, GCB, PG) independently confirmed the diagnosis of MSA from data available at the last follow-up evaluation according to international criteria [1]. Data were collected as described previously [16].

Patients were categorized as probable or possible MSA according to the consensus criteria and classified as MSA-P or MSA-C on the basis of the predominant motor involvement at the time of the last follow-up visit [1]. Occurrence of other symptoms and signs (parkinsonism, cerebellar and pyramidal involvement, orthostatic hypotension, urinary symptoms, stridor and rapid eye movement sleep behaviour disorder [RBD]) and latency from disease onset were recorded from clinical history and neurological examination. Symptoms and signs were categorized as early if presenting within 3 years of disease onset. Timing and latency of the milestones of disease progression (frequent falls, wheelchair dependence, severe dysphagia or percutaneous endoscopic gastrostomy, severe dysarthria, urinary catheterization) were also recorded. Causes of death were collected from medical reports, when available. Disease duration was defined as the interval in years from first symptom onset to death or to the end of this study.

The following instrumental/laboratory tests were analysed, when available: (1) brain magnetic resonance imaging or computed tomography (if magnetic resonance imaging was not possible); (2) neuropsychological evaluation [25]; (3) video-polysomnography (VPSG) [12]; (4) head-up tilt test and other cardiovascular reflex tests [26]; (5) effect of levodopa (if applicable) assessed by (a) a standardized oral levodopa kinetic-dynamic test or (b) improvement of part III of the Unified Parkinson's Disease Rating Scale after increasing levodopa up to 1 g/day [27]; (6) cardiac  $^{123}\text{I}$ -metaiodobenzylguanidin single-photon emission computed tomography (SPECT); (7) cerebral  $^{123}\text{I}$ -ioflupane SPECT. Stridor and RBD diagnosis required confirmation by VPSG.

Continuous positive airway pressure was introduced as a treatment option for stridor in 2001 in our centre. CPAP, as a non-invasive therapy, was mostly used as first-line symptomatic therapy for mild stridor. Tracheostomy was performed in the following conditions:

presence of wakefulness stridor, immobile vocal cords on laryngoscopy, failure of CPAP pressure to abolish nocturnal stridor, CPAP de-vice intolerance or subacute/acute respiratory failure.

Time of stridor treatment (CPAP or tracheostomy) and latency from stridor onset were collected. For patients treated with CPAP, tolerability of device and compliance ( $\geq 4$  h per night) were collected. After CPAP titration, follow-up VPSG was performed every 6–12 months or if necessary in order to verify the efficacy of CPAP treatment and to adjust device parameters as appropriate.

Survival data were defined on the basis of time to death from the first symptom of disease. Patients and/or their relatives were contacted by telephone and questioned regarding the clinical course and the time and the cause of death (if applicable) when the patient missed a clinical evaluation within 12 months.

## Ethical standards

The study was conducted in agreement with the principles of good clinical practice. The study protocol was approved by the local ethics committee of the local health service of Bologna, Italy (Cod. CE 09070, 17093 and 18056). All patients gave written informed consent for study participation.

## Statistical analysis

All clinical and polysomnographic variables were collected using an ad hoc anonymized and standardized form and entered into an ad hoc database for statistical analysis.

The normality of continuous parameter distributions was checked using the skewness-kurtosis test. Variables were expressed as mean  $\pm$  standard deviation (SD) or median along with interquartile range (IQR), as appropriate. The *t* test, Wilcoxon rank-sum test or one-way ANOVA were performed to compare continuous variables as appropriate. Categorical variables were described by their absolute and/or relative frequencies and compared using the chi-squared test.

Kaplan–Meier curves were performed to graphically analyse the overall death survival from disease onset and the log-rank test to compare survival between patient subgroups. In patients with stridor, Kaplan–Meier curves were used to analyse survival probability from stridor onset and the log-rank test was performed to compare survival amongst patient subgroups (stridor patients without treatment, treated with CPAP and treated with tracheostomy).

Preliminary analyses were performed in the stridor subgroup to identify variables associated with survival. Survival data were defined on the basis of time to death from the first symptom of disease. Univariate Cox regression analyses were performed studying the following variables: age at disease onset, sex, predominant clinical phenotype, first domain of onset (autonomic, parkinsonian, cerebellar), early stridor onset, early RBD onset.

Therefore, to identify whether stridor treatment and type of stridor treatment were associated with survival, univariate analyses were performed. Survival data in this analysis were defined from stridor onset to death. Parameters with a value of  $p < 0.1$  on univariate analysis were entered into the multivariable model.

A *p* value lower than 0.05 (two-sided) was considered significant. Statistical analyses were performed using the statistical software STATA®, version 14.0.

## RESULTS

A total of 182 (107 male) patients with MSA were included in the study: three patients met the consensus criteria for definite MSA, 139 for probable MSA and 40 for possible MSA. Ninety-two patients were classified as having MSA-C and the other 90 as having MSA-P. Mean age at disease onset was  $57.3 \pm 8.3$  years; mean disease duration was  $7.8 \pm 3.9$  years. At the time of the analysis 141 (77.5%) were deceased. The most common causes of death were sudden death (death during sleep, respiratory failure and cardiorespiratory arrest), bronchopneumonia and urinary infection. The risk of death estimated by Kaplan–Meier analysis (Figure S1) did not differ between MSA-C and MSA-P patients (log-rank test,  $p = 0.5128$ ). Demographic and clinical features of the study sample are shown in [Table 1](#).

Of the total sample, 75 patients were diagnosed with stridor. Concerning stridor treatment, 22 patients were treated with tracheostomy and 29 with CPAP, whilst 24 patients did not receive treatment. Amongst patients without treatment two patients did not tolerate CPAP and refused tracheostomy, nine patients refused any treatment or otorhinolaryngology visit, two patients were recently diagnosed with stridor and are waiting for CPAP titration, whilst 11 did not receive treatment for unknown reasons (deceased from 1992 to 1997, missing data).

Amongst patients treated with tracheostomy, four patients were treated with CPAP before tracheostomy: one did not tolerate CPAP, three patients were treated with CPAP for a range of 3–9 months and required tracheostomy (two patients for respiratory failure and one patient for the occurrence of diurnal stridor).

Demographic and clinical features of the sample with stridor are shown in [Table 2](#). There was no difference in sex, age at disease onset, diagnosis certainty (definite, probable, possible), mode of disease onset, occurrence of evaluated symptoms during the course of disease, rate of milestones of disease progression, deaths, and percentage of early stridor onset and of early RBD onset between the three groups. Causes of death were well defined only in 32 patients with stridor (10 patients without treatment, eight patients treated with tracheostomy and 14 patients treated with CPAP). No significant differences were found between the three groups ([Table 2](#)).

Patients treated with tracheostomy showed a trend toward longer latency of stridor treatment compared to patients treated with CPAP (2 [1–3] vs. 1 [0–2] years, respectively,  $p = 0.0755$ ). Patients treated with tracheostomy showed a longer disease duration compared to those treated with CPAP or without treatment ( $5.9 \pm 2.9$  vs.

**TABLE 1** Demographic and clinical characteristics of the study sample

	MSA motor subtype			pvalue <sup>a</sup>
	Total MSA sample	MSA-C	MSA-P	
	182	92	90	
Sex				
Male, n (%)	107 (58.8)	56 (60.9)	51 (56.7)	0.565
Female, n (%)	75 (41.2)	36 (39.1)	39 (43.3)	
Age at onset, years	57.29 ± 8.35	56.9 ± 7.8	57.7 ± 8.9	0.5440
Disease duration, years	7.79 ± 3.86	7.6 ± 3.9	8.0 ± 3.8	0.4841
Diagnosis certainty				
Definite, n (%)	3 (1.6)	2 (2.2)	1 (1.1)	0.788
Probable, n (%)	139 (76.4)	71 (77.2)	68 (75.6)	
Possible, n (%)	40 (22.0)	19 (20.6)	21 (23.3)	
Deceased				
Yes, n (%)	141 (77.5)	71 (77.2)	70 (77.8)	0.922
No, n (%)	41 (22.5)	21 (22.8)	20 (22.2)	
Long survival <sup>b</sup> , n (%)	11 (6.0)	5 (5.4)	6 (6.7)	0.727
Symptom of disease onset				
Autonomic, n (%)	101 (57.4)	51 (55.4)	50 (59.5)	0.584
Cerebellar, n (%)	66 (37.5)	62 (67.4)	4 (4.8)	<b>&lt;0.001</b>
Parkinsonism, n (%)	60 (34.1)	7 (7.6)	53 (63.1)	<b>&lt;0.001</b>
Milestones of disease progression				
Frequent <sup>c</sup> falls, n (%)	105 (57.7)	50 (54.4)	55 (61.1)	0.098
Wheelchair dependence, n (%)	107 (58.8)	58 (63.0)	49 (54.4)	0.601
Urinary catheterization, n (%)	72 (39.6)	37 (40.2)	35 (38.9)	0.224
Unintelligible speech, n (%)	53 (29.1)	29 (31.5)	24 (26.7)	0.759
Severe dysphagia/PEG, n (%)	41 (22.5)	20 (21.7)	21 (23.3)	0.567
Stridor, n (%)	75 (41.2)	43 (46.7)	32 (35.6)	0.311
Stridor at onset, n (%)	10 (5.5)	8 (8.7)	2 (2.2)	0.055
Latency of stridor onset, years	3 (1–5)	3 (1–5)	4 (3–5.5)	0.0622
Disease duration after stridor onset, years	3.9 ± 2.8	4.6 ± 2.8	3.2 ± 2.7	<b>0.0482</b>
VPSG-confirmed RBD, n (%)	138 (75.8)	73 (79.4)	65 (72.2)	0.101
Latency of RBD onset, years	0 [(-2)–2]	0 [(-2)–2]	0 [(-2)–3]	0.2126

Note: Data are expressed as mean ± standard deviation or median (interquartile range). Statistically significant *p* values are denoted in bold.

Abbreviations: MSA, multiple system atrophy; MSA-C, multiple system atrophy with predominant cerebellar phenotype; MSA-P, multiple system atrophy with predominant parkinsonism phenotype; *n*, sample size; PEG, percutaneous endoscopic gastrostomy; RBD, rapid eye movement sleep behaviour disorder; VPSG, video-polysomnography.

<sup>a</sup>Between C and P.

<sup>b</sup>Disease duration ≥15 years.

<sup>c</sup>Frequent was defined as at least three falls per year or documentation of frequent or several falls.

3.4 ± 2.0 vs. 2.6 ± 2.1 years, respectively, *p* = 0.0002) and a longer disease duration after stridor treatment compared to those treated with CPAP (3 [2–5] vs. 2 [1–3] years, *p* = 0.0068). Kaplan–Meier curves from stridor onset showed a difference in survival amongst

patients treated with tracheostomy (*n* = 22), those treated with CPAP (*n* = 29) and those without treatment (*n* = 24) (*p* = 0.0058, log-rank test) (Figure 1). This statistical significance was related to the difference in mortality between patients treated with tracheostomy

**TABLE 2** Demographic and clinical features of the study sample with stridor

	Total sample with stridor	Number treated	Treated with tracheostomy	Treated with CPAP	pvalue
	75	24	22	29	
Men, n (%)	39 (52.0)	10 (41.7)	11 (50.0)	18 (62.1)	0.326
Age at MSA onset, years	55.9 ± 8.4	54.4 ± 7.0	57.2 ± 8.2	56.2 ± 9.6	0.5169
Deceased, n (%)	55 (73.3)	18 (75.0)	16 (72.7)	21 (72.4)	0.975
Disease duration, years	8.0 ± 3.9	7.7 ± 4.1	9.3 ± 4.6	7.3 ± 2.5	0.1545
Long survival <sup>a</sup> , n (%)	6 (8.0)	2 (8.3)	3 (13.6)	1 (3.5)	0.413
Diagnosis certainty					
Definite, n (%)	2 (2.7)	0 (0.0)	2 (9.1)	0 (0.0)	0.084
Probable, n (%)	60 (80.0)	17 (70.8)	18 (81.8)	25 (86.2)	
Possible, n (%)	13 (17.3)	7 (29.2)	2 (9.1)	4 (13.8)	
MSA subtype					
MSA-P, n (%)	32 (42.7)	10 (41.7)	9 (40.9)	13 (44.8)	0.955
MSA-C, n (%)	43 (57.3)	14 (58.3)	13 (59.1)	16 (55.2)	
Symptoms at MSA onset					
Parkinsonism, n (%)	17 (22.7)	6 (25.0)	3 (13.6)	8 (27.6)	0.441
Cerebellar, n (%)	23 (30.7)	9 (37.5)	7 (31.8)	7 (24.1)	0.622
Autonomic, n (%)	49 (65.3)	15 (62.5)	15 (68.2)	19 (65.5)	0.896
Early stridor onset	35 (46.7)	10 (41.7)	13 (59.1)	12 (41.4)	0.381
Disease duration after stridor onset, years	3.9 ± 2.8	2.6 ± 2.1	5.9 ± 2.9	3.4 ± 2.0	<b>0.0002</b>
Latency for stridor treatment	1 (0–3)	–	2 (1–3)	1 (0–2)	0.0755*
Disease duration after stridor treatment, years	2 (1–4)	–	3 (2–5)	2 (1–3)	<b>0.0068*</b>
Symptoms during the course of disease					
Parkinsonism, n (%)	66 (88.0)	20 (83.3)	20 (90.9)	26 (89.7)	0.688
Cerebellar, n (%)	66 (88.0)	21 (87.5)	21 (95.5)	24 (82.8)	0.518
Pyramidal signs, n (%)	61 (81.3)	21 (87.5)	17 (77.3)	23 (79.3)	0.660
Urinary urgency/frequency, n (%)	66 (88.0)	22 (91.7)	20 (90.9)	24 (82.8)	0.752
Urinary retention, n (%)	42 (56.0)	11 (45.8)	13 (59.1)	18 (62.1)	0.485
Urinary incontinence, n (%)	49 (65.3)	16 (66.7)	18 (81.8)	15 (51.7)	0.073
Symptomatic OH, n (%)	61 (81.3)	19 (79.2)	19 (86.4)	23 (79.3)	0.913
VPSG-confirmed RBD, n (%)	69 (92.0)	22 (91.7)	20 (90.9)	27 (93.1)	0.909
Milestone of disease progression					
Frequent <sup>b</sup> falls, n (%)	48 (64.0)	15 (62.5)	13 (59.1)	20 (69.0)	0.658
Urinary catheterization, n (%)	36 (48.0)	10 (41.7)	12 (54.5)	14 (48.3)	0.555
Unintelligible speech, n (%)	25 (33.3)	8 (33.3)	11 (50.0)	6 (20.7)	0.079
Dysphagia/PEG, n (%)	23 (30.7)	6 (25.0)	10 (45.5)	7 (24.1)	0.187
Wheelchair dependence, n (%)	51 (68.0)	18 (81.8)	17 (58.6)	29 (72.5)	0.161

Note: Data are expressed as n (%), mean ± SD or median (interquartile range). Statistically significant p values are denoted in bold ( $p \leq 0.05$ ).

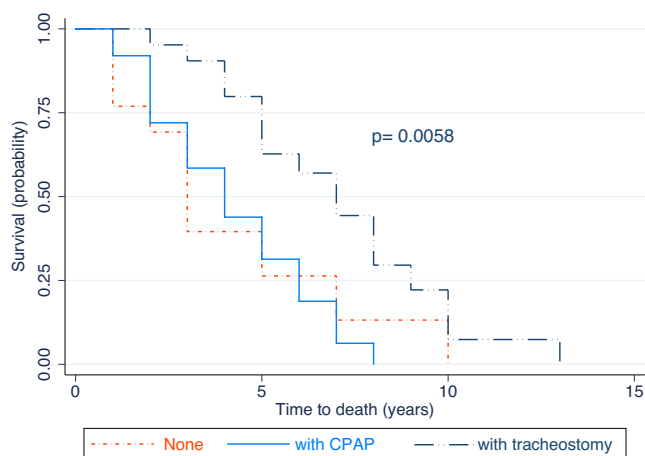
Abbreviations: CPAP, continuous positive airway pressure; MSA, multiple system atrophy; MSA-C, multiple system atrophy with predominant cerebellar phenotype; MSA-P, multiple system atrophy with predominant parkinsonism phenotype; OH, orthostatic hypotension; PEG, percutaneous endoscopic gastrostomy; RBD, rapid eye movement sleep behaviour disorder; VPSG, video-polysomnography.

<sup>a</sup>Disease duration  $\geq 15$  years.

<sup>b</sup>Frequent was defined as at least three falls per year or documentation of frequent or several falls. \*Between treatments (Wilcoxon rank-sum test).

and those without treatment ( $p = 0.0230$ , log-rank test) and between patients treated with tracheostomy and those treated with CPAP ( $p = 0.0012$ , log-rank test). The incidence rate of death was

12 per 100 person-years in patients treated with tracheostomy, 21 per 100 person-years in those treated with CPAP and 23 per 100 person-years in those without treatment.



**FIGURE 1** Kaplan-Meier survival curves for probability of death (from stridor onset) in MSA patients with stridor without treatment, treated with tracheostomy and treated with CPAP. CPAP, continuous positive airway pressure [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

In the univariate Cox regression analyses, patients without treatment showed an increased risk of death compared to those treated with tracheostomy (hazard ratio [HR] = 2.31, 95% confidence interval [CI] 1.02–5.21,  $p = 0.045$ ) without differences from those treated with CPAP (HR = 0.98, 95% CI 0.44–2.17,  $p = 0.959$ ). Tracheostomy reduced the risk of death (HR = 0.33, 95% CI 0.16–0.71,  $p = 0.04$ ) compared to treatment with CPAP.

As in the stridor subgroup univariate Cox regression analyses identified autonomic onset (HR = 1.84, 95% CI 1.01–3.39,  $p = 0.041$ ), early stridor onset (HR = 3.17, 95% CI 1.74–5.77,  $p < 0.001$ ) and early RBD onset (HR = 19.28, 95% CI 2.51–47.84,  $p < 0.001$ ) as factors associated with survival, a multivariable model was performed. After adjustment for these confounders and for latency of stridor treatment, tracheostomy showed a protective effect on survival compared with CPAP (reference value) showing an HR = 0.38, 95% CI 0.16–0.90,  $p = 0.029$ .

Repeating the multivariate model and considering tracheostomy as the reference value, CPAP remained an independent predictor of mortality compared to tracheostomy (HR = 2.63, 95% CI 1.11–6.26,  $p = 0.029$ ).

## DISCUSSION

This is the largest monocentric and long-term follow-up study comparing survival between treatment with CPAP and tracheostomy in MSA patients with stridor. Treatment with tracheostomy showed longer survival compared with both treatment with CPAP or no treatment (incidence rate of death 12 vs. 21 vs. 23 per 100 person-years, respectively). Both patients without treatment and patients treated with CPAP showed an increased risk of death in univariate Cox regression compared to those treated with tracheostomy. Tracheostomy remained an independent factor associated

with longer survival (HR = 0.38,  $p = 0.029$ ) in patients with stridor, also after adjustment for other confounders (autonomic onset, early stridor onset, early RBD onset) and although patients treated with tracheostomy showed a trend toward longer latency for stridor treatment from stridor onset.

These results, conducted on a larger sample, confirm our previous retrospective data on 42 MSA patients with stridor suggesting longer disease duration in patients who had undergone tracheostomy compared with those treated with CPAP [16]. Furthermore, they demonstrate that this treatment remains an independent predictor of survival in the multivariable analysis.

Only a single study described the impact on survival of these two types of stridor treatments in a small sample of MSA patients. In this study, the authors suggested that CPAP had no effect on survival as all five patients treated with CPAP died a mean of 2.4 years after the sleep evaluation, whilst the effect on survival was extremely variable in the four patients receiving tracheostomy (two patients died 1 year after the sleep evaluation and the other 2 patients were alive 1.9 and 7 years later) [18].

Another five studies evaluated the effect of tracheostomy or CPAP on MSA survival. One study on 49 patients with definite MSA showed that tracheostomy reduces the risk of death (HR = 0.21, 95% CI 0.08–0.56,  $p < 0.01$ ) and sudden death (HR = 0.15, 95% CI 0.02–0.98,  $p < 0.05$ ) in MSA [17].

According to one study on 13 MSA patients with stridor receiving CPAP, this treatment is effective for eliminating stridor during sleep as treated patients had similar median survival of MSA patients without stridor (77 vs. 88 months,  $p = 0.6914$ ) [19]. Sudden death was subsequently reported in two of 13 patients following CPAP initiation [28]. These data were confirmed in a recent study reporting similar survival between the 12 patients who were treated for stridor (93 months) and the 28 patients without any stridor at baseline (119 months,  $p = 0.57$ ). In this study patients received fixed CPAP when stridor was isolated, auto-adjusting CPAP when it was combined with obstructive sleep apnoea, and adaptive servo-ventilation when combined with central sleep apnoea [29].

Recently, one retrospective study on 139 MSA patients compared the impact of tracheostomy alone and tracheostomy invasive ventilation (TIV) on survival [30]. In the total sample, tracheostomy was performed in 53 patients, 21 of whom were ventilated. In this study stridor was clinically assessed at the bedside, tracheostomy was performed when the stridor was severe and CPAP provided insufficient efficacy, and TIV was performed when hypoxaemia ( $\text{SpO}_2 < 90\%$  or  $\text{PaO}_2 < 60$  mmHg) or hypercarbonaemia ( $\text{PaCO}_2 > 60$  mmHg) was confirmed through saturation monitoring or blood gas analysis. After propensity score matching analysis, tracheostomy showed a significant prolongation of median survival compared with no tracheostomy (10.1 vs. 7.5 years,  $p = 0.001$ ) and TIV significantly prolonged survival compared with tracheostomy alone (17.8 vs. 9.2 years,  $p = 0.023$ ). On Cox regression analysis, the HR for tracheostomy was 0.35 (95% CI 0.17–0.68,  $p = 0.002$ ) and TIV was 0.22 (95% CI 0.07–0.89,  $p = 0.032$ ) [30]. However, this study included MSA patients with advanced stage of disease, hospitalized

until death. In this setting a high rate of MSA patients required TIV (21/53 patients with tracheostomy). For this reason the findings of this study are difficult to generalize across all MSA patients and in particular across those managed in the home setting. Moreover, this invasive treatment, whose daily duration is not specified in the article, severely impacts quality of life, limiting patients' independence and mobility and preventing verbal communication.

In our study there was no difference in survival between patients with stridor treated with CPAP and those without treatment. As CPAP tolerance could impact these results this confounder was prevented, considering as CPAP-treated only patients with good adherence ( $\geq 4$  h per night) and evaluating CPAP tolerance, compliance and efficacy during the follow-up. In this subgroup only three of 35 patients with titrated CPAP did not tolerate this treatment and this result confirmed previous studies focusing on CPAP tolerance and compliance [19,29].

Tracheostomy could positively impact survival in MSA patients with stridor compared to CPAP because this treatment bypasses upper airway obstruction at laryngeal level, relieves distressing stridor and could reduce the risk of sudden death. However, as reported in previous studies [17], tracheostomy did not prevent sudden death which, in MSA, could be related to a bilateral vocal cord paralysis but also to a disruption of the cardiorespiratory drive contributing to other conditions such as central apnoea, respiratory dysrhythmia, reduced respiratory chemosensitivity and impaired arousal responses to hypoxia [13].

The objective of the present study was to evaluate the impact of this treatment on survival of MSA patients with stridor, without gathering data on quality of life. Tracheostomy could impact quality of life by reducing patient autonomy and limiting verbal communication and these aspects should be considered. In our sample, nine patients refused any treatment and two patients who did not tolerate CPAP refused tracheostomy. These patients, eligible for tracheostomy, discussed the risks and benefits of this treatment with specialists (neurologists, sleep disorder experts, otorhinolaryngologists), palliative care physicians and their relatives and refused any invasive treatment (tracheostomy, percutaneous endoscopic gastrostomy, parenteral nutrition etc.).

The strengths of our study are that all patients were seen and diagnosed in a single centre, ensuring uniformity of data. Patients of a retrospective cohort were evaluated at least once a year during the disease course, instrumental/laboratory tests were performed during the disease course when specific conditions were suspected by history or examination, and data were systematically collected. Moreover, cardiovascular autonomic failure and stridor were instrumentally documented.

However, different limits should be discussed. Treatment selection was based on severity of stridor, presence of stridor during wakefulness, laryngoscopy features and CPAP intolerance and inefficacy. However, the choice was not based on a uniform and standardized protocol because the study covers a long period of time (1991–2020). CPAP was introduced as a treatment option for stridor in 2001 in our centre. However, the first studies applying this

treatment, previously used for obstructive sleep apnoea syndrome, to stridor were published in 2000 [18,31]. Data on causes of death were collected by talking with relatives when medical records were not available and were detailed in about half of patients. No differences in causes of death were found amongst stridor patients without treatment, treated with tracheostomy and treated with CPAP but, for the small numbers of subjects, this analysis should be taken with caution. Data on quality of life were not systematically collected at baseline and during subsequent follow-up visits.

Our results demonstrated that tracheostomy improves survival in MSA patients with stridor compared to CPAP. Considering the rarity of MSA, a prospective, larger, multicentric, randomized study should be conducted to provide definitive proof of the benefits of tracheostomy in MSA patients with stridor. However, the randomized nature of the study should be performed with caution and with rigorous inclusion criteria to guarantee ethical issues as in specific situations (e.g., bilateral complete vocal cord abduction/restriction or diurnal stridor) tracheostomy is demanded.

In our experience, a multidisciplinary approach including neurologists and sleep disorder experts, otorhinolaryngologists, phoniatrists, anaesthesiologists and palliative care physicians is required to discuss with eligible patients CPAP/tracheostomy modality, risks/benefits and follow-up. Moreover, integration amongst specialists, palliative care physicians, general practitioners, nurses, home carers and caregivers is recommended to guarantee compliance, prevent complications and improve the long-term management of these patients.

## CONFLICT OF INTEREST

Dr Giannini reports no disclosures. Professor Provini reports no disclosures. Outside the present work, Professor Provini has received honoraria for speaking engagements or consulting activities from Sanofi, Bial, Fidia, Vanda Pharmaceutical, Zambon, Eisai Japan and Italfarmaco. Dr Cani reports no disclosures. Dr Cecere reports no disclosures. Dr Mignani reports no disclosures. Dr Guaraldi reports no disclosures. Dr Di Mirto reports no disclosures. Professor Cortelli reports no disclosures. Professor Calandra-Buonaura reports no disclosures. Outside the present work, Professor Calandra-Buonaura has received honoraria for speaking engagements or consulting activities from Abbvie, Bial and Zambon.

## AUTHOR CONTRIBUTIONS

Giulia Giannini: Data curation (lead); formal analysis (lead); methodology (equal); writing—original draft (lead). Federica Provini: Data curation (equal); formal analysis (equal); investigation (equal); writing—review and editing (supporting). Ilaria Cani: Data curation (equal); formal analysis (equal); investigation (equal). Annagrazia Cecere: Data curation (supporting); formal analysis (supporting). Francesco Mignani: Data curation (supporting); formal analysis (supporting). Pietro Guaraldi: Formal analysis (supporting); funding acquisition (supporting); writing—review and editing (supporting). Cristian Vincenzo Francesco Di Mirto: Writing—review and editing (equal). Pietro Cortelli: Conceptualization (equal); investigation

(equal); methodology (equal); resources (equal); supervision (equal); writing—review and editing (equal). Giovanna Calandra-Buonaura: Conceptualization (lead); investigation (equal); methodology (equal); supervision (lead); writing—review and editing (equal).

#### DATA AVAILABILITY STATEMENT

Anonymized data that support the findings of this study are available from the corresponding author, upon reasonable request.

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#### REFERENCES

- Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*. 2008;71(9):670-676. doi:10.1212/01.wnl.0000324625.00404.15
- Wenning GK, Geser F, Krismer F, et al. The natural history of multiple system atrophy: a prospective European cohort study. *Lancet Neurol*. 2013;12(3):264-274. doi:10.1016/S1474-4422(12)70327-7
- Low PA, Reich SG, Jankovic J, et al. Natural history of multiple system atrophy in North America: a prospective cohort study. *Lancet Neurol*. 2015;14(7):710-719. doi:10.1016/S1474-4422(15)00058-7
- Coon EA, Sletten DM, Suarez MD, et al. Clinical features and autonomic testing predict survival in multiple system atrophy. *Brain*. 2015;138(Pt 12):3623-3631. doi:10.1093/brain/awv274
- Papapetropoulos S, Tuchman A, Laufer D, Papatsoris AG, Papapetropoulos N, Mash DC. Causes of death in multiple system atrophy. *J Neurol Neurosurg Psychiatry*. 2007;78(3):327-329. doi:10.1136/jnnp.2006.103929
- Tada M, Kakita A, Toyoshima Y, et al. Depletion of medullary serotonergic neurons in patients with multiple system atrophy who succumbed to sudden death. *Brain*. 2009;132(Pt 7):1810-1819. doi:10.1093/brain/awp110
- Zhang L, Cao B, Zou Y, et al. Causes of death in Chinese patients with multiple system atrophy. *Aging Dis*. 2018;9(1):102-108. doi:10.14336/AD.2017.0711
- Abbott SM, Videnovic A. Sleep disorders in atypical parkinsonism. *Mov Disord Clin Pract*. 2014;1(2):89-96. doi:10.1002/mdc3.12025
- Iranzo A. Sleep and breathing in multiple system atrophy. *Curr Treat Options Neurol*. 2007;9(5):347-353.
- Jecmenica-Lukic M, Poewe W, Tolosa E, Wenning GK. Premotor signs and symptoms of multiple system atrophy. *Lancet Neurol*. 2012;11(4):361-368. doi:10.1016/S1474-4422(12)70022-4
- Chokroverty S. Sleep, breathing and neurological disorders. In: Chokroverty S, ed. *Sleep Disorders Medicine: Basic Science, Technical Considerations and Clinical Aspects*. Butterworth-Heinemann; 1994:295.
- Vetrugno R, Liguori R, Cortelli P, et al. Sleep-related stridor due to dystonic vocal cord motion and neurogenic tachypnea/tachycardia in multiple system atrophy. *Mov Disord*. 2007;22(5):673-678. doi:10.1002/mds.21384
- Benarroch EE. Brainstem integration of arousal, sleep, cardiovascular, and respiratory control. *Neurology*. 2018;91(21):958-966. doi:10.1212/WNL.0000000000006537
- Cortelli P, Calandra-Buonaura G, Benarroch EE, et al. Stridor in multiple system atrophy: consensus statement on diagnosis, prognosis, and treatment. *Neurology*. 2019;93(14):630-639. doi:10.1212/WNL.0000000000008208
- 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;361:243-249. doi:10.1016/j.jns.2016.01.007
- Giannini G, Calandra-Buonaura G, Mastrolilli F, et al. Early stridor onset and stridor treatment predict survival in 136 patients with MSA. *Neurology*. 2016;87(13):1375-1383. doi:10.1212/WNL.0000000000003156
- Tada M, Onodera O, Tada M, et al. Early development of autonomic dysfunction may predict poor prognosis in patients with multiple system atrophy. *Arch Neurol*. 2007;64(2):256-260. doi:10.1001/archneur.64.2.256
- Silber MH, Levine S. Stridor and death in multiple system atrophy. *Mov Disord*. 2000;15(4):699-704. doi:10.1002/1531-8257(200007)15:4<699::aid-mds1015>3.0.co;2-I
- Iranzo A, Santamaria J, Tolosa E, et al. Long-term effect of CPAP in the treatment of nocturnal stridor in multiple system atrophy. *Neurology*. 2004;63(5):930-932. doi:10.1212/01.wnl.0000137043.76383.a4
- Vetrugno R, Provini F, Cortelli P, et al. Sleep disorders in multiple system atrophy: a correlative video-polysomnographic study. *Sleep Med*. 2004;5(1):21-30. doi:10.1016/j.sleep.2003.07.002
- Figuerola JJ, Singer W, Parsaik A, et al. Multiple system atrophy: prognostic indicators of survival. *Mov Disord*. 2014;29(9):1151-1157. doi:10.1002/mds.25927
- Wenning GK, Ben Shlomo Y, Magalhães M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. *Brain*. 1994;117(Pt 4):835-845. doi:10.1093/brain/117.4.835
- Kuhlo W, Doll E, Franck MC. Successful management of Pickwickian syndrome using long-term tracheostomy [in German]. *Dtsch Med Wochenschr*. 1969;94(24):1286-1290. doi:10.1055/s-0028-111209
- Campanini A, De Vito A, Frassinetti S, Vicini C. Role of skin-lined tracheotomy in obstructive sleep apnoea syndrome: personal experience. *Acta Otorhinolaryngol Ital*. 2004;24(2):68-74.
- Stanzani-Maserati M, Gallassi R, Calandra-Buonaura G, et al. Cognitive and sleep features of multiple system atrophy: review and prospective study. *Eur Neurol*. 2014;72(5-6):349-359. doi:10.1159/000364903
- Baschieri F, Calandra-Buonaura G, Doria A, et al. Cardiovascular autonomic testing performed with a new integrated instrumental approach is useful in differentiating MSA-P from PD at an early stage. *Parkinsonism Relat Disord*. 2015;21(5):477-482. doi:10.1016/j.parkrel.2015.02.011
- Calandra-Buonaura G, Doria A, Lopane G, et al. Pharmacodynamics of a low subacute levodopa dose helps distinguish between multiple system atrophy with predominant parkinsonism and Parkinson's disease. *J Neurol*. 2016;263(2):250-256. doi:10.1007/s00415-015-7961-7
- Ghorayeb I, Yekhle F, Bioulac B, Tison F. Continuous positive airway pressure for sleep-related breathing disorders in multiple system atrophy: long-term acceptance. *Sleep Med*. 2005;6(4):359-362. doi:10.1016/j.sleep.2004.10.002
- Rekik S, Martin F, Dodet P, et al. Stridor combined with other sleep breathing disorders in multiple system atrophy: a tailored treatment? *Sleep Med*. 2018;42:53-60. doi:10.1016/j.sleep.2017.12.008
- Nishida K, Sakashita K, Yamasaki H, Futamura N. Impact of tracheostomy invasive ventilation on survival in Japanese patients with multiple system atrophy. *Parkinsonism Relat Disord*. 2022;97:107-111. doi:10.1016/j.parkrel.2022.01.008



31. Iranzo A, Santamaria J, Tolosa E. Continuous positive air pressure eliminates nocturnal stridor in multiple system atrophy. Barcelona Multiple System Atrophy Study Group. *Lancet*. 2000;356(9238):1329-1330. doi:[10.1016/s0140-6736\(00\)02824-5](https://doi.org/10.1016/s0140-6736(00)02824-5)

#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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