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Predictors of survival in progressive supranuclear palsy and multiple system atrophy: a systematic review and meta-analysis

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ABSTRACT

Objective: To undertake a systematic review and meta-analysis of studies that investigated prognostic factors and survival in patients with progressive supranuclear palsy (PSP) and multiple system atrophy (MSA).

Methods: Publications of at least 10 patients with a likely or confirmed diagnosis of PSP or MSA were eligible for inclusion. Methodological quality was rated using a modified version of the Quality in Prognostic Studies tool. For frequently examined prognostic factors, hazard ratios (HR) derived by univariate and multivariate analysis were pooled in separate subgroups; other results were synthesised narratively and HRs could not be reported here.

Results: Thirty-seven studies presenting findings on 6193 patients (1911 PSP, 4282 MSA) fulfilled the inclusion criteria. We identified the following variables as unfavourable predictors of survival: In PSP: PSP-Richardson's phenotype (univariate HR: 2.53; 95% CIs: 1.69, 3.78), early dysphagia and early cognitive symptoms. In MSA: severe dysautonomia and early development of combined autonomic and motor features but not MSA phenotype (multivariate HR: 1.22; 95% CIs: 0.83, 1.80).

In PSP and MSA survival was predicted by early falls (multivariate HR: 2.32; 95% CIs: 1.94, 2.77), the NNIPPS Parkinson plus score and the Clinical Global Impression disease severity score but not sex (multivariate HR: 0.93; 95% CIs: 0.67, 1.28). There was conflicting evidence regarding the prognostic effect of age at onset and stridor.

Conclusion: Several clinical variables were strongly associated with shorter survival in PSP and MSA. Results on most prognostic factors were consistent across methodologically diverse studies; however, the lack of commonality of prognostic factors investigated is a significant limitation.

Key words: Progressive supranuclear palsy, multiple system atrophy, survival, prognosis, prognostic factors, systematic review, meta-analysis

PROSPERO registration number: CRD42016032968. Registered on 21st of January 2016

ABBREVIATIONS

MSA = multiple system atrophy; MSA-C = MSA-Cerebellar; MSA-P = MSA-Parkinsonism; NNIPPS = Neuroprotection and Natural History in Parkinson Plus Syndromes; PSP = progressive supranuclear palsy; PSP-P = PSP-Parkinsonism; PSP-RS = PSP-Richardson's syndrome

INTRODUCTION

Progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) are rare, debilitating adult-onset neurodegenerative conditions. Their estimated prevalence is 2-7 per 100 000.[1-4] PSP is characterised by the accumulation of abnormally phosphorylated tau protein in the basal ganglia, frontal lobe and brainstem, whereas MSA is characterised by the accumulation of alpha synuclein positive glial cytoplasmic inclusion bodies [5] affecting the basal ganglia, cerebellum, pons and substantia nigra.[6] PSP can be divided into PSP-Parkinsonism (PSP-P) and PSP-Richardson's syndrome (PSP-RS) [7] and MSA can be classified into MSA-Cerebellar (MSA-C) and MSA-Parkinsonism (MSA-P) subtypes.[8] Diagnostic criteria have been proposed for the clinical diagnosis of PSP and MSA;[9-11] however, pathological brain examination at autopsy remains the gold standard for diagnostic classification.

Prognosis of PSP and MSA is poor. The mean survival after diagnosis is only 3-4 years.[12, 13] To date, there are no narrative or systematic reviews on prognostic factors in PSP and MSA. Predictors of survival were investigated in numerous studies, including several prospective multicentre studies,[14-16] single centre clinical studies,[17, 18] post-mortem studies [19, 20] and a meta-analysis of pathologically confirmed case studies.[21] Researching prognosis of PSP and MSA is challenging in view of their rarity, insidious onset and heterogeneity of clinical presentation. Therefore, studies are frequently underpowered and at risk of diagnostic ascertainment bias or selection bias depending on whether participants were diagnosed clinically or recruited post-mortem from a brain-bank. A systematic review and meta-analysis is therefore desirable to increase power and to investigate and quantify the methodological and statistical heterogeneity across studies. Here, we sought to summarise, synthesise and contrast published studies that investigated the association between potential prognostic factors and survival.

METHODS

Study registration and inclusion criteria

This work adheres to the preferred reporting items for systematic reviews and meta-analyses standards (PRISMA).[22] A protocol was registered with PROSPERO, registration number: CRD42016032968. Studies of any design, reporting on one or more potential prognostic factors predicting survival in PSP and/or MSA patients were eligible for inclusion. Participants were patients identified by study authors as having a likely or confirmed diagnosis of PSP, MSA, Steele-Richardson-Olszewski syndrome, striatonigral degeneration, olivopontocerebellar atrophy or Shy-Drager syndrome. The following prognostic factors were considered: demographic variables, symptoms, clinical signs, disease phenotypes, rating scales, biomarkers and imaging findings. Exclusion criteria were as follows: 1) meeting abstracts or conference proceedings, 2) articles in languages other than English, German or French, 3) case studies or studies including fewer than 10 participants and 4) statistical analysis other than time-to-event analysis. Studies were also eligible if they investigated the difference in survival between PSP and MSA.

Identification of studies

The electronic databases of Medline, Embase, CINAHL and the Cochrane library were searched from inception until December 2015/January 2016 for studies conducted on humans; no language restrictions were employed. The search strategy included a combination of keywords and MeSH terms (see online protocol). For studies retrieved in full-text, hand searching of reference lists and citation searches were performed. Grey literature searches were performed in several grey literature databases.

Methodological quality assessment and data extraction

Studies were individually graded for risk of bias by one reviewer (SAG), using a modified version of the Quality in Prognostic Studies tool.[23] A random sample of five papers was reviewed by a second reviewer (RAS) to check that there was no systematic bias in the method followed by the primary reviewer. The study's risk of bias was rated as low, moderate or high on 14 items according to pre-specified criteria (supplementary table 1). A summary score was not calculated in keeping with recommendations by the Cochrane Collaboration.[24] One reviewer (SAG) extracted data from all included studies using a pre-specified data extraction sheet and a second reviewer independently extracted results reported by studies included in the main text; there were no disagreements. For three studies, corresponding authors were contacted to provide clarification on missing data; however, none could provide these.

Statistical analysis

Hazard ratios derived by univariate and multivariate analysis were pooled in separate subgroups in generic inverse variance meta-analyses in Review Manager 5.3 using a random effects model. Hazard ratios adjusted for age and/or sex were included in the subgroup containing hazard ratios derived by multivariate analysis. The meta-analytic summary includes the pooled estimate for each subgroup and its 95% confidence intervals. Statistical heterogeneity was quantified using the I^2 test; I^2 represents the percentage of heterogeneity that cannot be attributed to chance. Where only Kaplan-Meier curves were reported by studies, methods by Tierney and collaborators [25] were used to extract hazard ratios from published Kaplan-Meier curves (12 prognostic factors, 8 studies). Kaplan-Meier curves were inspected for severe violations of the proportional hazards assumption prior to data extraction. Anonymised patient data published by Birdi and colleagues [26] were analysed in SPSS version 23.0 with univariate Cox regression. Sensitivity analysis was undertaken to gauge the effect of including studies at high risk of diagnostic ascertainment bias in meta-analysis. Results of such studies were

graphically displayed in forest plots but were not weighted in the pooled effect estimate. Publication bias was examined for by inspecting funnel plots for the two most commonly reported prognostic factors. Results were synthesised narratively where heterogeneity across study definitions of a prognostic factor did not allow meta-analysis. A p-value <0.05 was considered statistically significant.

RESULTS

The search yielded the following results: Medline: 934 results, Embase: 1420 results, CINAHL: 155 results and the Cochrane library: 38 results. The selection process is illustrated in figure 1. A total of 40 publications describing 37 studies, investigating 34 distinct patient cohorts were therefore included in narrative synthesis, of which 22 studies were also included in one or more meta-analyses. Meta-analysis was possible for seven prognostic factors: sex, age at disease onset, MSA phenotype, PSP phenotype, onset of falls, levodopa response and orthostatic hypotension.

Eleven studies recruited PSP patients,[12, 19, 26-34] 20 studies recruited MSA patients [15-18, 21, 35-51] and six studies recruited both PSP and MSA patients.[3, 9, 13, 14, 20, 52, 53] Seven studies reported pathological confirmation of diagnosis in 100% of patients. Studies reported on a total of 6193 patients including 4282 MSA patients of whom 759 had a pathologically confirmed diagnosis and 614 were included in post-mortem studies. There were 1911 PSP patients of whom 415 had a pathologically confirmed diagnosis and 250 were included in post-mortem studies. The mean age at disease onset ranged from 61.0 to 67.2 years in PSP and from 54.0 to 64.5 years in MSA and the proportion of male and female patients was approximately equal. The study characteristics can be found in supplementary table 2 and the risk of bias ratings in supplementary table 3; differences in symptom profile between clinical and post-mortem studies are reported in supplementary table 4.

Overall survival

The cumulative survival in PSP and MSA is shown in figure 2 and 3 respectively (supplementary figures 1 and 2 for colour images). Ten studies reported on patients that survived beyond 15 years after disease onset, of which three studies reported pathological confirmation of diagnosis in 100% of patients. Median survival from disease onset ranged from 5.3 to 10.2 years. One study [43] reported a median survival of 13 years but was judged to be at high risk of diagnostic ascertainment bias. Studies on MSA patients generally reported higher median survival than studies on PSP patients; however, studies including both MSA and PSP patients found similar survival between PSP and MSA. In the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) study PSP was associated with longer survival only when adjusted for dysautonomia, disease severity, disease duration and the Schwab and England Activities of Daily Living scale in multivariate analysis.[14]

Demographic factors

Table 1 summarises the evidence on frequently examined prognostic factors. Ten studies (n=2728) comparing survival between male and female patients were combined in meta-analysis (figure 4). The pooled hazard ratio in the subgroup containing hazard ratios derived by univariate analysis was 1.05 (0.95, 1.18), $I^2=32\%$ and n=2102, whereas the pooled hazard ratio in the subgroup containing hazard ratios derived by multivariate analysis was 0.93 (0.67, 1.28), $I^2=34\%$ and n=675. There were no significant differences between subgroups ($p=0.45$). Five studies only reported p-values but not hazard ratios and could not be included in meta-analysis,[17, 28, 30, 38, 53] one of which reported a significant effect of sex on survival in multivariate analysis.[28]

	Negative prognostic factor	Total nr of studies	<u>Meta-analysis</u> Pooled HR (95% confidence intervals)				<u>Narrative synthesis</u>	
			Univariate HR	I ²	Multivariate HR*	I ²	Nr of studies reporting a significant effect on survival	HRs (95% confidence intervals) or other effect measures of studies reporting a significant effect on survival of the negative prognostic factor UV = univariate MV = multivariate
PSP	PSP-RS (vs PSP-P phenotype)	4	2.53 (1.69, 3.78)	18%	2.37 (1.21, 4.64)	n=1		
	Early development of dysphagia	4					4	MV: 3.91 (1.39, 11.0) MV: 2.84 (1.51, 5.34) MV: 2.3 (1, 5.3) 1.9 year difference median survival
	Early development of cognitive symptoms	4					2	MV: 3.6 (1.6, 8.2) MV: 1.99 (1.17, 3.38)
	Vertical supranuclear gaze palsy	5					2	MV: 2.74 (1.52, 4.94) UV: 1.12 (1.10, 1.31)
MSA	MSA-P (vs MSA-C phenotype)	8	1.12 (0.97, 1.29)	9%	1.22 (0.83, 1.80)	19%		
	Severe dysautonomia: -Mild vs severe (2 studies) -CGI dysautonomia score (1 study) -CASS (2 studies)	5					5	2.3 year difference median survival 3.5 year difference median survival MV: 1.41 (1.19, 1.67) MV: 1.07 (1.02, 1.11) MV: 2.8 (1.01, 9.26)
	Development of dysautonomia within 1, 2 and 2.5 years of MSA onset	3					3	UV: 1.24 (1.04, 1.49) MV: 6.0 (3.1, 11.7) MV: 3.4 (1.61, 7.15)
	Combined motor and autonomic symptoms within 3 years of MSA onset	2					2	UV: 2.65 (1.42, 4.93) 3 year difference median survival
	Orthostatic hypotension	2	1.24 (1.04, 1.49)	0%	1.29 (1.07, 1.56)	0%		
	Dysautonomia present at MSA onset	5					0	NA

	Bladder symptoms	5					Conflicting results and heterogeneous definitions of prognostic factor	
	Stridor	6					2	MV comparing untreated stridor to no stridor: 3.0 (1.63, 5.53) Reduced survival after 6 years as evident from Kaplan Meier curve
PSP and MSA	Male sex	10	1.05 (0.95, 1.18)	32%	0.93 (0.67, 1.28)	34%		
	Age at disease onset: -above median age (9 studies) -per year increase (6 studies)	14	1.92 (1.50, 2.44) 1.01 (1.0, 1.02)	0% 23%	1.75 (1.32, 2.32) 1.10 (0.98, 1.23)	63% 68%		
	Early onset of falls	6	1.62 (0.55, 4.77)	87%	2.32 (1.94, 2.77)	0%		
	Levodopa response	4	0.87 (0.73, 1.02)	1%	0.60 (0.31, 1.14)	n=1		
	NNIPPS Parkinson plus score	1					1	MV: 1.01 (1.01, 1.02)
	Clinical Global Impression disease severity score	1					1	MV: 1.28 (1.09, 1.51)
	Hoehn and Yahr staging scale: -Overall score (2 studies) -Stage 5 (1 study)	3					1	MV stage 5: 12.45 (1.93, 80.93)
	PSP Rating Scale	2					2	No effect sizes reported
	Unified MSA Rating Scale: -overall score -activities of daily living sub-score	2					1	Activities of daily living sub-score MV: 1.04 (1.01, 1.07)
	Northwestern University Disability Score	1					0	NA
	Shorter interval between disease onset and first clinical milestone	2					2	UV: 3.4 (1.4, 8.3) PSP MV: 1.25 (1.11, 1.4) MSA MV: 1.72 (1.47, 2.04)

Table 1. Summary of evidence on frequently examined prognostic factors predicting survival. A more detailed breakdown of results, including non-significant results, is available in the supplementary material. *Refers to hazard ratio derived by pooling hazard ratios calculated by multivariate analysis in individual studies. CASS = Composite Autonomic Scoring Scale; HR = hazard ratio; MSA-C = MSA-Cerebellar; MSA-P = MSA-Parkinsonism; MV = multivariate analysis; NNIPPS = Neuroprotection and Natural History in Parkinson Plus Syndromes; PSP-P = PSP-Parkinsonism; PSP-RS = PSP-Richardson's; UV = univariate analysis

Fourteen studies (n=2954) investigating the effect of age at disease onset on survival were combined in meta-analysis (supplementary figure 3). Nine studies compared the survival of patients aged above and below the median age at disease onset reported by each study. The pooled hazard ratio in the subgroup containing hazard ratios derived by univariate analysis was 1.92 (1.50, 2.44), $I^2=0\%$ and n=288, and the pooled hazard ratio in the subgroup containing hazard ratios derived by multivariate analysis was 1.75 (1.32, 2.32), $I^2=63\%$ and n=973. Subgroups were not significantly different ($p=0.74$). Six studies reported the prognostic effect of age at disease onset per year increase, the pooled hazard ratio in the subgroup containing hazard ratios derived by univariate analysis was 1.01 (1.0, 1.02), $I^2=23\%$ and n=1669, and the pooled hazard ratio in the subgroup containing hazard ratios derived by multivariate analysis was 1.10 (0.98, 1.23), $I^2=68\%$ and n=260. Six studies only reported p-values but not hazard ratios and could not be included in meta-analysis,[10, 17, 28, 32, 50, 53] of which two studies reported a significant effect of age at disease onset on survival.[17, 28]

Disease phenotypes

Eight studies (n=1572) comparing survival of the MSA-P and MSA-C phenotypes were combined in meta-analysis (figure 5). The pooled hazard ratio in the subgroup containing hazard ratios derived by univariate analysis was 1.12 (0.97, 1.29), $I^2=9\%$ and n=1310, and the pooled hazard ratio in the subgroup containing hazard ratios derived by multivariate analysis was 1.22 (0.83, 1.80), $I^2=19\%$ and n=311. Subgroups were not significantly different ($p=0.67$). Four studies only reported p-values but not hazard ratios and could not be included in meta-analysis, none of which reported a significant effect of MSA phenotype on survival.[17, 41, 50, 53]

Four studies (n=268) comparing survival of the PSP-RS phenotype to the PSP-P phenotype were combined in meta-analysis (figure 6). The pooled hazard ratio in the subgroup containing hazard ratios derived by univariate analysis was 2.53 (1.69, 3.78), $I^2=18\%$ and n=268; one study (n=110) reported a hazard ratio derived by multivariate analysis of 2.37 (1.21, 4.64). One study only reported the difference in median survival (PSP-RS 6.8 years vs PSP-P 10.9 years).[27]

Onset of falls

Six studies (n=1116) investigating the effect of falls within 1-3 years of disease onset on survival were combined in meta-analysis (figure 7). The pooled hazard ratio in the subgroup containing hazard ratios derived by univariate analysis was 1.62 (0.55, 4.77), $I^2=87\%$ and n=777. The pooled hazard ratio in the subgroup containing hazard ratios derived by multivariate analysis was 2.32 (1.94, 2.77), $I^2=0\%$ and n=1073. The high statistical heterogeneity in the univariate subgroup is almost exclusively due to Figueroa 2014,[35] who found early falls to predict shorter survival in multivariate but not univariate analysis. Subgroups were not significantly different ($p=0.52$). One study only reported the difference in median survival (early falls 5.2 years vs late falls 6.8 years).[30]

Levodopa response

Four studies (n=1147) investigating the effect of levodopa response on survival were combined in meta-analysis (supplementary figure 4). The pooled hazard ratio in the subgroup containing hazard ratios derived by univariate analysis was 0.87 (0.73, 1.02), $I^2=1\%$ and n=960. One study (n=187) reported a hazard ratio derived by multivariate analysis of 0.60 (0.31, 1.14).

Symptoms and signs in MSA

Severe dysautonomia was found to predict shorter survival in MSA, as two studies comparing survival between patients with mild or absent and severe dysautonomia [15, 18] and three studies evaluating the Clinical Global Impression Dysautonomia score and/or Composite Autonomic Scoring

Scale [14, 18, 35] reported a significant effect on survival. Development of dysautonomia within 1, 2 or 2.5 years of MSA onset and the development of combined autonomic and motor features within 3 years of MSA onset predicted shorter survival in three studies [18, 20, 46] and two studies [17, 41] respectively. However, the presence of dysautonomia at MSA onset did not predict survival in five studies.[17, 18, 37, 41, 43] Orthostatic hypotension within 1 year of MSA onset predicted shorter survival in a meta-analysis of two studies [18, 35] whilst there was substantial heterogeneity regarding the effect of bladder symptoms on survival in five studies.[15, 16, 18, 35, 39] Two studies reported significantly reduced survival in the presence of stridor [45, 49] whilst two studies reported reduced survival in univariate but not multivariate analysis [18, 39] and two small studies failed to reach statistical significance [40, 46] (supplementary table 5).

Symptoms and signs in PSP

Four studies found early development of dysphagia to predict survival.[12, 29, 30, 33] There is conflicting evidence regarding the prognostic effect of vertical supranuclear gaze palsy examined in five studies: two studies with overlapping patient cohorts found vertical supranuclear gaze palsy to predict survival,[27, 29] two studies failed to show a predictive effect on survival [30, 33] and one study reported a predictive effect on survival in univariate but not multivariate analysis.[12] Early development of cognitive symptoms or dementia was a predictor of shorter survival in two studies [12, 29] but not in two lower quality studies [30, 32] (supplementary table 6).

Disease severity, progression and rating scales

There is evidence to support the use of the NNIPPS Parkinson plus score and Clinical Global Impression disease severity score for prognostic stratification from one study.[9, 14] Stage 5 of the Hoehn and Yahr staging scale likely predicts shorter survival as shown by one study [39] but otherwise the Hoehn and Yahr staging scale did not predict survival in two studies.[14, 16] Two studies found the PSP Rating Scale to predict survival [27, 28] whilst the Northwestern University Disability Score did not predict survival in one study.[47] The Unified MSA Rating scale did not predict survival in one study [15] although its activities of daily living sub-score predicted survival in one study.[16] A shorter interval between disease onset and first clinical milestone also predicted shorter survival in two studies [12, 20] (supplementary table 7).

Sensitivity analysis

Three studies [34, 42, 43] were excluded from meta-analysis due to high risk of bias ratings in the diagnostic certainty domain. Inclusion of the study by Sakushima and colleagues [43] in the meta-analysis of multivariate hazard ratios comparing survival in MSA-P and MSA-C resulted in MSA-P becoming a significant predictor of shorter survival. Otherwise, inclusion of the above studies did not affect the overall effect estimates (supplementary table 8).

Reporting bias

Funnel plots are shown in supplementary figures 5 and 6.

DISCUSSION

This is the first systematic review and meta-analysis of studies investigating prognostic factors in PSP and MSA. The following variables were identified as unfavourable predictors of survival: PSP-RS phenotype, early dysphagia and early cognitive symptoms in PSP; severe dysautonomia and early development of combined autonomic and motor features in MSA; and early falls, the NNIPPS Parkinson plus score and the Clinical Global Impression disease severity score in PSP and MSA. Conversely, MSA phenotype and sex did not predict survival. Survival was similar between PSP and MSA patients and between pathologically confirmed cases and clinically probable cases.

Many studies were too small to reach statistical significance; therefore, the increased power gained by combining studies in statistical and narrative syntheses yields more conclusive evidence on the validity of the above prognostic factors. This review examined the statistical heterogeneity (I^2) of prognostic results between clinically and methodologically diverse studies. This includes studies on PSP and MSA patients and studies on pathologically confirmed cases as well as clinically probable cases. I^2 values were low (<40%) in all meta-analyses except age at disease onset, indicating that differences between the results on prognostic factors across studies were mainly due to chance. However, the lack of commonality of prognostic factors investigated is a significant limitation.

The PSP-RS phenotype, compared to the PSP-P phenotype, was highly predictive of shorter survival in a meta-analysis of two clinical and two post-mortem studies. Early falls and early development of cognitive symptoms, which are characteristic of the PSP-RS phenotype,[7] also predicted shorter survival. The latter symptom predicted shorter survival in larger studies of higher quality whereas smaller studies failed to show a prognostic effect. The evidence regarding the prognostic effect of supranuclear gaze palsy remains inconclusive. Levodopa response, which is characteristic of the PSP-P phenotype did not predict longer survival in meta-analysis. This may be due to variation in the definition of levodopa response across studies. Early onset of dysphagia, which is common in both phenotypes, was predictive of shorter survival.

MSA phenotypes did not predict survival in a meta-analysis of mainly Western studies; this finding should be confirmed in Asian countries.[54] Interestingly, symptoms that indicate shorter survival in MSA, namely severe dysautonomia and early falls, occur with a similar prevalence in both phenotypes.[18]

There has been conflicting evidence on the prognostic effect of dysautonomia in previous studies, which may be due to heterogeneous definitions of dysautonomia. This review has identified trends in the literature and offers potential explanations to guide future research. Severity of dysautonomia, measured with rating scales or subjective impression, predicted survival. Similarly, urinary catheterisation, indicating severe impairment, was highly predictive of survival in two studies, whereas conflicting evidence was found regarding the effect of incomplete bladder emptying, which may range from mild to severe, on survival.

The development of dysautonomia within a specified period of MSA onset and the time until the development of combined motor and autonomic features, but not the presence of dysautonomia at MSA onset predicted survival. It can be hypothesised that the first two prognostic factors represent the same entity: studies investigating the prognostic effect of development of dysautonomia within a specified time of MSA onset may have included many patients presenting with motor onset who developed dysautonomia soon after. This hypothesis would be in keeping with a series of five long-term MSA survivors.[55] Similarly, a shorter interval between disease onset and first clinical

milestone predicted shorter survival. This review therefore emphasises the importance of rate of progression and severity of MSA symptoms as prognostic indicators.

There was conflicting evidence regarding the prognostic value of age at disease onset and stridor in MSA. The high statistical heterogeneity in the meta-analysis of age at disease onset may be due to variation in the median age of onset. Stridor was an independent predictor of survival in multivariate analysis in one study, which was the only study to control for the effect of stridor treatment on survival. The beneficial effect of stridor treatment on survival should be confirmed in a larger cohort of patients.

Few studies investigated rating scales thus further research is warranted. The NNIPPS Parkinson plus score and the Clinical Global Impression disease severity score were found to predict survival; the PSP Rating Scale may predict survival but effect sizes were not reported.

Limitations of primary studies

The small number of prospective studies and low proportion of pathologically confirmed cases are limitations of this review. The risk of diagnostic ascertainment bias was especially high in five studies, where PSP or MSA diagnosis was based on the subjective assessment of the treating neurologist or on diagnostic criteria that are not internationally accepted. Studies of the latter type were not weighted in the meta-analytic summary effect estimates.

Several studies did not report hazard ratios or Kaplan Meier curves and were therefore not included in meta-analysis. However, most p-values reported by studies excluded for this reason were in keeping with the respective meta-analytic estimates. Some studies did not report on insignificant results, which may have led to publication bias. Failure to quantify follow-up and missing data has not allowed us to adequately assess the risk of attrition bias and sampling bias in some studies. Many studies excluded erectile dysfunction from the definition of MSA onset whilst some studies excluded all autonomic symptoms, which may have overestimated mean age at onset and thus underestimated disease duration. Similarly, several prognostic factors such as severe dysautonomia were not sufficiently well defined. Nonetheless, in view of the low statistical heterogeneity in most meta-analyses it is likely that bias arising from retrospective data collection, attrition bias and variations in the definition of MSA onset has not substantially influenced the review outcomes.

Limitations of the review methodology include its restriction to articles published in English, French or German and the low specificity of the search strategy, which increases the risk of missing relevant studies. The presence of reporting bias cannot be excluded given the limitations of funnel plots where several prognostic factors are reported by individual studies.

CONCLUSION

The present review is the first to summarise, synthesise and contrast evidence on prognostic factors in patients with PSP and MSA and it identified several clinical variables that were strongly associated with survival (table 1). Results on most prognostic factors were consistent across methodologically diverse studies, including both clinical and post-mortem studies. However, the lack of commonality of prognostic factors investigated is a significant limitation.

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COMPETING INTEREST

The authors declare that they have no competing interest

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AUTHOR CONTRIBUTIONS

SAG performed the study selection, risk of bias assessment, data extraction, statistical analysis and drafted the manuscript. RAS reviewed a random sample of five papers. All authors participated in study design, revised the protocol, contributed to interpretation of the results, critically revised the manuscript for important intellectual content, read, and approved the final version of this manuscript.

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FIGURE LEGENDS

Fig 1. Flow chart of study selection process

Fig 2. Line graph (black and white) showing cumulative survival of PSP patients extracted from Kaplan-Meier curves of individual studies. Each line represents one study. Post-mortem studies are marked with a star. PSP = progressive supranuclear palsy

Fig 3. Line graph (black and white) showing cumulative survival of MSA patients extracted from Kaplan-Meier curves of individual studies. Each line represents one study. Post-mortem studies are marked with a star. MSA = multiple system atrophy

Fig 4. Forest plot comparing survival between male and female patients

Fig 5. Forest plot comparing survival between MSA-P and MSA-C patients. MSA-C = multiple system atrophy cerebellar subtype; MSA-P = multiple system atrophy parkinsonism subtype

Fig 6. Forest plot comparing survival between PSP-RS and PSP-P patients. PSP-P = progressive supranuclear palsy parkinsonism subtype; PSP-RS = progressive supranuclear palsy Richardson's subtype

Fig 7. Forest plot comparing survival between patients experiencing early falls (EF) and patients not experiencing early falls (no EF)