LONGITUDINAL STUDY OF A COHORT OF MSA-C PATIENTS IN SOUTH ITALY: SURVIVAL AND CLINICAL FEATURES.

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Aims: Multiple system atrophy is a progressive fatal neurodegenerative disorder. Two major forms of the disease are recognized, the parkinsonian (MSA-P) and the cerebellar(MSA-C). Factors predicting survival are not fully established. We conducted a retrospective study to determine the median time to loss of independent walk, to become wheel-chair bound, and to death and determinants. The study was conducted in a personal series of patients with MSA-C. Background: Twelve mainly retrospective studies are available. In some of them the clinical diagnosis was confirmed by autopsy. All of them considered both MSA-P and MSA-C. Mean age at onset varied from 52.5 to 60 years, the median time to wheel-chair varied from 5 to 6.7 years, and the median time to death varied from 6.2 to 10 years. A recent meta-analysis identified as unfavorable predictors of survival severe dysautonomia and early development of combined autonomic and motor features but not MSA phenotype, early falls but not sex. There was conflicting evidence regarding the prognostic effect of aging, age at onset and stridor (Ref 1-5).

TAB.1 MSA-C Cohort (n=62)

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Gender	
Female	30 (48.4)
Male	32 (51.6)
Age at onset	
mean ± std. dev.	56.5 ± 7.7
median [25th - 75th percentile]	57 [52 ; 63]
Age at examination	
mean ± std. dev.	61.8 ± 7
median [25th - 75th percentile]	62 [57 ; 67]
Nr of subjects reached Phase III nr missing=8	35 (64.8)
Nr of subjects reached Phase IV nr missing=29	25 (75.8)
Nr. of deaths nr missing=0	18 (29)
Probable	50 (80.7)
Possible	12 (19.3)

TAB.2 OCCURRENCE OF FEATURES AT BASAL AND LAST VISIT

	Basal %	Last Visit %
Nystagmus	6.8	15.8
Dysarthria	70.5	89.7
Tremor	29.5	65.5
Bradykinesia	34.4	53.7
Rigidity	31.8	61.4
Increased Tendon Jerks	70.5	74.1
Increased Tone LL	11.6	13.2
Babinski signs	6.8	23.0
Urinary Incontinence	45.5	87.0
Hypotension	18.6	27.5
Syncope	2.6	13.3
Impotence	75.0	76.2
Dysphagia	43.2	74.5
Stridor	3.1	25.0
REM Behaviour Disorder	77.5	77.4
Ldopa/DA-Agonist	-	30.9
Dystonia	-	31.1
MMSE (Abnormal)	-	9.1
Cerebellar atrophy	64.5	100.0
Pons atrophy	40.3	76.0
Hot bun sign	25.8	60.4
Putamen rim	6.5	14.0
DaTSCAN (Abnormal)	-	91.4
PET (Abnormal)	-	100.0
PNCS	-	13.9

TAB.3 KAPLAN-MEIER SURVIVAL CURVES FOR PROGRESSION AND DEATH

Age at death	
mean ± std. dev.	64.5 ± 6.9
median [25th - 75th percentile]	64 [60 ; 69]
	Median [95% C.I.]
Time to Death (years)	10 [9 to 11]
Age at Phase III	
mean ± std. dev.	61.2 ± 6.6
median [25th - 75th percentile]	61 [58 ; 66]
	Median [95% C.I.]
Time to phase III (years)	5 [4.4 to 5.6]
Age at Phase IV	
mean ± std. dev.	63.1 ± 6.7
median [25th - 75th percentile]	62 [60 ; 69]
	Median [95% C.I.]
Time to phase IV (years)	7 [6.4 to 7.6]

Patients and methods: Sixty-two patients with a probable (81%) or possible (19%) diagnosis of MSA-C were observed at the Department of Neurology, University Federico II of Naples, between 2006 and 2017. The demographic factors are reported in Table 1. Disease stages were according to Inherited Ataxia Progression Scale (Ref 6).
Statistics: The frequency of the clinical features was analyzed by Fischer exact test. Kaplan-Meier curves were used to graphically analyze the interval in years from first symptoms onset to different disease stages and death, and expressed as median values. Cox proportional hazards models were used to calculate univariate hazard ratio. Statistical significance was defined at p<0.005
Results: Mean age at onset was 56.5 years (±7.7), mean age at examination was 61.8 (±7.0) (Table 1). The most frequent features were: ataxia (98%), dysarthria (90%), urinary incontinence (87%), sexual dysfunction in males (76%), RBD (77%), increased tendon reflexes (74%), dysphagia (74%), tremor (65%), rigidity (61%). Signs with low occurrence were: nystagmus (16%), increased tone at lower limbs (13%), and abnormal MMSE (9%). MRI scan detected constant cerebellar atrophy, pontine atrophy in 76%, hot cross bun sign in 60%, putamen rim hyperintensity in 14% (Table 2). Thirty-five patients lost independent gait after a median time of 5 years, at the age of 61 years (Figure 1-Table 3). Twenty-five patients were confined to wheelchair after a median time of 7 years, at the age of 62 years (Figure 2-Table 3); Eighteen patients died after a median time of 10 years, at the age of 64 years (Figure 3-Table 3). As far as predictors are concerned only a later onset predicted an earlier reach to phase III (Table 4). Rigidity, stridor, RBD, use of L-DOPA agonist, were more frequent in deceased patients (Table 5).

TAB.4 PREDICTORS OF DISEASE PROGRESSION AND DEATH
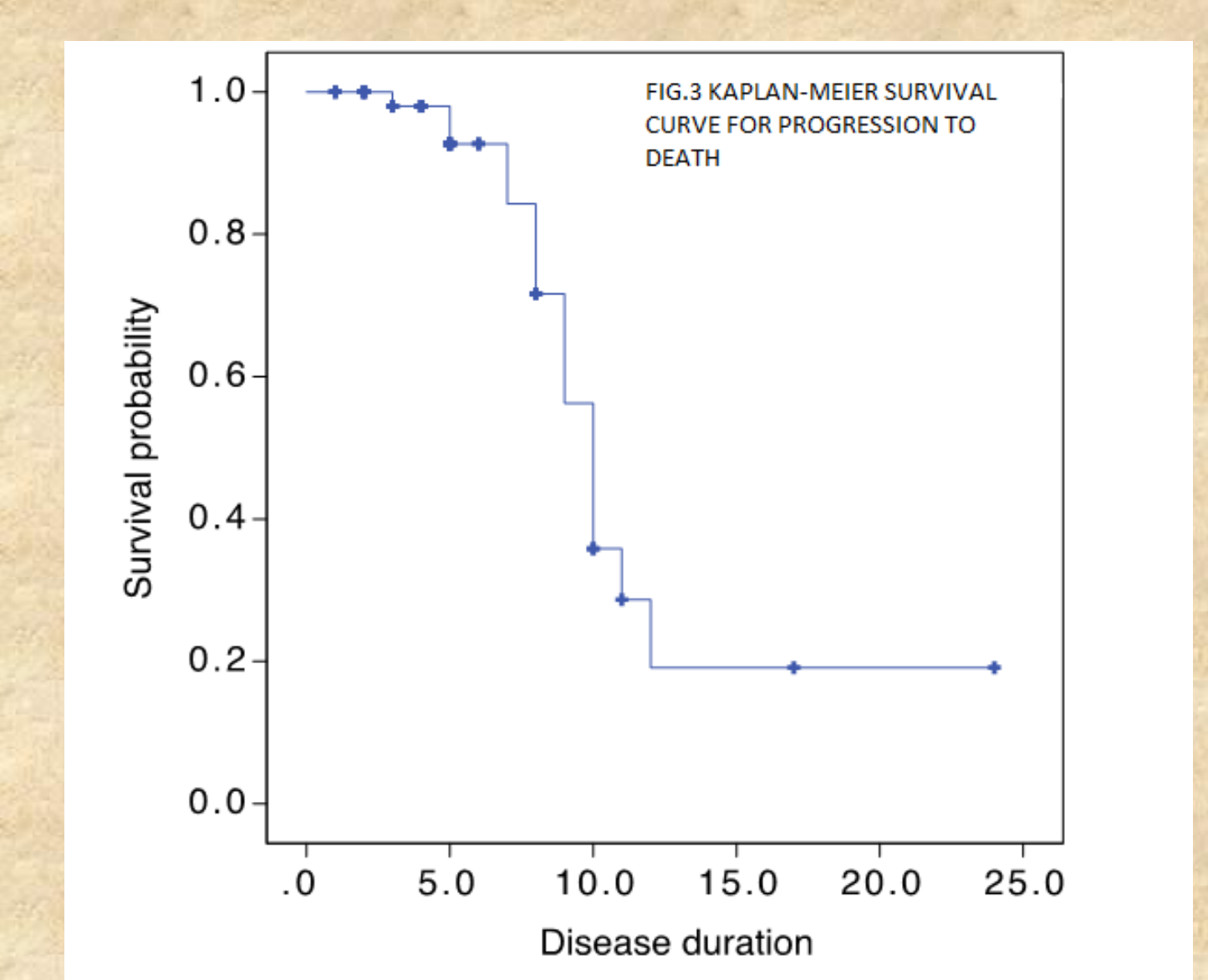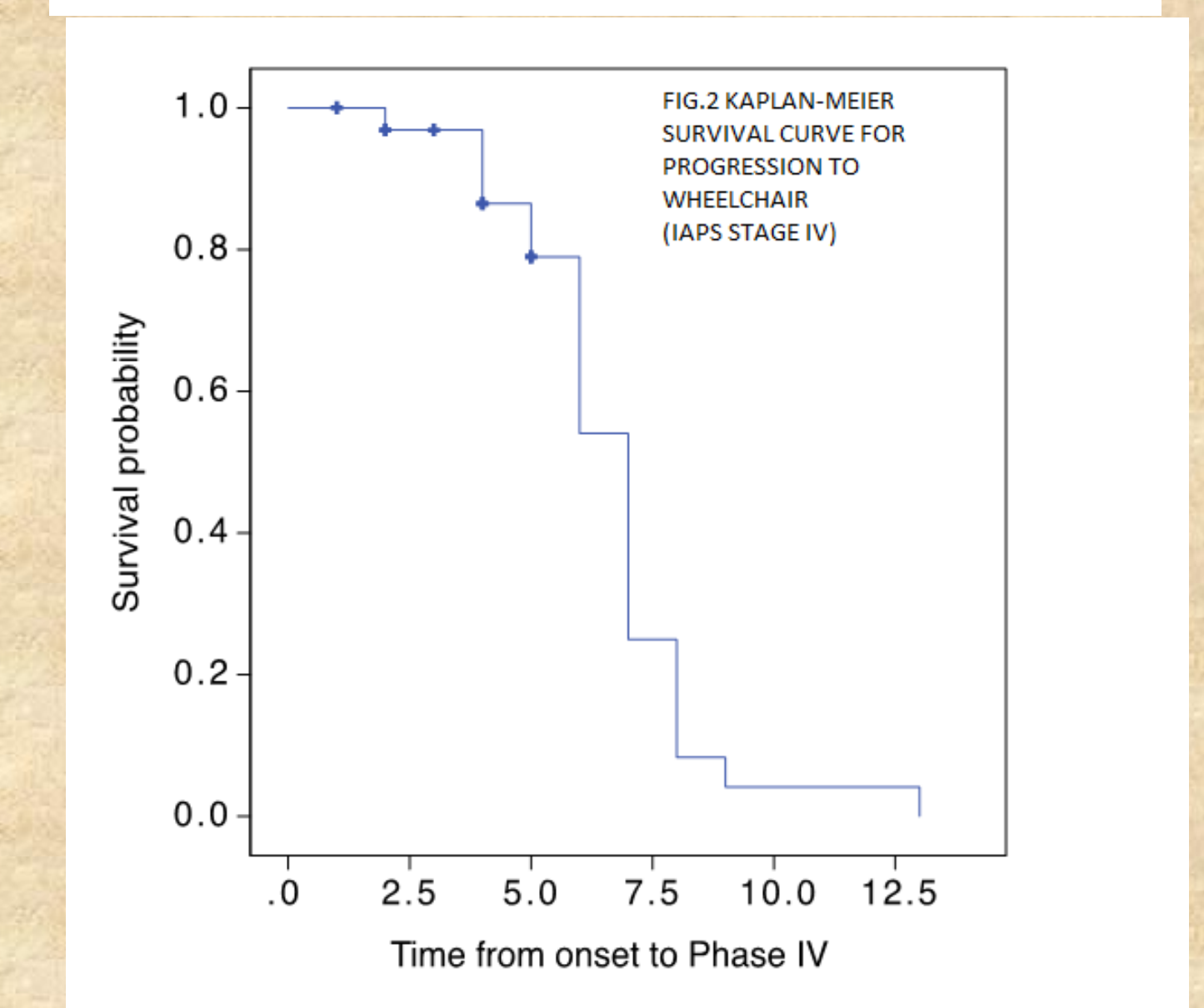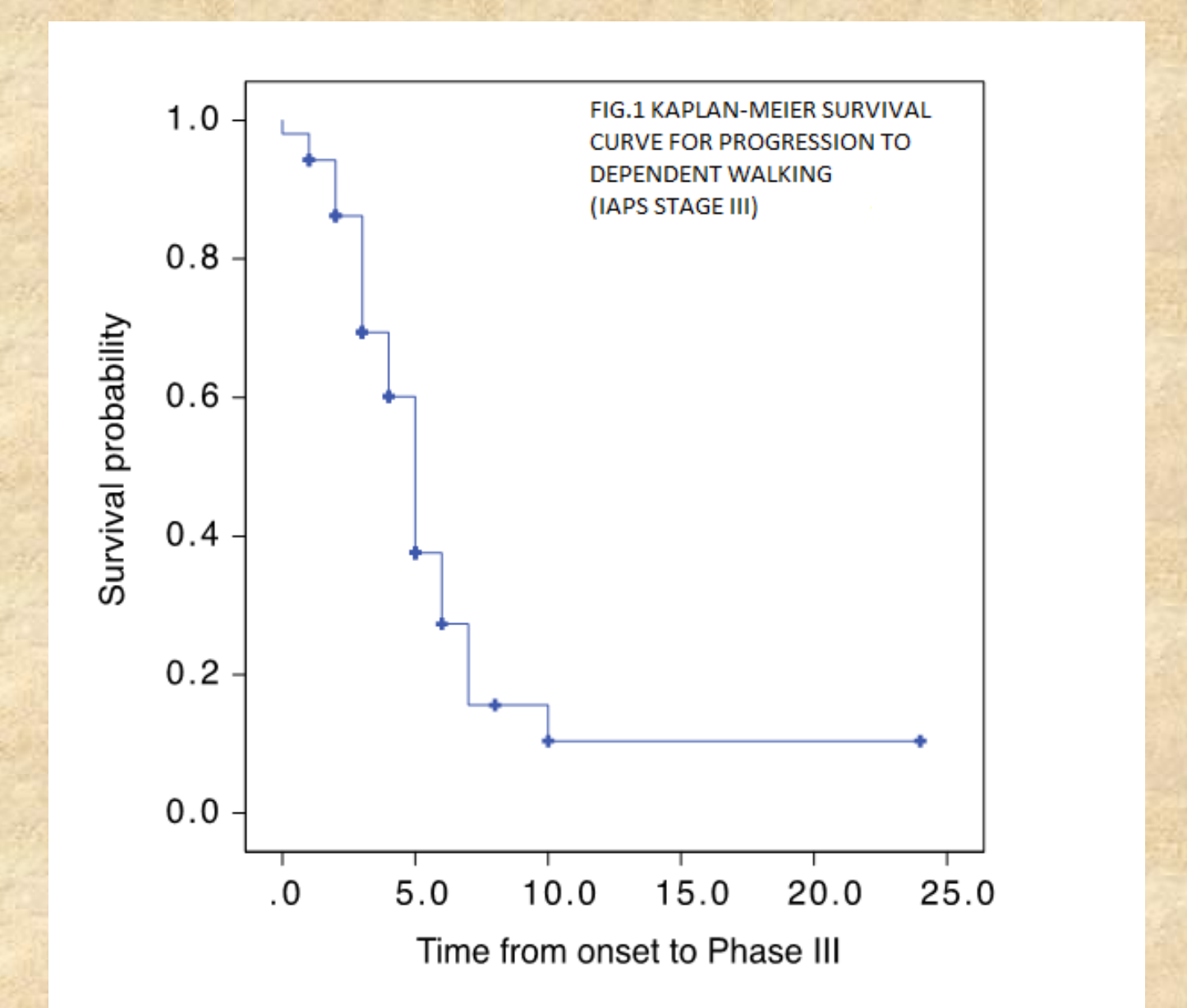
	PHASE III			PHASE IV			DEATH		
Predictors	H.R. [95% C.I.]	pvalue		H.R. [95% C.I.]	pvalue		H.R. [95% C.I.]	pvalue	
Gender (Female vs. Male)	1.13 [0.58 to 2.21]	711		1.58 [0.69 to 3.61]	0,279		1.05 [0.41 to 2.66]	0,924	
Diagnosis (Probable vs. Possible)	1.38 [0.33 to 5.84]	0,659		0.19 [0.03 to 1.07]	0,059		0.4 [0.09 to 1.86]	0,242	
Age at onset	1.06 [1.01 to 1.11]	0,012		1.03 [0.97 to 1.09]	0,363		1.05 [0.99 to 1.11]	0,1	
Nystagmus	1.23 [0.17 to 9.14]	0,842		1.91 [0.24 to 14.92]	0,539		1.64 [0.21 to 12.9]	0,637	
Dysarthria	0.7 [0.31 to 1.55]	0,375		0.81 [0.31 to 2.09]	0,656		1.49 [0.43 to 5.21]	0,531	
Tremor	0.87 [0.38 to 1.98]	0,741		0.58 [0.22 to 1.47]	0,248		0.94 [0.33 to 2.69]	0,914	
Bradykinesia	0.81 [0.28 to 2.31]	0,694		2.03 [0.54 to 7.63]	0,293		0.88 [0.23 to 3.44]	0,857	
Rigidity	1.89 [0.86 to 4.19]	0,114		1.77 [0.74 to 4.25]	0,201		1.72 [0.64 to 4.64]	0,283	
Increased Tendon Jerks	0.94 [0.41 to 2.14]	0,875		0.92 [0.38 to 2.22]	0,851		0.7 [0.27 to 1.83]	0,466	
Increased Tone LL	1.56 [0.46 to 5.24]	0,474		1.08 [0.31 to 3.74]	0,903		2.53 [0.8 to 7.99]	0,113	
Babinski signs	1.1 [0.26 to 4.68]	0,901		0.73 [0.1 to 5.47]	0,756		0.94 [0.12 to 7.18]	0,953	
Urinary Incontinence	1.07 [0.5 to 2.27]	0,859		1.27 [0.49 to 3.31]	0,628		1.2 [0.46 to 3.17]	0,71	
Hypotension	1.41 [0.59 to 3.41]	0,443		1.68 [0.48 to 5.85]	0,413		1.95 [0.39 to 9.82]	0,417	
Syncope	10.42 [1.08 to 100.13]	0,042		-			-		
Impotence	-			-			0.8 [0.07 to 8.86]	0,854	
Dysphagia	0.85 [0.4 to 1.8]	0,670		1.31 [0.55 to 3.13]	0,550		0.97 [0.37 to 2.57]	0,956	
Stridor	2.97 [0.37 to 23.72]	0,305		-			2.33 [0.53 to 10.22]	0,262	
RBD	1.4 [0.56 to 3.5]	0,474		1.39 [0.46 to 4.18]	0,555		-		
Cerebellar atrophy	1.47 [0.35 to 6.29]	0,601		1.14 [0.15 to 8.62]	0,898		-		
Pons atrophy	1.75 [0.76 to 4.01]	0,187		0.87 [0.36 to 2.11]	0,755		2.19 [0.7 to 6.88]	0,179	
Hbs	1.16 [0.54 to 2.48]	0,700		1.15 [0.47 to 2.84]	0,762		0.98 [0.34 to 2.8]	0,964	
Putamen rim	1.43 [0.49 to 4.16]	0,511		1.51 [0.5 to 4.57]	0,468		0.37 [0.05 to 2.78]	0,331	

TAB.5 COMPARISON BETWEEN DECEASED AND LIVING PATIENTS

	Death		
	No (n=44; 71%)	Yes (n=18; 29%)	pvalue
nystagmus	10.3	27.8	0,100
dysarthria	87.5	94.4	0,387
tremor	62.5	72.2	0,471
bradykinesia	47.2	66.1	0,177
rigidity	51.3	83.3	0,021
increased tendon jerks	82.5	55.6	0,035
increased tone	8.3	23.5	0,139
babinski signs	21.1	27.8	0,406
urinary incontinence	83.3	94.4	0,245
hypotension	27.3	27.8	0,608
syncope	10.0	20.0	0,311
impotence	75.0	80.0	0,662
dysphagia	69.7	83.3	0,235
stridor	14.3	43.8	0,037
RBD	68.6	94.4	0,031
LDOPA/DA- agonist	18.9	55.6	0,006
Dystonia	20.7	50.0	0,053
MMSE(abnormal)	-	22.2	0,156
cerebellar atrophy	100.0	100.0	-
pons atrophy	69.7	88.2	0,181
HBS	53.1	75.0	0,213
putamen rim	12.1	17.6	0,677
DaTSCAN (Abnormal)	94.7	87.5	0,582
PET-FDG (Abnormal)	100.0	100.0	-
PCNS	12.0	18.2	0,631

FIG.1 KAPLAN-MEIER SURVIVAL CURVE FOR PROGRESSION TO DEPENDENT WALKING (IAPS STAGE III)

FIG.2 KAPLAN-MEIER SURVIVAL CURVE FOR PROGRESSION TO WHEELCHAIR (IAPS STAGE IV)

FIG.3 KAPLAN-MEIER SURVIVAL CURVE FOR PROGRESSION TO DEATH

Discussion: The mean age at onset (56.5 years), disease duration to wheelchair (Phase IV, 7 years), and to death (10 years) fall in the values reported in literature. Time to loss of independent walking (Phase III, 5 years) has not being reported previously. No relevant determinants of survival have been found, in particular the autonomic features. In addition, the deceased patients differed from survivors in higher occurrence of parkinsonism, stridor, RBD, and lower occurrence of increased tendon jerks.

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