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TITLE PAGE

Cardiovascular diseases may play a negative role in the prognosis of ALS

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ABSTRACT

Background: Only a few studies considered the role of comorbidities on ALS prognosis and provided conflicting results.

Methods: our multicenter, retrospective study included patients diagnosed from 1/1/2009 to 31/12/2013 in 13 Referral Centers for ALS located in 10 Italian Regions. Caring neurologists collected a detailed phenotypic profile and follow-up data until death into an electronic database. Comorbidities at diagnosis were recorded by main categories and single medical diagnosis, with the aim of investigating their role on ALS prognosis.

Results: 2354 incident cases were collected, with a median survival time from onset to death/tracheostomy of 43 months. According to univariate analysis, together with well known clinical prognostic factors (age at onset, diagnostic delay, site of onset, phenotype, Revised El Escorial Criteria (R-EEC) and BMI at diagnosis), the presence of dementia, hypertension, heart diseases, chronic obstructive pulmonary disease, haematological and psychiatric diseases were associated with worse survival. In multivariate analysis age at onset, diagnostic delay, phenotypes, BMI at diagnosis, R-EEC, dementia, hypertension, heart diseases (atrial fibrillation and heart failure), and haematological diseases (disorders of thrombosis and haemostasis) were independent prognostic factors of survival in ALS.

Conclusions: our large, multicenter study demonstrated that, together with the known clinical prognostic factors on ALS survival, hypertension and heart diseases (i.e. atrial fibrillation and heart failure) as well as haematological diseases are independently associated to a shorter

survival. Our findings could suggest some possible mechanisms involved in disease progression, giving new interesting clues valuable for clinical practice and ALS comorbidities management.

MAIN TEXT

INTRODUCTION

Survival of Amyotrophic Lateral Sclerosis (ALS) patients from symptom onset is often reported to be 3-5 years, with a wide range of outcomes and considerable inter-individual variability[1].

This wide variability makes the formulation of an individualized prognosis extremely difficult, and disconcerts the patient and relatives who need to plan their choices in the light of the disease.

In addition, clinical variability impairs the conduct of clinical trials, due to its consequences on patients recruitment and interpretation of results[2].

In general, there is a consensus on the prognostic role of age at onset, diagnostic delay, genotype, clinical phenotype, severity and rate of disease progression, degree of diagnostic certainty and delay, and cognitive status[3].

Only a few studies considered the role of comorbidities on ALS prognosis, and the limited data available in the literature provide conflicting results[4–6]. In this context, our large multicenter Italian study, aims to evaluate the prognostic role of predetermined categories of comorbidities at diagnosis.

METHODS

Patients data collection

The study has been performed in 13 ALS Italian referral centers having a wide experience in multidisciplinary management of Motor Neuron Diseases (MND), located in 10 Italian Regions: ALS Centers of Turin, Padua, Genoa, Naples, Modena, Lecce, NEMO Clinical Centers in Milan, Rome, and Messina, Salvatore Maugeri Foundations in Milan and Mistretta, ALS Centers at San Raffaele Institute and Istituto Auxologico Italiano in Milan.

The study included patients diagnosed with ALS from January 1st,2009 to December 31st,2013 according to Revised El Escorial Criteria (R-EEC) for ALS diagnosis.

The methodology of cases ascertainment has already been described in detail elsewhere[7].

Briefly, each supervising neurologist collected a detailed phenotypic profile of all incident cases that were followed up until death/tracheosotmy or until the last observation date, set at December 31st, 2014.

For the specific purposes of this study we collected information (validated with clinical files) on comorbidities that were present at diagnosis including the presence of dementia, extrapyramidal syndromes (Parkinson's disease, atypical parkinsonisms) and other neurological diseases (cerebrovascular diseases, epilepsy, neuropathies/polyneuropathies, myelopathies, other rare syndromes), hypertension and cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and other respiratory disorders (OSAS, interstitial/granulomatous lung diseases, TBC, other infections, pneumothorax, pulmonary thromboembolisms, others), psychiatric disorders, gastrointestinal, haematological, autoimmune and neoplastic diseases. We also analysed other comorbidities not included in the above mentioned categories and including: dyslipidemia, eye disorders and glaucoma, peripheral vascular diseases, prostate and kidney diseases, bone and joint disorders, Paget's disease of the bone, otorhinolaryngological disorders. The information on presence/absence of the above mentioned diseases was collected by reference neurologists by filling in enclosed fields (eg. presence of heart diseases: yes/no); these fields were followed by open fields in which specialists were required to specify, in a text field, the type of disease from which the patient was suffering (with the exact clinical diagnosis (eg.persistent atrial fibrillation)).

They also collected information relating to smoking habit, weight/height at diagnosis, and drugs taken at the time of diagnosis with particular attention to the following pharmacological groups: riluzole, acetylsalicylic acid (ASA), anticoagulants, statins, Ca-antagonists, Beta-blockers, sartans, ACE-inhibitors, diuretics, digitalis. Charlson comorbidity index (CCI) was also calculated [8].The study was approved by the Ethical Committees of

the all participating ALS centers. Informed consent was not required according to Italian regulation, because this was a retrospective observational study.

Statistical Methods

Chi-square test was used to explore differences between groups for categorical data, T-test (or multiple comparison test) for continuous data. All tests were two tailed. Survival was calculated as the time from onset to death/tracheostomy (months) or censoring date (last day of follow-up,31 December 2014).

Kaplan-Meier survival curves followed by log-rank test were used to evaluate survival of different groups from disease onset. Univariate Cox regression was applied to derive unadjusted HRs for death/tracheostomy and for death. Multivariable Cox proportional hazards model (stepwise backward) with a retention criterion of $P<0.10$ was used to estimate covariate-adjusted risk of death/tracheostomy (from onset).

We included in the Cox regression analysis well known factors as reported previously[3], and based on clinical judgment. Data were analyzed using Stata 12 (Stata Corp,Texas,USA).

RESULTS

Clinical and demographic data of the 2354 incident cases collected by the 13 ALS centres in the 5 years of the study are reported in table 1.

Median tracheostomy-free survival from onset was 43 months (SE 1.18, CI 41-45). Overall 1-year, 2-years, 3-year, and 5-year survival rates were 93.19% (SE0.52%), 74.14% (SE0.93%), 56.56% (SE1.09%), and 37.16% (SE 1.20%), respectively.

To study the prognostic role of comorbidities that were present at diagnosis (table 2), we performed first a univariate analysis to test the role of individual comorbidities (presence or absence) on tracheostomy-free survival. Survival predictor variables at univariate analysis are shown in table 3 and included: presence of dementia, COPD, hypertension (Figure1), heart diseases (Suppplemental Figure- online only), haematological and psychiatric diseases. CCI was related to survival too. We then examined the different diseases included inside the above mentioned categories of disorders, considering single diseases or syndromes based on clinical

significance (Table 4). We found significant results for heart, haematological and psychiatric diseases and in particular a negative prognostic role for persistent AF and heart failure, hypertension, disorders of thrombosis and haemostasis, anxiety and other psychiatric disorders (table 4).

In relation to the above mentioned significant comorbidities at univariate analysis, we examined the role of drugs associated to those diseases and that patients were taken at time of diagnosis. The use of the following drugs was associated to a worse prognosis at univariate analysis: anticoagulants (HR1.65, 95%CI 1.18-2.31, p=0.004), ACE inhibitors (HR1.18, 95%CI 1.01-1.39, p=0.038), diuretics (HR1.15, 95%CI 1.01-1.36, p=0.042), digitalis (HR2.72, 95%CI 1.50-4.94, p<0.001), statins (HR1.24, 95%CI 1.03-1.49, p=0.025). All others examined drugs did not have a significant role on prognosis.

Subsequently, we performed a multivariable analysis (Cox multivariable model) including the following variables: age at onset (years), diagnostic delay (months), site of onset (bulbar/spinal/generalized), phenotypes (bulbar, classic, flail arm, flail leg, UMN-p, respiratory), riluzole treatment, BMI, R-EEC criteria (definite, clinically probable, probable-laboratory supported, possible), comorbidities at diagnosis (dementia, hypertension and cardiovascular diseases, COPD, psychiatric disorders, haematological diseases), CCI, and drugs taken at the time of diagnosis (ACE-inhibitors, diuretics, ASA, statins, anticoagulants, digitalis).

After dropping non-significant terms, the final model included age at onset, diagnostic delay, phenotypes, dementia, BMI, R-EEC criteria, hypertension, heart diseases and haematological diseases (Table 5). These factors were independent prognostic factors of survival in ALS.

Patients with cardiovascular comorbidities at diagnosis (hypertension, heart diseases, and haematological diseases) were older and more often with a bulbar onset (Supplemental Tables S1, S2, S3-online only).

DISCUSSION

We studied a large population coming from 13 ALS tertiary centers in Italy. The clinical features of our study population are similar to those already reported in previous studies [9-10], confirming that our cohort reflects the general population of patients with ALS, although coming from referral centers and not from a population-based registry. Our study also confirms the expected role of some well-known factors on ALS survival: age at diagnosis (with younger patients surviving longer), diagnostic delay (with shorter diagnostic delay indicating a more quick degenerative process and a shorter survival), phenotypes (worse survival for respiratory and bulbar phenotypes), BMI, degree of certainty at diagnosis according to R-EEC, and cognitive impairment [3,11].

However, the most interesting results regards the main objective of the study, namely the prognostic role of comorbidities that were present at diagnosis and in particular hypertension, heart diseases and haematological diseases.

To the best of our knowledge, only a few studies considered the possible prognostic role of comorbidities related to the cardiovascular system. Hypertension was related to a late ALS onset in a cohort of 1439 patients, but none of the examined comorbidities significantly affected survival [4]. Another study found that presence of hypertension and coronary heart disease was associated with shorter survival at univariate analysis, findings not confirmed in multivariable analysis. These comorbidities did not significantly affect either disease progression as measured by ALSFRS-R [5]. A third study documented an increase in the risk of death of 21.7% for patients with ALS who suffered from hypertension since five years [6]. Finally a recent population-based registry study performed in Italy, could not confirm with multivariable analysis the negative prognostic role of pre-morbid arterial hypertension detected at univariate analysis [12].

These conflicting results may be mainly due to methodological issues concerning design and population of the study (single ALS center cohort [4,5], case control study [6], population based register study [12], multiple ALS center cohort in the present study), sample size (from 111 [6] to 1439 [4] ALS patients and 2354 in our study), and study duration (covering a variable period up to 15 years [4–6,12]). Other methodological issues concern variables that have been taken into account: diverse diseases in some studies [4,5], only arterial

hypertension and other cardiovascular diseases/risk factors [6,12] in other studies. In contrast, our study considered almost all possible comorbidities and clinical diagnoses as indicated by referring neurologists, conferring more comprehensiveness to comorbidities assessment. Taking a broad view of prognostic factors may generate new knowledge with (as yet) unknown implications for developing new interventions [13]. Finally we considered comorbidities and related drugs use together in relation to ALS prognosis and also this may contribute to different results with respect to other researches.

As for the prognostic role of hypertension, we found that ALS patients affected by hypertension at diagnosis had a median survival of 37 months as opposed to 49 months instead of those who were not affected. The negative prognostic role of hypertension on ALS duration was confirmed by multivariable analysis. Unfortunately we could not detail the type of hypertension and its history in every single patient: duration, kind, severity, treatment effectiveness on blood pressure control should be studied to understand whether our data may be confirmed in further studies. It is possible, for instance, that only severe and badly controlled hypertension with complications may exert a significant effect on ALS survival through an altered neural perfusion that involves both direct (hypoxic) and indirect damage (microangiopathic mechanism)[6]. This hypothesis would require further prospective studies.

The few papers examining the prognostic role of heart diseases in ALS did not show a significant independent prognostic effect for them [4,5]; some studies, then, showed that heart diseases are less frequent in patients with ALS than the general population, and concluded that they could be somewhat protective against the onset of the disease [14,15]. We found a lower survival in ALS patients with heart diseases at diagnosis, with a median survival time of 35 months compared to 44 months of patients without heart diseases. This effect appeared to be largely attributable to heart failure and AF. Giving the high mortality rates of heart failure (20% in 1 year)[16] a negative prognostic role of this disease also in ALS is not surprising.

As for AF, autonomic imbalance has been reported in many conditions related to AF (e.g. sleep apnea, diabetes, depression, heart failure and extreme endurance activities) which exists in two autonomic subtypes (vagally-predominant, and adrenergically-predominant) [17]. In persistent AF increased sympathetic tone has been detected, and sympathetic over-activation

is an established risk factor for mortality because the cardiovascular system is continuously working in a high-energy mode which leads to exhaustion [17]. An imbalanced autonomic activity has been showed also in ALS course due to loss of neurons in the intermediate lateral nucleus resulting in increased risk of sudden cardiac death in association with QT prolongation [18-20]. In ALS patients with a dysregulation of the autonomic nervous system, a constant high-energy demand functioning associated to AF may contribute to further increase the risk of sudden cardiac death [18].

As previously reported, autonomic dysregulation would then have a higher frequency in patients with bulbar features than the other[20]. In agreement, in our study, among patients with AF, 41% had bulbar onset against 28% in subjects without AF (p=0.02).

It is also possible that the negative prognostic role of hypertension, AF, thrombotic and hemostasis disorders, has a unique underlying explanation, consisting in their clinical consequences such as embolism and ischemic stroke, cognitive decline, and heart failure that lead to early/anticipated mortality also in ALS population. Unfortunately we have no data on the exact cause of death in the patients of our cohort.

Finally, the above mentioned comorbidities may accelerate respiratory impairment in ALS patients, through an impaired perfusion that further imbalance gas exchange in addition to the inefficient ventilation caused by the disease.

The study has strengths and limitations. The major strengths are the extensive case collection, one of the largest in the world, and the assessment of many comorbidities together with drug use.

The major limitation is represented by the study population, consisting of referral centers population, and consequently somehow different from real world population.

Furthermore, multicentricity, that can be considered as instrumental in achieving the large sample of our study, may be associated with slight differences in the clinical practice of the various centers (although all third-level centers) and then in data collection, even with an ad-hoc research database, and after meetings aimed at training the reference neurologists.

Although we considered comorbidities at the time of diagnosis, the directionality of the association requires further research with different study design.

This study then has all the limitations of retrospective observational studies, which may introduce potentially confounding factors that cannot be controlled, and consequently create bias.

Other methodological drawbacks regards exposure misclassification, residual/unmeasured confounding, selection into the study, with potential introduction of other bias in the study. In addition, the use of Cox model with stepwise variable selection and inclusion of known prognostic factors cannot exclude that mediators might also be selected, inclusion of which could bias the estimated effects.Finally we did not have data on history, duration, severity and kind of medical control of the examined comorbidities, and on death cause, which should be the object of further prospective studies.

In conclusion, together with known clinical data, in our study, some cardiovascular diseases (hypertension, congestive heart failure, AF, disorders of thrombosis and haemostasis) were associated to a worse prognosis in ALS patients and may condition survival.

Despite several limitations, should these data be confirmed in further prospective studies examining in depth cardiovascular comorbidities, results can be helpful for daily clinical practice, not only for predicting disease progression, but also for an active monitoring and treatment of cardiovascular comorbidities associated to ALS.

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LEGENDS

Table 1:Patients characteristics

Table 2:Comorbidities that were present at diagnosis

Table 3:Prognostic role of the presence/absence of comorbidities at diagnosis (univariate analysis)

Table 4:Prognostic role of psychiatric, cardiac, haematological comorbidities at diagnosis (univariate analysis)

Table 5:Independent prognostic factors for ALS survival (multivariate Cox model)

Figure 1:Survival of ALS patients with or without hypertension at diagnosis

TABLES

Table 1: Patients characteristics

Explanatory variables	**All patients , N= 2354 n (%) m [SD[c]]**	**Males, N= 1298 n (%) m [SD]**	**Females N=1056 n (%) m [SD]**	**p-value**
ALS Onset				
Bulbar	580 (24.64)	248 (19.11)	332 (31.44)	**P<0.001***
Spinal	1555 (66.06)	923 (71.11)	632 (59.85)	
Generalized	42 (1.78)	24 (1.85)	18 (1.70)	
Phenotype				
Bulbar	440 (18.69)	188 (14.48)	252 (23.86)	**P<0.001***
Classic	1134 (48.17)	652 (50.23)	482 (45.64)	
Flail Arm	122 (5.18)	86 (6.63)	36 (3.41)	
Flail Leg	123 (5.22)	75 (5.78)	48 (4.55)	
UMNp[a]	139 (5.90)	67 (5.16)	72 (6.82)	
Respiratory	33 (1.40)	24 (1.85)	9 (0.85)	
Age at onset	64.21 [11.28]	63.52 [11.12]	65.04 [11.42]	**p=0.001***
Diagnostic delay	14.47 [15.62]	14.10 [15.93]	14.91 [15.22]	p=0.209
R-EEC				
Definite	659 (27.99)	329 (25.35)	330 (31.25)	**p=0.008***
Clinically probable	682 (28.97)	390 (30.05)	292 (27.65)	
Probable lab-supported	305 (12.96)	176 (13.56)	129 (12.22)	

Possible	407 (17.29)	241 (18.57)	166 (15.72)	
Dementia (Yes)	177 (7.52)	105 (8.09)	72 (6.82)	P=0.245
Dead at last observation (Yes)	1104 (46.90)	600 (46.22)	504 (47.73)	p=0.468
Riluzole (Yes)	1940 (82.41)	1074 (82.74)	866 (82.01)	p=0.323
Gastrostomy (Yes)	667 (28.33)	335 (25.81)	332 (31.44)	**P=0.002***
Non-invasive ventilation (Yes)	906 (38.49)	509 (39.21)	397 (37.59)	p=0.458
Invasive ventilation (Yes)	363 (15.42)	209 (16.10)	154 (14.58)	p=0.310
BMI[b] at diagnosis	24.25 [4.04]	24.44 [3.73]	24.03 [4.37]	**p=0.037***
Familiarity (Familial ALS)	138 (5.86)	72 (5.55)	66 (6.25)	P=0.496

[a]UMNp=Upper Motor Neuron predominant phenotype; [b]BMI= Body Mass Index; [c]SD=standard deviation; significant results in bold

Table 2: Comorbidities that were present at diagnosis

Comorbidities (at diagnosis)	Males, N= 1298 n (%)	Females N=1056 n (%)	Total N=2354 n (%)
Dementia	105 (8.08)	72 (6.81)	177 (7.52)
Parkinson's Disease	21 (1.62)	14 (1.39)	35 (1.49)
Other neurological diseases	198 (15.25)	140 (13.26)	338 (14.36)
Psychiatric diseases	95 (7.32)	133 (12.59)	228 (9.69)
Chronic Obstructive pulmonary disease	125 (9.63)	51 (4.83)	176 (7.48)
Other respiratory diseases	77 (5.93)	55 (5.21)	132 (5.61)
Hypertension	611 (47.07)	494 (46.78)	1105 (46.94)
Heart diseases	235 (18.10)	128 (12.12)	363 (15.42)
Haematological diseases	52 (4.01)	33 (3.12)	85 (3.61)
Diabetes	143 (11.02)	87 (8.24)	230 (9.77)
Autoimmune diseases	64 (4.93)	128 (12.12)	192 (8.16)
Cancer	140 (10.78)	128 (12.12)	268 (11.38)
Gastroenteric diseases	184 (14.17)	154 (14.58)	338 (14.26)

Table 3: Prognostic role of the presence/absence of comorbidities at diagnosis (univariate analysis)

Variables		Median survival (months)	HR	95 % CI	p-value
Dementia	Absence	44	1	(reference)	**<0.001***
	Presence	30	1.61	1.33-1.95	
Parkinson's Disease	Absence	43	1	(reference)	0.538
	Presence	51	0.86	0.53-1.39	
Other neurological diseases	Absence	44	1	(reference)	0.952
	Presence	35	1.00	0.86-1.18	
Psychiatric diseases	Absence	44	1	(reference)	**0.011***
	Presence	37	1.26	1.05-1.5	
COPD	Absence	43	1	(reference)	**0.024***
	Presence	35	1.26	1.03-1.53	
Other respiratory diseases	Absence	43	1	(reference)	0.310
	Presence	44	0.88	0.68-1.13	
Hypertension	Absence	49	1	(reference)	**<0.001***
	Presence	37	1.37	1.23-1.53	
Heart diseases	Absence	44	1	(reference)	**<0.001***
	Presence	35	1.37	1.19-1.58	
Haematological diseases	Absence	43	1	(reference)	**0.033***
	Presence	35	1.35	1.02-1.78	

Diabetes	Absence	43	1	(reference)	0.259
	Presence	39	1.11	0.93-1.33	
Autoimmune diseases	Absence	43	1	(reference)	0.445
	Presence	47	0.92	0.76-1-13	
Cancer	Absence	43	1	(reference)	0.560
	Presence	48	0.95	0.8-1.13	
Gastroenteric diseases	Absence	43	1	(reference)	0.847
	Presence	43	0.98	0.84-1.15	
Charlson Comorbidity Index	0	77	1	(reference)	**<0.001***
	1-3	42	1.65	1.37-2.00	
	4-6	36	2.06	1.69-2.51	
	>6	27	3.07	2.06-4.57	

Table 4: Prognostic role of psychiatric, cardiac, haematological comorbidities at diagnosis (univariate analysis)

Variables		Median survival (months)	HR	95 % CI	p-value
Psychiatric diseases	Absence	44	1	(reference)	
	Depressive disorders	44	1.30	0.68-2.51	0.431
	Anxiety disorders	37	1.21	1.00-1.47	**0.054***
	Substance related and addictive disorders	30	1.14	0.37-3.54	0.820
	Psychotic disorders	33	1.99	0.89-4.45	0.092
	Other psychiatric disorders[a]	22	4.44	1.66-11.87	**0.003***
Heart diseases	Absence	44	1	(reference)	
	Heart failure	9	10.44	2.60-41.92	**0.001***
	Ischemic heart disease	40	1.16	0.90-1.48	0.244
	Valvular heart disease	42	1.24	0.72-2.14	0.445
	Atrial fibrillation (persistent)	24	2.21	1.52-3.22	**<0.001***
	Atrial fibrillation (paroxysmal)	32	1.39	0.88-2.19	0.154
	Other arrhythmic syndromes	44	1.05	0.76-1.45	0.759
	Cardiomyopathies	/	0.76	0.25-2.37	0.640
	Atrial fibrillation + other heart diseases	21	2.49	1.37-4.50	**0.003**
	Multiple heart diseases without atrial fibrillation	44	1.81	0.86-3.81	0.116

Haematological diseases	Absence	43	1	(reference)	
	Anaemia	37	1.27	0.78-2.08	0.339
	Gammopathies	46	0.95	0.56-1.62	0.863
	Disorders of thrombosis and haemostasis	23	3.06	1.37-6.84	**0.006**
	Other syndromes	30	1.62	0.92-2.37	0.094

[a]Other psychiatric disorders = 5 patients with obsessive compulsive disorder (2) and psychogenic polydipsia (3)

Table 5: Independent prognostic factors for ALS survival (multivariate Cox model)

Variables	Groups/units	Hazard Ratio	95% CI	P > | z |
Diagnostic delay	Months	0.95	0.94-0.96	**<0.001***
Age at onset	Years	1.03	1.02-1.03	**<0.001***
Phenotype	Bulbar	1	(reference)	
	Classic	0.94	0.80-1.12	0.541
	Flail Arm	0.71	0.49-1.02	0.065
	Flail Leg	0.63	0.42-0.94	**0.025***
	UMN-p[b]	0.36	0.22-0.59	**<0.001***
	Respiratory	1.54	0.91-2.59	0.104
El Escorial diagnostic criteria	Definite	1	(reference)	
	Clinically Probable	0.71	0.60-0.84	**<0.001***
	Probable- Lab. Supported	0.51	0.39-0.66	**<0.001***
	Possible	0.57	0.46-0.71	**<0.001***
BMI[a]		0.97	0.95-0.99	**0.003***
Dementia	Yes/no	1.52	1.20-1.92	**0.001***
Hypertension	Yes/no	1.32	1.13-1.53	**<0.001***
Heart diseases	Absence	1	(reference)	
	Heart failure	6.33	1.55-25.84	**0.010***
	Ischemic heart	1.12	0.82-1.51	0.479

	disease			
	Valvular heart disease	1.27	0.60-2.70	0.524
	AF[c] (persistent)	2.27	1.43-3.60	**<0.001***
	AF[c] (paroxysmal)	2.27	1.37-3.76	**0.001***
	Other arrhythmic syndromes	1.03	0.63-1.68	0.895
	Cardiomyopathies	0.22	0.03-1.59	0.133
	AF[c] + other heart diseases	2.63	0.97-7.15	0.058
	Multiple heart diseases without AF[c]	1.54	0.68-3.49	0.301
Haematological diseases	Absence	1	(reference)	
	Anaemia	1.89	1.01-3.56	**0.047***
	Gammopathies	1.60	0.82-3.12	0.163
	Disorders of thrombosis and haemostasis	2.91	1.06-8.01	**0.038***
	Other syndromes	1.24	0.64-2.41	0.524

[a]BMI= Body Mass Index; [b]UMNp=Upper Motor Neuron predominant phenotype; [c]AF= Atrial Fibrillation; significant results in bold

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