Comorbidities do not influence the survival in Amyotrophic Lateral Sclerosis

E D'Errico [1], A Introna [1], G Graziano [2], A Scarafino [1], V Lepore [3], I Tempesta [1], R Cortese [1], G Scaglione [1], S Zoccolella [1], G Logroscino [1,4], IL Simone[1]

[1] Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari
[2] Scientific Direction, Cancer Institute «Giovanni Paolo II", Bari
[3] Department of Clinical Pharmacology and Epidemiology, Mario Negri Sud Foundation, Santa Maria Imbaro (CH), Italy
[4] Unit of Neurodegenerative Diseases, Department of Clinical Research in Neurology, University of Bari 'Aldo Moro', Tricase, Lecce, Italy.

Background and Objective: Amyotrophic lateral sclerosis (ALS) is a fatal rapidly progressive neurodegenerative disease, even if the survival seems to be increased in last decades.
The influence of different comorbidities on ALS survival has been evaluated, but the results have been often inconsistent.
Aim of the study: *to identify prognostic factors on ALS survival, including the influence of comorbidity.*

Materials and Methods*:* Source of the study was a prospective registry of incident ALS cases in a tertiary regional ALS Centre in the period from January 2000 to December 2013, followed until December 31, 2015.
Patients were classified according to age and site (spinal/bulbar) of symptoms onset, lower/upper motor neuron onset, time to generalization (TTG), delay from onset of symptoms to diagnosis (ODI), clinical phenotype, presence at symptom onset of one or more comorbidity including diabetes, autoimmune diseases and malignancies.
Uni- and multivariate survival analyses were performed by Kaplan–Meier analysis and the Cox proportional hazards model. The comparison between subgroups was performed by the Log_rank test. (Statistical Analysis System _SAS 9.2).

Results: 394 patients (163 M and 231 F) incident ALS were included.
One comorbidity was detected in 25.13% of patients (diabetes 11.17%, neoplasm 7.61% and autoimmune disease 9.14%); two or more comorbidities were observed in 2.23% of patients.
The median survival time from symptoms onset and from diagnosis was 46.3 months and 29.4 months respectively.
Comorbidities, considered individually or in association, did not influence the survival both in univariate and multivariate analysis (Figure 1).
Independent predictors of short survival from disease onset were bulbar phenotype (p= 0.0362); lower motor neuron onset (p=0.0420); shorter time to generalization (p=0.0002); short ODI (p<0.0001). Favorable factor related to survival was a younger age at onset (p<0.0001) (Table 1). Similar significance were detected when variables were evaluated from time of diagnosis.
Gender did not influence the survival, but women with age at onset > 62.5 years, bulbar onset and ODI < 12.96 months had shorter survival from disease onset compared to men with age at onset < 62.5 years, spinal onset and ODI >12.96 months (p=0.03).

Figure 1. Survival curves from time of disease onset stratified by presence of at least one co-morbidity and specifically diabetes, neoplasm, autoimmunity.

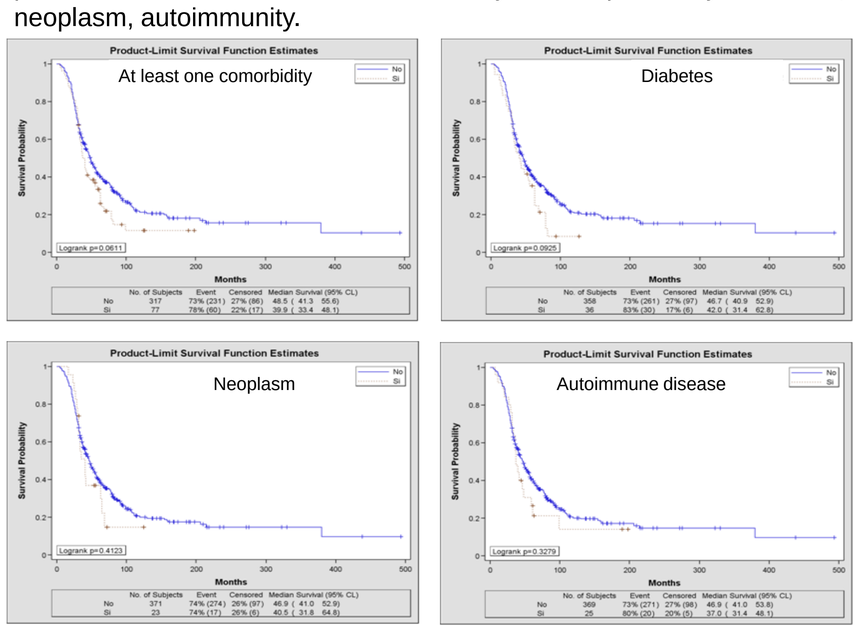

Table 1. Cox proportional Hazards by time of symptoms onset.

Variable	Hazard Ratio	p
ODI (<=12.96)	**2,208**	**<0,0001**
Gender (F)	**0.647**	**0.0015**
Bulbar phenotype	**3,824**	**0,0362**
Classic phenotype	2,984	0.0715
Prevalent UMN phenotype	1	0,995
Prevalent LMN phenotype	3,132	0.0756
Age of onset <=62.45	**0.562**	**<0.0001**
Lack of comorbidity	1.452	0.4448
No autoimmune disease	0.618	0.2999
No neoplastic disease	0.708	0.4514
No diabetic disease	0.504	0.1223
Bulbar onset	0.834	0.3815
LMN onset	**1.508**	**0.0420**
Generalisation time <= 13.06	**1.742**	**0.0002**
No PEG	**0.560**	**<0.0001**
No NIV	**1.387**	**0.0116**

Conclusions*:*
In this population-based study bulbar phenotype, TTG, age at onset, lower motor neuron onset and ODI were confirmed to influence ALS survival.
Gender influenced survival only when associated to other prognostic negative factors.
None of the investigated comorbidities had a prognostic role on the survival.
Larger ALS population studies and comparison with general population are needed to evaluate the influence of comorbidities on ALS risk and disease course.

Sin

References
1. Pupillo E, Messina P et al. Long-term survival in amyotrophic lateral sclerosis: a population-based study. Ann Neurol. 2014 Feb;75(2):287-97.
2. Paganoni S, Hyman T, et al. Pre-morbid type 2 diabetes mellitus is not a prognostic factor in amyotrophic lateral sclerosis. Muscle Nerve. 2015 Sep;52(3):339-43.
3. Sun Y, Lu CJ, et al. Risk of Amyotrophic Lateral Sclerosis in Patients With Diabetes: A Nationwide Population-Based Cohort Study. J Epidemiol. 2015;25(6):445-51.