Respiratory support in a population-based ALS cohort: demographic, timing and survival determinants

INTRODUCTION
Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease leading to a progressive loss of motor function and cognitive impairment of the frontotemporal type (FTD). Respiratory failure is a common symptom and can be treated with non-invasive mechanical ventilation (NIMV) and/or invasive mechanical ventilation (IMV) via tracheostomy. Studies on NIMV report a wide range of survival time, due to the heterogeneity of the clinical setting and patients’ characteristics, and very few data are available about NIMV and IMV in population-based cohorts. The aim of this study was to assess the outcome and prognostic determinants of ventilatory supports in a large population-based cohort of patients with ALS.

METHODS
The study population includes all patients with ALS diagnosed from 2008 to 2015 in the prospective population-based Piemonte and Valle d’Aosta Register for ALS. Demographic and clinical information, including those related to NIMV/IMV, were collected. The determinants of NIMV, IMV and NIMV to IMV transition were assessed with binary logistic regression analysis (backward). Additional details on methods and statistical analysis are reported in the online supplemental material.

RESULTS
During the study period, 1159 patients were diagnosed with ALS (median age at onset of 68.4 years (IQR 60.3–74.7); 540 females (46.6%); 395 (34.1%) bulbar onset). The characteristics of patients according to the different respiratory supports are reported in the online supplemental table 1. NIMV was performed by 391 (33.7%) patients, NIMV followed by IMV by 88 (7.6%), IMV by 81 (7.0%); 620 patients (53.5%) did not undergo ventilation.

The median survival time after NIMV initiation was 1.00 year (IQR 0.51–2.34). Factors related to the use of NIMV are reported in the online supplemental material. Pre-NIMV spirometry values were available for 308 (64.3%) patients. A dose–response effect of FVC% on the outcome of NIMV was found, with an increased survival at higher FVC% values ($p=0.0001$) (figure 1A). Therefore, we ran two Cox multivariable models for evaluating factors related to survival after NIMV (online supplemental table 2). In Model A, which excluded Forces Vital Capacity percent of expected (FVC%), a better outcome of NIMV was related to ALSFRS-R decline ($∆$ALSFRS-R $<$0.74 point/month, younger age, higher ALSFRS-R bulbar subscore and absence of chronic obstructive pulmonary disease. In Model B, which included FVC%, FVC% was the strongest determinant of NIMV outcome, followed by age, and higher ALSFRS-R upper limb subscore.

Eighty-eight (18.4%) of the 479 patients who initially performed NIMV subsequently underwent IMV. In 74 cases (84.1%), IMV was performed when the dependence on NIMV exceeded 20 hours/day, and in the remaining 14 for intervening acute events (infective or aspiration pneumonia). Factors related to the transition from NIMV to IMV are reported in the online supplemental material.

A total of 81 patients with ALS (7.0%) underwent directly IMV. In these cases, the events leading to IMV were acute respiratory infections (31, 38.3%), aspiration pneumonia (23, 28.4%) and sudden respiratory failure (27, 33.3%). Factors related to the use of IMV data are reported in the online supplemental material. Factors related to a better survival after IMV were younger age, lower $∆$ALSFRS-R, previous use of NIMV and to be married (online supplemental table 3).

The median survival time after IMV was 1.97 years (IQR 0.66–5.05); however, it was 3.00 years (IQR 0.70–8.54) for patients undergoing IMV after NIMV, and 1.58 years (IQR 0.59–3.66) ($p=0.014$) for those who performed directly IMV (figure 1B). Comparing survival from disease onset in all groups, patients who underwent IMV and/or NIMV had a significantly longer survival compared with non-ventilated patients (figure 1C). NIMV and IMV remained independently significant.
Although several studies have reported that NIMV increases survival, the effect on patients’ outcome of NIMV and IMV is still controversial.1-3 In our series, we found that patients who underwent NIVM alone or followed by IMV had a better outcome than non-ventilated ones independently from other prognostic factors. This is true also for patients with bulbar onset, differently from previous reports.2 Besides, we identified a positive correlation between higher FVC% values and better survival, thus supporting an earlier starting of NIMV, when patients’ ventilatory function is still partially preserved. Finally, the prognostic role of lower ∆ALSFRS-R before NIMV suggests that respiratory support does not modify the rate of functional decline.

A better survival after IMV was associated with younger age, ∆ALSFRS-R before IMV, and to be married. Notably, we also observed a better outcome of IMV in patients who previously underwent NIMV, likely because the intervention is planned in advance and not performed in an emergency setting.

This study is not without limitations. First, we could not include cognitive impairment in the multivariable models since patients with a diagnosis of comorbid FTD were less likely to undergo NIMV, hindering the possibility to unbiasedly assess the effect of cognitive impairment on survival. Second, most patients performing NIMV/IMV attended a multidisciplinary clinic, limiting the possibility to evaluate the effect of multidisciplinary care on mechanical ventilation outcome.

The real-world data of this large population-based study indicate that mechanical ventilation prolongs survival independently from other prognostic factors, including bulbar onset. In addition, our data will be useful for the management of patients and for designing clinical trials, which should keep into account the substantial effect of mechanical ventilation on the course of the disease and its demographic and clinical determinants.

Adriano Chio,1,2 Cristina Moglia,3 Antonio Canosa,4,6 Umberto Manera,5 Rosario Vasta,7 Maurizio Grassano1,8 Francesca Palumbo,1 Maria Claudia Torrieri,1 Luca Solero,1 Alessio Mattei,2 Fulvia Ribolla,2 Nicola Launaro,3 Fabiola De Marchi,2 Letizia Mazzini,9 Gabriele Mora,9 Andrea Calvo1

1Rita Levi Montalcini Department of Neuroscience, University of Turin, Turin, Italy
2Department of Pulmonology, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
3ALS Center, University Hospital, Novara, Italy
4Department of Health Science, Maggiore della Carità University Hospital, Novara, Italy
5Department of Neurology, University of Turin, Turin, Italy
6Department of Pulmonology, Azienda Sanitaria Locale Cuneo 1, Savignano, Italy
7Department of Health Science, Maggiore della Carità Hospital, Novara, Italy
8Department of Pulmonology, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
9Department of Pulmonology, Azienda Sanitaria Locale Cuneo 1, Savignano, Italy

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ORCID iDs
Adriano Chio http://orcid.org/0000-0001-9579-5341
Antonio Canosa http://orcid.org/0000-0001-5876-4079
Rosario Vasta http://orcid.org/0000-0002-0393-4736
Maurizio Grassano http://orcid.org/0000-0001-6714-6897
Maria Claudia Torrieri http://orcid.org/0000-0001-9312-7487
Andrea Calvo http://orcid.org/0000-0002-5122-7243

REFERENCES