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 NIVM was related to ALSFRS-R decline (ΔALSFRS-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 ΔALSFRS-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.
in Cox multivariable analysis (online supplemental table 4).

**DISCUSSION**

This is the first study to have systematically assessed in a large ALS population-based series the factors related to the choice to undergo mechanical ventilation and the determinants of survival. About 50% of our cohort underwent NIMV/IMV, confirming an improved adherence to current guidelines. Patients who used mechanical ventilation had an increased overall survival compared with non-ventilated patients. Main factors related to a better survival after NIMV/IMV were a higher FVC% and a lower ∆ALSFRS-R at time of ventilation.

In the last two decades, respiratory support via NIMV has become the standard treatment of respiratory failure in ALS. The use of IMV is less explored and neurologists’ attitudes are considerably less uniform. In general, when discussing the option of IMV, much emphasis is put on patients’ personal motivations and to inform that IMV may prolong survival but does not modify disease progression or quality of life and may increase caregivers’ burden.2,4

Younger age and attending an ALS multidisciplinary clinic resulted to be independently related to patients’ decision to perform NIMV. Younger age was also an independent determinant of the use of IMV, together with male sex, ∆ALSFRS-R at diagnosis and bulbar onset. These two latter factors are a novel finding of our study and may be due to the rapid progression of respiratory impairment in fast progressors, and the scarce tolerance of NIMV interface or aspiration pneumonia in patients with bulbar impairment. Another important novel observation of our study is that patients with comorbid FTD had a 50% chance to undergo mechanical ventilation compared with patients with normal cognition. Finally, our data revealed that the sex inequality in the use of mechanical ventilation is declining, although not completely.

In our cohort, ~20% of patients performing NIMV chose to undergo IMV. The main reasons for the transition from NIMV to IMV was significantly more frequent in patients followed by multidisciplinary clinics and it was almost invariably planned in advance by the patients. The main reasons for the transition were the use of NIMV for more than 20 hours/day, acute respiratory infections and increased difficulty in clearing secretions.

Although several studies have reported that NIMV increases survival, the effect on patients’ outcome of NIMV and IMV is still controversial.3-5 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. 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 multivariate 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,4,5 Umberto Manera,5 Rosario Vasta,6 Maurizio Grassano,7 Francesca Palumbo,6 Maria Claudia Torriero,9 Luca Solero,9 Alessio Mattei,10 Fulvia Ribolla,10 Nicola Launard,11 Fabiola De Marchi,11 Letizia Mazzini,11 Gabriele Mora,11 Andrea Calvo15

1Rita Levi Montalcini’ Department of Neuroscience, University of Turin, Turin, Italy; 2ALS Center, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; 3Department of Neuroscience, University of Turin, Turin, Italy; 4Rita Levi Montalcini’ Department of Neuroscience, University of Turin, Turin, Italy; 5Rita Levi Montalcini’ Department of Neuroscience, University of Turin, Turin, Italy; 6Rita Levi Montalcini’ Department of Neuroscience, University of Turin, Turin, Italy; 7Rita Levi Montalcini’ Department of Neurology, University of Turin, Italy; 8Rita Levi Montalcini’ Department of Neurology, University of Turin, Italy; 9Rita Levi Montalcini’ Department of Neurology, University of Turin, Italy; 10Rita Levi Montalcini’ Department of Neurology, University of Turin, Italy; 11Rita Levi Montalcini’ Department of Neurology, University of Turin, Italy; 12Rita Levi Montalcini’ Department of Neurology, University of Turin, Italy; 13Rita Levi Montalcini’ Department of Neurology, University of Turin, Italy; 14Rita Levi Montalcini’ Department of Neurology, University of Turin, Italy; 15Rita Levi Montalcini’ Department of Neurology, University of Turin, Italy

**Correspondence to** Professor Adriano Chio, Department of Neuroscience, University of Turin, 10124 Turin, Italy; achio@uni.to

**Twitter** Alessio Mattei @mattae_ Alessio

**Acknowledgements** Our special thanks to our colleagues Dr Giuseppe Tabbia, Dr Marco Michele Bardessoni, Dr Michela Belloccia, Dr Chiara Chiapperio, Dr Paola Calvi, Dr Elena Rindone, Dr Luana Focaraccio, Dr Cinzia Ferrero, Dr Enio Mantellini, Dr Lorenzo Appendini, Dr Biagio Polla, Dr Alessandro Mastinu, Andrea Tagliabue and Sandro Longu for their valuable collaboration in ALS patients respiratory management.

**Contributors** A Chio: Study concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding; study supervision. CM: Data collection; critical revision of the manuscript for important intellectual content; administrative, technical and material support. A Canosa: Data collection; data analysis; critical revision of the manuscript for important intellectual content. CR: Data collection; data analysis; critical revision of the manuscript for important intellectual content. L: Data collection; critical revision of the manuscript for important intellectual content. M: Data collection; critical revision of the manuscript for important intellectual content. A: Data collection; data analysis; drafting of the manuscript; study supervision. FP: data collection; critical revision of the manuscript for important intellectual content; administrative, technical and material support. MG: Data collection; critical revision of the manuscript for important intellectual content; administrative, technical and material support. LS: Data collection; drafting of the manuscript; study supervision. FR: Data collection; critical revision of the manuscript for important intellectual content; administrative, technical and material support. AM: Data collection; critical revision of the manuscript for important intellectual content; administrative, technical and material support. NV: Data collection; critical revision of the manuscript for important intellectual content; administrative, technical and material support.

**Funding** None.

**Ethical approval** Ethics committee approval was obtained from the ethics committee of the Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Turin, Italy.

**Conflict of interest** None.

**Data sharing** Available from the corresponding author on reasonable request.

**Guarantor** A Chio.

**Supplemental material** Supplementary tables 1-4 are available as online supplemental material.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Accepted** 11 July 2022.
manuscript for important intellectual content; study supervision. A Calvo: Study concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision.

**Funding** This work was supported by the Italian Ministry of Health (Ministero della Salute, Ricerca Sanitaria Finalizzata, grant RF-2016-02362405); the Progetti di Rilevante Interesse Nazionale programme of the Ministry of Education, University and Research (grant 20175WSM8); the European Commission’s Health Seventh Framework Programme (FP7/2007–2013 under grant agreement 259867); and the Joint Programme–Neurodegenerative Disease Research (Strength, ALS-Care and Brain-Mend projects), granted by Italian Ministry of Education, University and Research. This study was performed under the Department of Excellence grant of the Italian Ministry of Education, University and Research to the “Rita Levi Montalcini” Department of Neuroscience, University of Turin, Italy, and to the Department of Health Sciences, University of Eastern Piedmont, Novara, Italy.

**Disclaimer** The funders had no role in data collection or analysis and did not participate in writing or approving the manuscript.

**Competing interests** CM, A Canosa, UM, RV, FP, MCT, LS, AM, FR, NL, FDM, LM, GM: No disclosures. A Calvo has received a research grant from Cytokinetics. A Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Denali Pharma, Cytokinetics, Lilly and Amylyx.

**Patient consent for publication** Not applicable. 

**Ethics approval** This study involves human participants and was approved by the Comitato Etico Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Torino (#355732), and Comitato Etico Azienda Ospedaliero-Universitaria Maggiore della Carità, Novara (#6739A4). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or conclusions discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**OPEN ACCESS**

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on non-commercial terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/. © Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

- Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-327968).

GM and AC contributed equally.

To cite Chio A, Moglia C, Canosa A, et al. J Neurol Neurosurg Psychiatry 2022;0:1–3. doi:10.1136/jnnp-2021-327968

Accepted 5 September 2021

**ORCID id**

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 Torri http://orcid.org/0000-0001-9312-7497

Andrea Calvo http://orcid.org/0000-0002-5122-7243

**REFERENCES**


