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Adherence to riluzole therapy in patients with amyotrophic lateral sclerosis in three Italian regions—The CAESAR study

Sabrina Giometto[1] | Marco Finocchietti[2] | Olga Paoletti[3] | Niccolò Lombardi[4] | Maria Grazia Celani[5] | Francesco Sciancalepore[6] | Ersilia Lucenteforte[1] | Ursula Kirchmayer[2] | CAESAR study group

[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[2]Department of Epidemiology, ASL Roma 1, SSR Lazio, Rome, Italy

[3]Regional Health Agency of Tuscany, Florence, Italy

[4]Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

[5]Hospital of Perugia, Neurophysiopathology, Perugia, Italy

[6]National Center for Disease Prevention and Health Promotion, Italian National Institute of Health, Rome, Italy

Correspondence
Marco Finocchietti, Department of Epidemiology ASL Roma 1, SSR Lazio, Cristoforo Colombo 112, Rome, Italy.
Email: m.finocchietti@deplazio.it

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Abstract

Purpose: Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease. Riluzole may increase survival and delay the need for mechanical ventilation. The CAESAR project ('Comparative evaluation of the efficacy and safety of drugs used in rare neuromuscular and neurodegenerative diseases', FV AIFA project 2012-2013-2014) involves evaluating prescribing patterns, and analysing effectiveness and comparative safety of drugs, in patients with neurodegenerative diseases. The aim of this study is to evaluate adherence to riluzole in patients with ALS during the first year of use, identifying adherence clusters.

Methods: A retrospective cohort study was conducted using administrative data from Latium, Tuscany, and Umbria. We identified subjects with a new diagnosis of ALS between 2014 and 2019, with the first dispensation of riluzole within 180 days of diagnosis. We considered a two-year look-back period for the characterization of patients, and we followed them from the date of first dispensing of riluzole for 1 year. We calculated 12 monthly adherence measures, through a modified version of the Medication Possession Ratio, estimating drug coverage with Defined Daily Dose. Adherence trajectories were identified using a three-step method: (1) calculation of statistical measures; (2) principal component analysis; (3) cluster analysis. Patient characteristics at baseline and during follow-up were described and compared between adherence groups identified.

Results: We included 264 ALS patients as new users of riluzole in Latium, 344 in Tuscany, and 63 in Umbria. We observed a higher frequency of males (56.2%) and a mean age of 67.4 (standard deviation, SD, 10.4) in the overall population. We identified two clusters in all regions: one more numerous, including adherent patients (60%, 74%, 88%, respectively), and another one including patients who discontinued therapy (40%, 26%, 12%, respectively). In Tuscany patients discontinuing riluzole more frequently died (28.6% vs. 15.4%, *p*-value <0.01). Additionally, low-adherers had a higher frequency of central nervous system disorders (69.0% vs. 52.5%, *p*-value 0.01), and a greater use of non-pharmacological treatments (*p*-values ≤0.01 for

invasive ventilation and tracheostomy). We did not observe any differences in Lazio, whereas in Umbria we observed a higher use of drugs for dementia-related psychiatric problems among low-adherers (57.1% vs. 7.8%, respectively, *p*-value <0.01), although with small numbers.

Conclusion: Most ALS patients who start riluzole adhere to therapy during the first year. Patients who discontinue therapy early show greater fragility and mortality.

KEYWORDS
adherence, administrative databases, amyotrophic lateral sclerosis, riluzole

Key Points

- The objective of this study is to provide a description of the longitudinal utilization of riluzole and classify subjects based on their adherence patterns in a population-based study.
- To the best of our knowledge, this is the first study evaluating longitudinal adherence to riluzole in ALS patients.
- Less than half of ALS patients initiate riluzole treatment within 180 days from diagnosis.
- During the first year, the majority of ALS patients who initiate riluzole treatment within 180 days of diagnosis demonstrate adherence to therapy.
- Patients who discontinue therapy early show greater fragility and mortality.

Plain Language Summary

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease affecting the nervous system. Riluzole is a medication that has shown potential to increase survival. The CAESAR project aims to evaluate effectiveness, and safety of drugs used in rare neuromuscular and neurodegenerative diseases. This study focuses on evaluating adherence to riluzole among ALS patients during the first year of treatment and identifying adherence clusters. It is a retrospective cohort study based on administrative data from three Italian regions: Latium, Tuscany, Umbria. ALS patients who received their first dispensation of riluzole within 180 days of diagnosis were included. Researchers calculated monthly adherence measures, and used statistical methods to identify adherence clusters. The analysis revealed two adherence clusters: one group comprised patients adherent to riluzole therapy, while the other included patients who discontinued treatment. Patients who discontinued riluzole showed a higher mortality. Additionally, low adherers showed a higher frequency of central nervous system disorders and had a greater use of non-pharmacological treatments. In conclusion, most ALS patients who initiated riluzole treatment adhered to therapy. These findings provide insights into the adherence patterns related to riluzole treatment in ALS patients, which can assist healthcare professionals in optimizing patient management strategies.

1 | INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a fatal heterogeneous neurodegenerative disease characterised by progressive muscular paralysis reflecting the degeneration of motor neurons in the cerebral cortex, brain stem and spinal cord, generally rapid as well as associated frontotemporal spectrum dysfunction.[1] The estimated prevalence in the European population is 2.6–3.0/100 000 inhabitants and is higher in males, affecting 1.2–1.5 males for every female.[2] The estimated incidence ranged from 1.92 in North Europe to 2.35 in West Europe.[3] In Italy, prevalence estimates have been produced using prospective registries, and range between 7.54, 7.89 and 11.2.[4–6] While the risk of developing ALS is highest between 50 and 75 years of age, there is heterogeneity in the age of manifestation.[7,8] The site of disease onset, rate of progression, and survival also vary widely, but in most cases, respiratory failure leads to death 3–4 years after onset.[8,9] Riluzole is the first drug that has demonstrated efficacy in slowing disease progression and increasing survival in clinical trials.[10] These results have also been observed in observational studies.[11–14] Furthermore, riluzole is currently the only approved drug for ALS in Italy.[15] As a chronic drug, adherence to therapy is necessary to achieve the expected benefits. Low levels of adherence to chronic therapies have significant negative effects on the effectiveness of the treatment, and therefore on the patient's quality of life and on the economic expenditure of the healthcare system.[16] The adherence to therapy can be influenced by several aspects, such as social, economic, healthcare, disease characteristics,

and type of therapy.[17] Specifically, a higher adherence to riluzole treatment seems to prolong survival or tracheostomy-free time.[14]

However, scientific evidence regarding adherence to riluzole treatment in patients with ALS and associated factors is limited. The evidence comes from a few observational studies published in the past 5 years. The studies included between 45 and 681 patients and reported average adherence values ranging from 75% to 91%.[14,18–20] However, the results of these studies do not provide information on the pattern of riluzole use, as they report single adherence values for the entire observation period, expressed as Medication Possession Ratio (MPR), Proportion of Days Covered (PDC), or self-reporting scale.[14,18–20] Investigating the longitudinal pattern allows to capture the dynamic nature of adherence and takes into account the timing of treatment interruptions.

The present study aims to describe the use of riluzole over time and to cluster patients according to adherence behaviour. Moreover, selected characteristics (demographic information, complications, comorbidities, pharmacological and non-pharmacological therapy, healthcare service use) were explored as potential predictors of adherence. The study is part of the CAESAR project ('Comparative evaluation of the efficacy and safety of drugs used in rare neuromuscular and neurodegenerative diseases', AIFA call FV 2012-13-14).[21]

2 | METHODS

We conducted a retrospective cohort study on subjects newly diagnosed with ALS between 2014 and 2019, who received their first dispensation of riluzole within 180 days of diagnosis. The study employed administrative databases from the regions of Latium, Tuscany, and Umbria. The study protocol was published on the ENCePP website with the registry number EUPAS37983.

2.1 | Data source

We employed the following administrative databases from each Italian region in the study, which were linked to one another through a pseudo-anonymised unique key:

- Health care enrolment registry, which included demographic data (date of birth, sex) and regional start and end dates of enrolment in the public health care assistance. All citizens residing in Italy are covered by the National Healthcare System administered at regional level and, therefore, included in the databases used in this study.
- Hospital discharge registry, which included ICD-9-CM diagnosis codes (both primary and secondary) and procedure codes, and dates of hospital admission and discharge.
- Emergency department visits, which included ICD-9-CM diagnosis codes (both primary and secondary) and procedure codes, and dates of access and discharge to emergency care.
- Exemption from co-payment registry, which included the Italian exemption code, and dates of exemption release. In Italy, citizens pay a co-payment for any healthcare service. However, citizens with chronic illnesses are entitled to full or partial exemption from the co-payment.
- Outpatient services registry, which included specialist examinations and diagnostic tests coded according to the national nomenclature.
- Drug dispensing records, for all drugs reimbursed for outpatients, which included Anatomical Therapeutic Chemical (ATC) and national marketing authorization (AIC) codes, number of packages dispensed, and dispensation dates.

The Latium region produced the scripts for the creation of analytical datasets in all three regions based on a common data model. Then, each region analysed its own data locally, sharing only summary tables on aggregated data, thus complying with the national and regional privacy legislation.

2.2 | Study population and cohort selection

Subjects with a diagnosis of ALS were defined as one of the following: hospital discharge with primary diagnosis coded as ICD-9-CM 335.20 or with secondary diagnosis when discharged from neurology ward; ALS specific co-payment exemption (code RF0100); primary diagnosis of ALS from Emergency Department visits between 2014 and 2019, and no diagnosis of ALS in the previous 3 years. Among these newly diagnosed ALS patients, those who received a dispensation of riluzole (ATC code N07XX02) within 180 days of diagnosis, and had not received a dispensation in the previous year, were identified (new users). A time-window of 180 days from diagnosis was considered, as it had previously been observed that an early initiation of therapy within this period allows for a gain in terms of survival months.[13] The date of first diagnosis was defined as the cohort enrolment date. Subjects who were younger than 18 years, not enrolled in the regional healthcare service on that date or during the three previous years, and those who died within 30 days of diagnosis were excluded. Subjects were followed for 1 year from the date of the first riluzole dispensation (index date), and were censored for death or emigration from the region of residence, in order to avoid misclassification, as administrative data do not allow for reliable data after a change of residence to another region.

2.3 | Variable of interest: pattern of adherence

To identify patterns of riluzole use over time, we computed 12 monthly adherence measures during the one-year-observation period. To this end, we applied a modified version of the MPR, which is defined as the ratio of the total drug supply to the duration of the observation period[22]: to calculate the numerator, we subtracted the days not covered by the drug from the observation period, taking into account overlapping periods of drug coverage that occurred when the end of one dispensation's coverage was after the start of the next dispensation. For each patient, we used the Defined Daily Dose (DDD) to calculate drug coverage. We then calculated adherence by dividing the numerator by the number of days of the individual follow-up, which was considered as the denominator.

2.4 | Covariates

We considered the following characteristics as covariates: demographic information (age and gender), ALS specific covariates (abnormality of gait, limb cramp, dysphagia, salivary secretion disturbance, injury-related fractures, nutritional disorders, limb or generalised pain, upper limb paraplegia and diplegia, pneumonitis caused by solids and liquids, pressure ulcer, quadriplegia and quadriparesis, sleep disorders), and comorbidities (acute and chronic respiratory failure, anxiety disorders, dysthymic disorder, presenile/senile dementia), which were referenced to the two-year prior to the cohort enrolment date (look-back period). We also considered pharmacological therapies typically prescribed to treat ALS symptoms (bronchial hypersecretion, constipation, cramps/spasms/fasciculation, decubitus, depression/anxiety, dementia, dementia related psychiatric disorders, fatigue, gastro-esophageal reflux, hypersalivation, insomnia, oral candidiasis, pain, psycho-analeptic, thrombosis/embolisms) and non-pharmacological treatments (invasive and non-invasive ventilation, percutaneous endoscopic gastrostomy, tracheostomy), which were referenced to the 1 year preceding the enrolment date (see Appendix S1–S4 in Supporting Information for specific codes).

2.5 | Statistical analysis

Adherence trajectories were identified using a three-steps method[23]: (i) calculation of 24 summary statistical measures of intra-subject variability of monthly adherence. To perform the first step, at least three consecutive non-missing adherence values are required, since some statistical measures are based on the second difference. Values of adherence equal to 0 are instead accepted. The adherence values are zero in case of no dispensation in the corresponding period of time; instead, missing adherence is reported in case of censoring of the subject. Thus, in this first step, we included only patients who met this criterion; (ii) principal component analysis was used to avoid redundancy of information. Among the 24 summary statistical measures

FIGURE 1 Flowchart of patients selection and cohort identification for the study analysis, reporting numbers overall and by region.

TABLE 1 Characteristics of ALS patients included in the cohort at baseline.

	N = 671 (100.0%)
Sex, M	377 (56.2)
Age, mean (SD)	67.4 (10.4)
ALS-specific covariates*,§ (2 years before enrolment date)	
Dysphagia	24 (3.6)
Abnormality of gait	12 (1.8)
Paraplegia and diplegia of upper limbs	9 (1.3)
Fractures caused by injury	59 (8.8)
Malnutrition	7 (1.0)
Acute respiratory failure	13 (1.9)
Chronic respiratory failure	12 (1.8)
Acute and chronic respiratory failure	9 (1.3)
Depressive disorders	15 (2.2)
Other comorbidities*,§ (2 years before enrolment date)	
Neoplasms	48 (7.2)
Endocrine, nutritional and metabolic diseases	118 (17.6)
Diseases of the blood and blood-forming organs	15 (2.2)
Mental disorders	35 (5.2)
Disorders of the central nervous system	496 (73.9)
Disorders of the peripheral nervous system	60 (8.9)
Diseases of the circulatory system	208 (31.0)
Diseases of the respiratory system	67 (10.0)
Diseases of the digestive system	50 (7.5)
Diseases of the genitourinary system	43 (6.4)
Diseases of the musculoskeletal system and connective tissue	122 (18.2)
Injury and poisoning	168 (25.0)
Drug therapy*,§ (1 year before enrolment date)	
Psychoanaleptics	5 (0.7)
Drugs against bronchial hypersecretion	117 (17.4)
Drugs against gastroesophageal reflux	358 (53.4)
Drugs against cramps, spams and muscular fasciculation	125 (18.6)
Drugs against depression, anxiety, and emotional frailty	161 (24.0)
Drugs against dementia and dementia related psychiatric disorders	14 (2.1)
Drugs against hypersalivation	2 (0.3)
Drugs against pain	292 (43.5)
Anticoagulants	281 (41.9)
Total number symptomatic drugs, mean (SD)	2.4 (1.9)
Number of other drugs (ATC 4th level)	
≤1	140 (20.9)
2–5	304 (45.3)
6+	227 (33.8)
Non-pharmacological treatments*,§ (1 year before enrolment date)	
Non-invasive ventilation	11 (1.6)
Invasive ventilation	2 (0.3)
Tracheostomy	1 (0.1)
Percutaneous endoscopic gastrostomy (PEG)	3 (0.4)

Abbreviations: ALS, amyotrophic lateral sclerosis; ATC, anatomical therapeutic chemical; SD, standard deviation.
*Related codes are reported in Appendix.
§Only variables present in at least 1% of the cohort are represented.

calculated in the first step, those explaining the highest proportion of variance were selected; (iii) cluster analysis was performed using the k-means method, after standardising the previously chosen measures, to group subjects with similar adherence patterns. The number of clusters was determined by combining a mathematical criterion (i.e., calculating 30 indicators based on distance measurements between clusters and following the majority rule) and a clinical plausibility criterion.

To identify potential predictors of adherence, patients' sociodemographic and clinical and therapeutic characteristics, predefined according to neurological expertise practice, were compared between clusters using a Chi-squared test, or a two-tailed t-test, as appropriate. An alpha level of 0.01 defined statistical significance.

The analyses were conducted using R software, version 4.2.1, and the following packages: AdhereR for the calculation of adherence,[24] Nbclust for the selection of the number of clusters,[25] and traj Package for the identification of trajectories.[26]

2.6 | Sensitivity analysis

We conducted two sensitivity analyses: the first one calculating monthly adherence using the PDC, that is, considering the number of days covered by the medication over the total number of observed days, without taking into account overlapping coverage periods, and the second one censoring patients for hospital admission and reconsidering them at the hospital discharge, as information on inpatient drug therapy was not available.

3 | RESULTS

We identified 2635 subjects with ALS diagnosis between 2014 and 2019: 1385 in Latium, 1020 in Tuscany, and 230 in Umbria (Figure 1). Of these, 736, 755, and 145, respectively, were incident cases of ALS, who met the inclusion and exclusion criteria. The final cohorts included 264, 344 and 63 patients who started riluzole treatment within 180 days of the cohort enrolment date, respectively. We excluded 149 subjects out of 736 (20%), 265 out of 755 (35%), and 34 out of 145 (25%) due to prevalent use of riluzole, respectively, and 323 out of 587 (55%), 146 out of 490 (30%), and 48 out of

TABLE 2 Characteristics of ALS patients included in the cohort during follow-up.

	N = 671 (100.0%)
Death	154 (23.0)
ALS-specific covariates*,§ (1 year after index date)	
Dysphagia	67 (10.0)
Pneumonitis due to solids and liquids	22 (3.3)
Abnormality of gait	7 (1.0)
Fractures caused by injury	45 (6.7)
Malnutrition	8 (1.2)
Pressure ulcer	8 (1.2)
Sleep disturbances	67 (10.0)
Acute respiratory failure	95 (14.2)
Chronic respiratory failure	81 (12.1)
Acute and chronic respiratory failure	121 (18.0)
Anxiety state	8 (1.2)
Depressive disorders	6 (0.9)
Other comorbidities*,§ (1 year after index date)	
Neoplasms	19 (2.8)
Endocrine, nutritional and metabolic diseases, and immunity disorders	79 (11.8)
Diseases of the blood and blood-forming organs	18 (2.7)
Mental disorders	22 (3.3)
Disorders of the central nervous system	354 (52.8)
Disorders of the peripheral nervous system	12 (1.8)
Diseases of the circulatory system	170 (25.3)
Diseases of the respiratory system	268 (39.9)
Diseases of the digestive system	41 (6.1)
Diseases of the genitourinary system	41 (6.1)
Diseases of the musculoskeletal system and connective tissue	26 (3.9)
Symptoms, signs, and ill-defined conditions	174 (25.9)
Injury and poisoning	151 (22.5)
Drug therapy*,§ (1 year after index date)	
Psychoanaleptics	268 (39.9)
Drugs against bronchial hypersecretion	197 (29.4)
Drugs against gastroesophageal reflux	379 (56.5)
Drugs against cramps, spams and muscular fasciculation	399 (59.5)
Drugs against depression, anxiety, and emotional frailty	355 (52.9)
Drugs against dementia and dementia related psychiatric disorders	50 (7.5)
Drugs against hypersalivation	15 (2.2)
Drugs against insomnia	14 (2.1)
Drugs against pain	235 (35.0)
Anticoagulants	322 (48.0)
Total number symptomatic drugs, mean (SD)	4.6 (2.9)
Number of other drugs (ATC 4th level)	
≤1	96 (14.3)
2–5	289 (43.1)
6+	286 (42.6)
Non-pharmacological treatments*,§ (1 year after index date)	
Non-invasive ventilation	94 (14.0)
Invasive ventilation	72 (10.7)
Tracheostomy	50 (7.5)
Percutaneous endoscopic gastrostomy (PEG)	97 (14.5)

Abbreviations: ALS, amyotrophic lateral sclerosis; ATC, anatomical therapeutic chemical; SD, standard deviation.
*Related codes are reported in Appendix.
§Only variables present in at least 1% of the cohort are represented.

111 (43%) because they did not receive the medication within 180 days from diagnosis, respectively.

Patient characteristics are summarised in Table 1 (baseline characteristics) and Table 2 (characteristics during follow-up). Table 1 shows a higher frequency of males (56.2%) and a mean age of 67.4 (standard deviation, SD, 10.4) in the overall study population. In the 2 years prior to diagnosis, the most commonly observed complication was fractures caused by accidents (8.8%). The most frequent comorbidity was disorders of the central nervous system (73.9%). Regarding treatment in the year prior to diagnosis, the most frequently observed pharmacological treatment apart from gastroprotection (53.4%) were drugs against pain (43.5%), followed by anticoagulants (41.9%), and drugs against depression and anxiety (24.0%). The percentage of non-pharmacological treatments was low, ranging from 0.1% to 1.6%. We observed a frequency of 23.0% of patients who died during the one-year follow-up period (Table 2). The most commonly observed complication was acute and chronic respiratory failure (18.0%), and the most frequent comorbidities were disorders of the central nervous system (52.8%), and diseases of the respiratory system (39.9%). More than half of the patients were treated with drugs against cramps and spasms (59.5%), drugs against gastroesophageal reflux (56.5%), and drugs against depression and anxiety (52.9%). The frequency of non-pharmacological treatments ranged between 7.5% and 14.5%, with PEG and non-invasive ventilation on top. We observed differences between regions in some of the characteristics considered (Appendix S5a and S5b). In general, we observed an increase in the frequency of comorbidities, use of pharmacological and non-pharmacological treatments during the follow-up period compared to baseline.

Two adherence trajectories to riluzole therapy were identified in all regions (Figure 2). In Latium, Tuscany and Umbria, a larger group of high-adherers (60.2%, 74.1%, and 87.9%, respectively) had adherence values above 90% in the first two regions, and around 80% in Umbria, throughout the follow-up. In a smaller group (39.8%, 25.9%, and 12.1%, respectively) adherence declined to values around 50% after 4 months in Latium and Tuscany, and after less than 2 months in

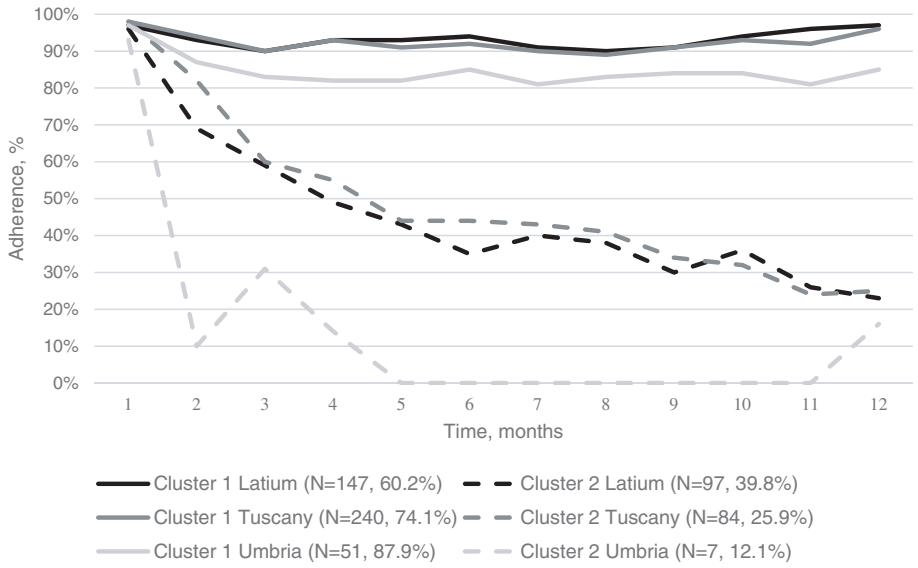

FIGURE 2 Trajectories of adherence to riluzole in incident ALS patients new-users of the drug in the three Italian regions: Latium, Tuscany, and Umbria.

Umbria, with around 20% being adherent at the end of the follow-up period. Both sensitivity analyses conducted, which excluded overlapping drug coverage in the first analysis and censored for hospital admission and reintroduced at discharge in the second analysis, confirmed the results obtained in the main analysis (Appendix S6 and S7).

Comparing characteristics between the adherent and non-adherent patient groups at baseline (Table 3), we observed differences between clusters and regions for age, gender, and several clinical and therapeutic features, frequently showing higher proportions of complications, comorbidities and drug therapy in low-adherers. Yet, the only statistically significant results were detected for diseases of the respiratory system in Umbria (57.1% vs. 7.8%, *p*-value <0.01), based on small numbers.

Regarding the comparison during follow-up (Table 4), differences were similar to those at baseline, with generally higher proportions across clusters and regions, but only few cases of statistical significance. Death occurred more frequently in low-adherers, and this was particularly evident in Tuscany (28.6% in low-adherers vs. 15.4% in high-adheres, *p*-value <0.01). Regarding ALS specific covariates, respiratory failure was more frequently reported in low-adherers in Tuscany and Umbria (Tuscany: acute respiratory failure and acute and chronic respiratory failure 29.8% in low-adherers vs. 13.3% in high-adheres, *p*-value <0.01, and 29.8% vs. 15.4%, *p*-value 0.01, respectively). Similarly, in Tuscany low-adherers had a higher prevalence of central nervous system disorders (69.0% vs. 52.5%, *p*-value 0.01), diseases of the circulatory system (39.3% vs. 21.2%, *p*-value <0.01), and diseases of the respiratory system (53.6% vs. 32.9%, respectively, *p*-value <0.01). Also higher proportions of use of non-pharmacological treatments were observed in low-adherers, especially in Tuscany for invasive ventilation and tracheostomy (19.0% vs. 7.1%, 17.9% vs. 4.2%, *p*-values <0.01, <0.01, respectively). In Umbria, differences were observed between the two adherence groups in terms of medication use during follow-up, with a higher use of drugs for dementia-related psychiatric problems among low-adherers (57.1% vs. 7.8%, respectively, *p*-value <0.01). However, these are small numbers, as the region has a small population.

4 | DISCUSSION

In this study, we investigated adherence to riluzole treatment in ALS patients across three Italian regions: Latium, Tuscany and Umbria. We observed that the majority of ALS patients who initiated treatment with riluzole within 180 days of diagnosis are adherent to therapy during the first year. To the best of our knowledge, this is the first study evaluating longitudinal adherence to riluzole ALS patients.

Previous studies evaluating adherence to riluzole in ALS patients reported a single mean or median value[14,19,20] or adherence classes,[18] over the entire follow-up period. The first of these studies is an Italian multicentre study published in 2018, which calculated adherence through the PDC over a follow-up period of up to 7 years. It reported a mean adherence of 75% and a median adherence of 90%. Additionally, a protective effect of longer periods of riluzole use in terms of survival was observed, resulting in an almost doubled gain in months.[14] The second one is an Italian single-centre study published in 2018, which evaluated adherence in 45 patients through the Morisky Medication Adherence Scale.[18] The study described 27% patients as highly adherent, 35% patients as moderately adherent, and 38% patients as poorly adherent. The third one is a Portuguese single-centre study published in the same year, which assessed adherence using hospital records of 77 patients and calculated drug coverage using DDDs.[19] This study showed a mean MPR of 91% and a median of 99%. Finally, an American single-centre study published in 2022 evaluated adherence based on self-reported medication use by 508 patients.[20] This study reported a median PDC of 64%.

Our adherence values were consistent with those described in literature, with slight differences presumably attributable to the measurement used to quantify adherence. MPR produces higher values,

TABLE 3 Characteristics of ALS patients at baseline, stratified by region and adherence cluster.

	Latium		Tuscany		Umbria	
	High-adherence cluster ($N = 147$)	Low-adherence cluster ($N = 97$)	High-adherence cluster ($N = 240$)	Low-adherence cluster ($N = 84$)	High-adherence cluster ($N = 51$)	Low-adherence cluster ($N = 7$)
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Sex, M	90 (61.2)	47 (48.5)	133 (55.4)	46 (54.8)	27 (52.9)	4 (57.1)
Age (mean (SD))	65.4 (9.4)	65.9 (11.0)	67.3 (10.9)	69.1 (10.4)	68.8 (9.7)	68.7 (12.0)
ALS-specific covariates*,§ (2 years before enrolment date)						
Dysphagia	3 (2.0)	2 (2.1)	8 (3.3)	6 (7.1)	1 (2.0)	-
Abnormality of gait	-	2 (2.1)	6 (2.5)	4 (4.8)	-	-
Paraplegia and diplegia of upper limbs	1 (0.7)	-	4 (1.7)	3 (3.6)	-	-
Fractures caused by injury	12 (8.2)	6 (6.2)	25 (10.4)	7 (8.3)	3 (5.9)	1 (14.3)
Malnutrition	2 (1.4)	2 (2.1)	2 (0.8)	-	-	-
Acute respiratory failure	5 (3.4)	3 (3.1)	3 (1.2)	-	-	-
Chronic respiratory failure	5 (3.4)	3 (3.1)	3 (1.2)	1 (1.2)	-	-
Acute and chronic respiratory failure	1 (0.7)	2 (2.1)	3 (1.2)	-	1 (2.0)	1 (14.3)
Anxiety state	-	-	1 (0.4)	1 (1.2)	3 (5.9)	-
Depressive disorders	2 (1.4)	-	5 (2.1)	5 (6.0)	-	1 (14.3)
Other comorbidities*,§ (2 years before enrolment date)						
Neoplasms	11 (7.5)	7 (7.2)	15 (6.2)	3 (3.6)	3 (5.9)	-
Endocrine, nutritional and metabolic diseases	19 (12.9)	15 (15.5)	52 (21.7)	13 (15.5)	6 (11.8)	3 (42.9)
Diseases of the blood and blood-forming organs	1 (0.7)	2 (2.1)	6 (2.5)	2 (2.4)	2 (3.9)	-
Mental disorders	3 (2.0)	1 (1.0)	14 (5.8)	8 (9.5)	4 (7.8)	1 (14.3)
Disorders of the central nervous system	86 (58.5)	56 (57.7)	202 (84.2)	69 (82.1)	42 (82.4)	-
Disorders of the peripheral nervous system	9 (6.1)	6 (6.2)	24 (10.0)	13 (15.5)	5 (9.8)	-
Diseases of the circulatory system	37 (25.2)	26 (26.8)	80 (33.3)	26 (31.0)	18 (35.3)	2 (28.6)
Diseases of the respiratory system	15 (10.2)	13 (13.4)	19 (7.9)	6 (7.1)	4 (7.8)[a]	4 (57.1)[a]
Diseases of the digestive system	14 (9.5)	8 (8.2)	13 (5.4)	10 (11.9)	2 (3.9)	-
Diseases of the genitourinary system	10 (6.8)	3 (3.1)	18 (7.5)	3 (3.6)	4 (7.8)	-
Diseases of the musculoskeletal system and connective tissue	17 (11.6)	19 (19.6)	45 (18.8)	19 (22.6)	12 (23.5)	-
Injury and poisoning	34 (23.1)	24 (24.7)	62 (25.8)	21 (25.0)	8 (15.7)	3 (42.9)
Drug therapy at baseline*,§ (1 year before enrolment date)						
Psychoanaleptics	-	1 (1.0)	4 (1.7)	-	-	-
Drugs against bronchial hypersecretion	25 (17.0)	19 (19.6)	39 (16.2)	15 (17.9)	8 (15.7)	2 (28.6)
Drugs against gastroesophageal reflux	86 (58.5)	62 (63.9)	111 (46.2)	43 (51.2)	29 (56.9)	5 (71.4)
Drugs against cramps, spams and muscular fasciculation	33 (22.4)	23 (23.7)	38 (15.8)	17 (20.2)	6 (11.8)	-

TABLE 3 (Continued)

	Latium		Tuscany		Umbria	
	High-adherence cluster (*N* = 147)	Low-adherence cluster (*N* = 97)	High-adherence cluster (*N* = 240)	Low-adherence cluster (*N* = 84)	High-adherence cluster (*N* = 51)	Low-adherence cluster (*N* = 7)
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Drugs against depression, anxiety, emotional frailty	28 (19.0)	20 (20.6)	56 (23.3)	28 (33.3)	14 (27.5)	2 (28.6)
Drugs against dementia and dementia related psychiatric disorders	1 (0.7)	2 (2.1)	7 (2.9)	2 (2.4)	2 (3.9)	-
Drugs against pain	67 (45.6)	44 (45.4)	98 (40.8)	41 (48.8)	16 (31.4)	4 (57.1)
Anticoagulants	63 (42.9)	41 (42.3)	100 (41.7)	31 (36.9)	22 (43.1)	4 (57.1)
Total number symptomatic drugs, mean (SD)	2.4 (1.8)	2.6 (1.8)	2.2 (1.9)	2.6 (2.2)	2.3 (2.2)	2.9 (2.3)
Number of other drugs (ATC 4th level)						
≤1	18 (12.2)	21 (21.6)	54 (22.5)	20 (23.8)	14 (27.5)	3 (42.9)
2–5	78 (53.1)	37 (38.1)	115 (47.9)	36 (42.9)	22 (43.1)	-
6+	51 (34.7)	39 (40.2)	71 (29.6)	28 (33.3)	15 (29.4)	4 (57.1)
Non-pharmacological treatments*,§ at baseline (1 year before enrolment date)						
Non-invasive ventilation	5 (3.4)	3 (3.1)	1 (0.4)	-	1 (2.0)	1 (14.3)
Invasive ventilation	-	-	-	1 (1.2)	-	1 (14.3)
Tracheostomy	-	-	-	-	-	1 (14.3)
Percutaneous endoscopic gastrostomy (PEG)	-	-	-	1 (1.2)	-	-

Abbreviations: ALS, amyotrophic lateral sclerosis; ATC, anatomical therapeutic chemical; SD, standard deviation.
*Related codes are reported in Appendix.
§Only variables present in at least 1% of the cohort are represented.
[a]*p*-value from *t*-test or Chi-squared test lower than 0.01.

even above 100%, whereas PDC produces lower values by not considering overlapping coverage periods. Since we used a modified version of the MPR, which accounts for overlapping medication coverage but cannot report values higher than 100%, our findings were intermediate between the results reported by Paróla et al. and Geronimo et al. Furthermore, since we separated subjects into two groups by clustering them based on their adherence pattern, our results cannot be entirely compared to those of other studies in literature. The cluster analysis yielded one larger group including high adherers and a smaller group including patients who discontinued riluzole treatment early. These findings indicate that most ALS patients who initiate riluzole treatment within 180 days of diagnosis remain adherent during the first year of use.[13]

We also investigated potential differences in clinical and therapeutic conditions associated with the different adherence clusters and found that patients discontinuing riluzole treatment more frequently die and are generally more fragile. This suggests that treatment with riluzole, which impacts life expectancy, may be discontinued when the patient enters a critical condition, close to end-of-life, in order to alleviate the burden of drug intake. During this phase, pharmacological treatments aimed at reducing symptoms become more important, with the most frequent ones being dyspnoea, pain, and fatigue.[27] Accordingly, patients in the low-adherence group more frequently underwent non-pharmacological treatment following the initiation of riluzole therapy, such as ventilation, tracheostomy, and PEG, which are proxies for a decline in patients' health conditions. These findings are in line with the fact that riluzole is contraindicated after tracheostomy.[28] Our findings of a general increase in the frequency of comorbidities, use of pharmacological and non-pharmacological treatments during the follow-up period compared to baseline may be partly explained by closer monitoring of patients and response to their health needs after the diagnosis.

The present study has several strengths. First, since this is a population-based study, the identified cohort is not selected, and the analysis includes a large cohort, despite the rarity of the disease. The drugs under study are all reimbursed by the health care service and are therefore well retrievable. Even if information on individual doses is not available in our databases, in the case of riluzole, the DDD is a valid proxy, as it corresponds to the standard dose used in clinical practice in Italy. Second, this is a multicentre study, providing evidence from different Italian regions that represent approximately

TABLE 4 Characteristics of ALS patients during follow-up, stratified by region and adherence cluster.

	Latium		Tuscany		Umbria	
	High-adherence cluster (*N* = 147)	Low-adherence cluster (*N* = 97)	High-adherence cluster (*N* = 240)	Low-adherence cluster (*N* = 84)	High-adherence cluster (*N* = 51)	Low-adherence cluster (*N* = 7)
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Death	17 (11.6)	17 (17.5)	37 (15.4)[a]	24 (28.6)[a]	14 (27.5)	2 (28.6)
ALS-specific covariates[*,§] during follow-up (1 year after index date)						
Dysphagia	5 (3.4)	4 (4.1)	30 (12.5)	17 (20.2)	8 (15.7)	-
Pneumonitis due to solids and liquids	-	-	9 (3.8)	6 (7.1)	2 (3.9)	-
Abnormality of gait	-	-	5 (2.1)	2 (2.4)	-	-
Fractures caused by injury	12 (8.2)	4 (4.1)	17 (7.1)	8 (9.5)	3 (5.9)	1 (14.3)
Malnutrition	1 (0.7)	1 (1.0)	2 (0.8)	2 (2.4)	2 (3.9)	-
Pressure ulcer	1 (0.7)	2 (2.1)	-	2 (2.4)	2 (3.9)	-
Sleep disturbances	1 (0.7)	-	3 (1.2)	-	-	-
Acute respiratory failure	7 (4.8)	4 (4.1)	32 (13.3)[a]	25 (29.8)[a]	13 (25.5)	2 (28.6)
Chronic respiratory failure	30 (20.4)	16 (16.5)	18 (7.5)	8 (9.5)	7 (13.7)	1 (14.3)
Acute and chronic respiratory failure	24 (16.3)	15 (15.5)	37 (15.4)[a]	25 (29.8)[a]	11 (21.6)	1 (14.3)
Anxiety state	-	1 (1.0)	5 (2.1)	-	1 (2.0)	1 (14.3)
Depressive disorders	-	-	4 (1.7)	1 (1.2)	1 (2.0)	-
Other comorbidities[*,§] during follow-up (1 year after index date)						
Neoplasms	1 (0.7)	-	8 (3.3)	2 (2.4)	3 (5.9)	-
Endocrine, nutritional and metabolic diseases, and immunity disorders	13 (8.8)	7 (7.2)	26 (10.8)	17 (20.2)	13 (25.5)	2 (28.6)
Diseases of the blood and blood-forming organs	2 (1.4)	-	6 (2.5)	3 (3.6)	4 (7.8)	2 (28.6)
Mental disorders	2 (1.4)	3 (3.1)	10 (4.2)	3 (3.6)	3 (5.9)	1 (14.3)
Disorders of the central nervous system	71 (48.3)	44 (45.4)	126 (52.5)[a]	58 (69.0)[a]	31 (60.8)	4 (57.1)
Disorders of the peripheral nervous system	-	1 (1.0)	6 (2.5)	3 (3.6)	2 (3.9)	-
Diseases of the circulatory system	35 (23.8)	23 (23.7)	51 (21.2)[a]	33 (39.3)[a]	18 (35.3)	-
Diseases of the respiratory system	61 (41.5)	34 (35.1)	79 (32.9)[a]	45 (53.6)[a]	25 (49.0)	4 (57.1)
Diseases of the digestive system	10 (6.8)	7 (7.2)	14 (5.8)	9 (10.7)	1 (2.0)	-
Diseases of the genitourinary system	7 (4.8)	4 (4.1)	13 (5.4)	8 (9.5)	5 (9.8)	1 (14.3)
Diseases of the musculoskeletal system and connective tissue	5 (3.4)	2 (2.1)	11 (4.6)	5 (6.0)	1 (2.0)	1 (14.3)
Symptoms, signs, and ill-defined conditions	25 (17.0)	21 (21.6)	70 (29.2)	30 (35.7)	17 (33.3)	1 (14.3)
Injury and poisoning	34 (23.1)	15 (15.5)	64 (26.7)	23 (27.4)	10 (19.6)	2 (28.6)
Drug therapy[*,§] during follow-up (1 year after index date)						
Psychoanaleptics	47 (32.0)	23 (23.7)	144 (60.0)	41 (48.8)	4 (7.8)	-
Drugs against bronchial hypersecretion	37 (25.2)	38 (39.2)	69 (28.7)	30 (35.7)	15 (29.4)	4 (57.1)

TABLE 4 (Continued)

	Latium		Tuscany		Umbria	
	High-adherence cluster ($N = 147$)	Low-adherence cluster ($N = 97$)	High-adherence cluster ($N = 240$)	Low-adherence cluster ($N = 84$)	High-adherence cluster ($N = 51$)	Low-adherence cluster ($N = 7$)
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Drugs against gastroesophageal reflux	84 (57.1)	57 (58.8)	132 (55.0)	55 (65.5)	36 (70.6)	5 (71.4)
Drugs against cramps, spams and muscular fasciculation	70 (47.6)	35 (36.1)	193 (80.4)	61 (72.6)	21 (41.2)	1 (14.3)
Drugs against depression, anxiety, emotional frailty	66 (44.9)	41 (42.3)	154 (64.2)	49 (58.3)	31 (60.8)	5 (71.4)
Drugs against dementia and dementia related psychiatric disorders	15 (10.2)	5 (5.2)	12 (5.0)	8 (9.5)	4 (7.8)[a]	4 (57.1)[a]
Drugs against hypersalivation	6 (4.1)	5 (5.2)	1 (0.4)	1 (1.2)	2 (3.9)	-
Drugs against insomnia	-	-	11 (4.6)	2 (2.4)	1 (2.0)	-
Drugs against pain	60 (40.8)	38 (39.2)	82 (34.2)	28 (33.3)	20 (39.2)	3 (42.9)
Anticoagulants	74 (50.3)	34 (35.1)	129 (53.8)	43 (51.2)	23 (45.1)	4 (57.1)
Total number symptomatic drugs, mean (SD)	4.1 (2.7)	3.8 (2.6)	5.4 (3.0)	5.6 (3.3)	4.0 (2.4)	5.7 (4.3)
Number of other drugs (ATC 4th level)						
≤1	18 (12.2)	12 (12.4)	30 (12.5)	6 (7.1)	12 (23.5)	1 (14.3)
2–5	65 (44.2)	52 (53.6)	99 (41.2)	38 (45.2)	12 (23.5)	2 (28.6)
6+	64 (43.5)	33 (34.0)	111 (46.2)	40 (47.6)	27 (52.9)	4 (57.1)
Non-pharmacological treatments[*,§] during follow-up (1 year after index date)						
Non-invasive ventilation	33 (22.4)	14 (14.4)	19 (7.9)	15 (17.9)	8 (15.7)	1 (14.3)
Invasive ventilation	15 (10.2)	12 (12.4)	17 (7.1)[a]	16 (19.0)[a]	5 (9.8)	1 (14.3)
Tracheostomy	8 (5.4)	9 (9.3)	10 (4.2)[a]	15 (17.9)[a]	6 (11.8)	1 (14.3)
Percutaneous endoscopic gastrostomy (PEG)	17 (11.6)	16 (16.5)	31 (12.9)	20 (23.8)	11 (21.6)	1 (14.3)

Abbreviations: ALS, amyotrophic lateral sclerosis; ATC, anatomical therapeutic chemical; SD, standard deviation.
*Related codes are reported in Appendix.
[§]Only variables present in at least 1% of the cohort are represented.
[a]*p*-value from *t*-test or Chi-squared test ≤0.01.

18% of the Italian population. Moreover, the use of trajectory methodology allows for a better understanding of the use of riluzole by ALS patients, taking into account the timing of treatment interruptions with respect to other methodologies. Finally, the algorithm used to identify ALS patients from administrative healthcare databases was compared to the existing ALS registry of the Latium Region which was established in 2014 through the collaboration of 25 clinical centres, and showed a good performance to identify ALS cases. The study also has some limitations. Our data do not provide information on the duration or the severity of the disease, and our enrolment date may not be the true start of the disease.

Assessing adherence to riluzole is crucial. An increase in survival has been observed in ALS patients treated with riluzole in randomised clinical trials, where drug administration is controlled and therefore patients adhere to therapy,[10] and in observational studies.[11–14] However, all real-world studies have adopted an intention-to-treat approach, classifying patients as users even in the presence of only one prescription of riluzole, with the exception of a few.[12,14,29,30]

For this reason, further observational studies are needed to evaluate the increase in survival and time free from invasive ventilation in relation to adherence to riluzole treatment. Furthermore, given the high proportion of patients who do not initiate riluzole treatment within 180 days from diagnosis, a potential alert is brought to the attention of prescribers. In addition, the results show how the majority of patients maintain a high level of adherence, but there is still a moderate percentage that discontinues the treatment during the first

year of use; this may suggest a need for increased monitoring of patient adherence to therapy.

AUTHOR CONTRIBUTIONS

Conceptualization: Ersilia Lucenteforte and Ursula Kirchmayer. *Methodology*: Sabrina Giometto and Ersilia Lucenteforte. *Software*: Sabrina Giometto, Marco Finocchietti and Olga Paoletti. *Formal analysis*: Sabrina Giometto and Ersilia Lucenteforte. *Writing-original draft preparation*: Sabrina Giometto, Ersilia Lucenteforte and Ursula Kirchmayer. *Writing-review and editing*: all authors. *Supervision*: Ersilia Lucenteforte and Ursula Kirchmayer. *Project administration*: Ursula Kirchmayer. *Funding acquisition*: Ursula Kirchmayer. All authors have read and agreed upon the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

E.L. was involved as investigator of observational studies funded by the pharmaceutical company Galapagos in compliance with the ENCEPP Code of Conduct, and she has carried out consultancy for Angelini. The other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The individual data that support the findings of this study are not publicly available due to privacy issues, but are available in an aggregate form from the corresponding author upon reasonable request.

ETHICS STATEMENT

Patient consent was waived due to the anonymisation of data used in the study.

ORCID

Marco Finocchietti https://orcid.org/0009-0008-4265-448X
Niccolò Lombardi https://orcid.org/0000-0002-9666-0438
Ersilia Lucenteforte https://orcid.org/0000-0001-5608-5902

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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