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ORIGINAL ARTICLE

Pharmacological and non-pharmacological treatments in amyotrophic lateral sclerosis: an Italian real-world data study

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Abstract

Background and purpose: The purpose was to describe the use patterns of pharmacological and non-pharmacological therapies and investigate potential determinants of riluzole use in patients newly diagnosed with amyotrophic lateral sclerosis (ALS) in three Italian regions.

Methods: Amyotrophic lateral sclerosis patients were selected from administrative healthcare databases of Latium, Tuscany and Umbria from 1 January 2014 to 31 December 2019 based on hospital- and disease-specific co-payment exemption data. The first trace of ALS was considered the index date. Incident ALS cases were those without a trace of ALS during the 3-year look back. Patients were described in terms of demographics, clinical characteristics and drug use at baseline, and were classified into four categories based on riluzole use in the 2 years before and 1 year after the index date: prevalent, incident, former users and non-users. Use of symptomatic pharmacological and non-pharmacological therapies was described across these categories during 12 months after the index date. Determinants of riluzole use were also investigated.

Results and conclusions: A total of 1636 ALS incident subjects were detected in the three regions, mainly aged 65–74 years. Patients were generally fragile with a high prevalence of comorbidities at baseline. Riluzole was used by 27.4% of the overall study cohort at baseline and steeply increased in the first year after the index date differently between regions (Latium 61.2%, Tuscany 85.0%, Umbria 76.5%), with about half of the subjects being incident users. In the 12 months after the index date, also symptomatic therapies increased, in riluzole users and non-users. Determinants analysis showed that higher patient severity and complexity were associated with a lower likelihood of being treated with riluzole.

KEYWORDS
amyotrophic lateral sclerosis, determinants of use, pharmaco-utilization, riluzole

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive, heterogeneous neurodegenerative disorder characterized by the degeneration of upper and lower motor neurons, and associated frontotemporal spectrum dysfunction. Patients experience progressive muscular atrophy and weakness, typically leading to respiratory failure and death within 3–5 years [1]. People with ALS display an array of symptoms encompassing direct consequences of neuronal degeneration (e.g., muscle atrophy, dysphagia, respiratory failure) and also secondary to direct symptoms including mental disorders, hypoventilation symptoms and pain [2].

Amyotrophic lateral sclerosis, the most prevalent adult motor neuron disease, exhibits varying global incidence and prevalence [3]. A recent meta-analysis with focus on the global population with ALS reported that both prevalence and incidence were lowest in South Asia (1.57 and 0.42 per 100,000 persons, respectively) and highest in West Europe (9.62 and 2.76 per 100,000 persons), with higher estimates amongst males compared to females [4]. A recent Italian epidemiological study aligns with the European estimates reported in the meta-analysis, reporting ALS prevalence and incidence rates ranging between 9.90 and 12.31 per 100,000 persons and between 1.9 and 4.2 per 100,000 persons, respectively [5].

Although no known treatment can reverse the damage caused by ALS, certain medications can help slow the progression of the disease. To date, in Italy, riluzole is the only disease-modifying drug reimbursed by the Italian public healthcare system for ALS treatment. As a glutamate antagonist, riluzole inhibits glutamate release, which may help prevent nerve cell damage [6, 7]. It delays the onset of ventilator dependence or tracheostomy without exerting therapeutic effect on motor and lung function [8]. Clinical trials have shown that, compared to placebo, riluzole may increase median survival by 2–3 months in patients with ALS [9, 10]. Nevertheless, real-world evidence suggests that riluzole could potentially offer a considerably more substantial extension of survival, enhancing median survival times by 6–19 months [7, 8, 11]. Apart from riluzole, a series of symptomatic pharmacological and non-pharmacological therapies are often employed to enhance the patient's quality of life by mitigating prevalent symptoms of the disease, such as muscle cramps, depression, insomnia and pain [12]. When ALS progresses to the point of impairing the ability to breathe, speak and move, tracheostomy and subsequent invasive mechanical ventilation can be performed. It has been suggested that invasive mechanical ventilation may prolong median survival time by 8 months to about 3 years amongst patients in the advanced stage of ALS [13]. In the later stages of ALS, recent guidelines recommend implementing percutaneous endoscopic gastrostomy (PEG) when weight loss surpasses 10% from baseline and prior to the forced vital capacity dropping below 50% of predicted levels. This helps maintain adequate oral intake and offers an alternative route for drug administration [14, 15].

Epidemiological studies on ALS, due to the rarity of the disease, often focus on limited geographical areas or specific clinical contexts, hindering the assessment of potential geographical variations in treatment. Current ALS epidemiological data derive from studies conducted up to 2014 which rely on small sample sizes [16–21]. Moreover, there is limited evidence regarding the prevalence of the use of combined treatments (i.e., pharmacological and non-pharmacological interventions) amongst ALS patients.

In light of this, the aim of the present real-world study was to describe the use patterns of pharmacological and non-pharmacological therapies and investigate potential determinants of riluzole use in patients newly diagnosed with ALS in three Italian regions, Latium, Tuscany and Umbria, between 2014 and 2019, leveraging the multicentre Italian project 'Comparative Effectiveness and Safety of Drugs used in Rare Neuromuscular and Neurodegenerative Diseases—the CAESAR study'.

METHODS

Study design and setting

This is a retrospective cohort study on patients newly diagnosed with ALS, based on administrative healthcare data of three Italian regions, namely Latium, Tuscany and Umbria (about 10 million inhabitants). The study protocol was published on the ENCePP website (EUPAS37983).

Data sources

This study utilized administrative healthcare data comprising pseudonymized patient-level information from various databases recording healthcare services reimbursed by the National Healthcare Service (NHS) and delivered to all residents enrolled with the Regional Healthcare Service (RHS). Enrolment is based on the registration with a general practitioner in Italy and is offered to all residents. For this study, the population registry, which contains demographic and vital status information on subjects enrolled with the RHS, was linked to the mortality registry, hospital discharge records, emergency room visits, disease-specific co-payment exemptions and drug dispensings from community and hospital pharmacies to outpatients.

Study population and cohort selection

Patients with ALS were selected amongst subjects registered in one of the three data sources between 1 January 2014 and 31 December 2019 according to the following algorithm: ≥1 hospital discharge record of ALS (primary diagnosis: International Classification of Diseases 9th Revision Clinical Modification [ICD-9-CM] 335.20) AND/OR ≥1 hospital discharge record of ALS (secondary diagnosis: ICD-9-CM 335.20 if discharged from neurological ward) AND/OR ≥1 discharge record from the emergency room of ALS (primary

diagnosis: ICD-9-CM 335.20) AND/OR ≥1 record of new co-payment exemption for ALS (code RF0100). The date of the patient's first trace of ALS in any of the data banks was considered as the index date and assumed as a proxy for the first clinical diagnosis of ALS in each patient. Patients aged less than 18 years, not enrolled in the RHS at the index date or with less than 3 years of look back were excluded. The study population was restricted to incident ALS cases, excluding subjects with a trace of ALS during the 3-year look back.

Description of the study cohort

Incident ALS patients were characterized in terms of demographic and clinical features, including major complications, comorbidities and recorded therapies in the 2 years preceding the index date, predefined by clinicians (Tables S1–S5). Incident ALS patients were divided into four categories, based on their riluzole use in the 2 years before and 1 year after the index date: (1) former users (≥1 dispensing in the 2 years before and no dispensing in the year after the index date), (2) prevalent users (≥1 dispensing in the 2 years before and ≥1 dispensing in the year after the index date), (3) incident users (nothing dispensed in the 2 years before and ≥1 dispensing in the year after the index date), (4) non-users (nothing dispensed either in the 2 years before or in the year after the index date). For each of the above-mentioned categories, use of symptomatic pharmacological and non-pharmacological therapies was investigated during the 12 months after the index date. Drugs taken into consideration were predefined on the basis of clinical guidelines [22, 23] and revised by clinicians dropping drugs not refunded by the Italian NHS and therefore not traceable in our data. A detailed list of drugs and Anatomical Therapeutic Chemical (ATC) codes and non-pharmacological treatment with ICD-9-CM codes is reported in Tables S4 and S5.

Statistical analysis

The descriptive analysis of the cohort at baseline was performed on age, sex, clinical characteristics and use of ALS-related pharmacological and non-pharmacological therapies, displaying only those variables observed in a minimum of 1% for ALS-specific complications and therapies and 5% for other conditions. Categorical variables are reported as patient counts and percentages. The four categories of riluzole users are stratified by region and reported through a sunburst chart. Use of pharmacological and non-pharmacological treatments at 12 months after the index date are presented through histograms. Differences between regions are represented by *p* values with a 5% threshold. A logistic regression analysis considering all characteristics mentioned above was computed to identify determinants of riluzole use, separately for each region. A forest plot was used to visualize model coefficients and their respective confidence intervals. The statistical software SAS and R version 4.0.3 were used for data analysis. All analyses presented in this paper were based on

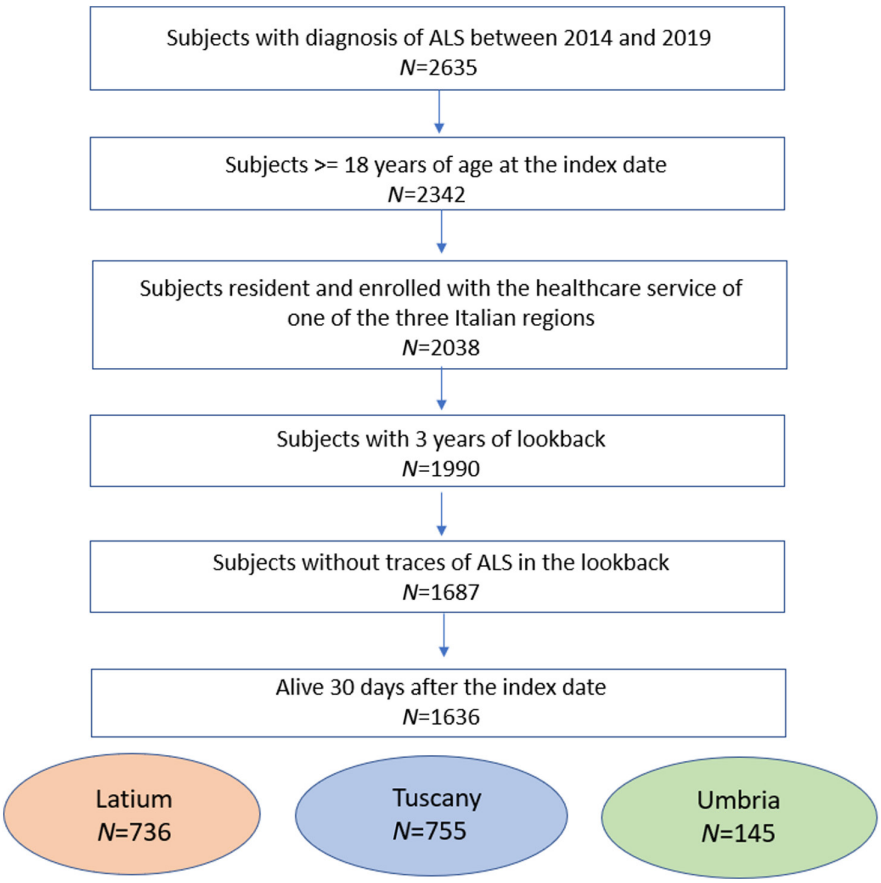


FIGURE 1 Flowchart of the cohort selection.

TABLE 1 Characteristics of the amyotrophic lateral sclerosis (ALS) patients at baseline by region and overall.

	Latium		Tuscany		Umbria		Total	
	736		755		145		1636	
	n	%	*n*	%	*n*	%	*n*	%
Characteristics of the patients at index date								
Gender								
Male	400	54.3%	389	51.5%	81	55.9%	870	53.2%
Female	336	45.7%	366	48.5%	64	44.1%	766	46.8%
Age in classes								
18–64	274	37.2%	236	31.3%	46	31.7%	556	34.0%
65–74	255	34.6%	283	37.5%	58	40.0%	596	36.4%
75+	207	28.1%	236	31.3%	41	28.3%	484	29.6%
Clinical information in the 2 years before the index date								
Major complications[a]								
Fractures caused by injury	51	6.9%	87	11.5%	11	7.6%	149	9.1%
Dysphagia	31	4.2%	39	5.2%	6	4.1%	76	4.6%
Staggering gait	7	1.0%	25	3.3%	1	0.7%	33	2.0%
Paraplegia, superior diplegia	6	0.8%	18	2.4%	3	2.1%	27	1.7%
Problems related to nutrition	18	2.4%	8	1.1%	1	0.7%	27	1.7%
Comorbidities[a]								
Other motoneuron disease[b]	78	10.6%	85	11.3%	8	5.5%	171	10.5%
Chronic respiratory failure	64	8.7%	9	1.2%	1	0.7%	74	4.5%
Acute respiratory failure	33	4.5%	31	4.1%	4	2.8%	68	4.2%
Acute and chronic respiratory failure	40	5.4%	17	2.3%	2	1.4%	59	3.6%
Depression-related disorders	10	1.4%	24	3.2%	3	2.1%	37	2.3%
Comorbidities in groups[c]								
Nervous system and sense organ diseases	495	67.3%	600	79.5%	117	80.7%	1212	74.1%
Central nervous system diseases	469	63.7%	564	74.7%	113	77.9%	1146	70.0%
Diseases of the circulatory system	228	31.0%	248	32.8%	55	37.9%	531	32.5%
Injuries and poisonings	191	26.0%	229	30.3%	31	21.4%	451	27.6%
Symptoms, signs and undefined morbid states	181	24.6%	197	26.1%	37	25.5%	415	25.4%
Endocrine, nutritional, metabolic and immune disorders	118	16.0%	139	18.4%	27	18.6%	284	17.4%
Musculoskeletal system and connective tissue diseases	109	14.8%	140	18.5%	30	20.7%	279	17.1%
Diseases of the respiratory system	161	21.9%	95	12.6%	21	14.5%	277	16.9%
Diseases of the digestive system	77	10.5%	73	9.7%	14	9.7%	164	10.0%
Peripheral nervous system diseases	56	7.6%	91	12.1%	14	9.7%	161	9.8%
Genitourinary system diseases	53	7.2%	55	7.3%	16	11.0%	124	7.6%
Mental disorders	34	4.6%	54	7.2%	20	13.8%	108	6.6%
Tumours	45	6.1%	41	5.4%	14	9.7%	100	6.1%

[a]Only observations occurring in >1% in the total group are reported.

[b]ICD-9 codes starting with 335.2 (excluding 335.20, corresponding to ALS).

[c]Only observations occurring in >5% in the total group are reported.

data routinely collected for administrative purposes. The data generated and analysed during the study are not publicly available in line with Italian privacy regulations.

RESULTS

A total of 2635 ALS patients were identified. After applying the exclusion criteria, the study population was made up of 1636 ALS incident subjects, distributed across the three regions as follows: 736 in Latium, 755 in Tuscany and 145 in Umbria (Figure 1). As reported in Table 1, the majority of subjects were men (53%) and in the age class 65–74 (36%). Amongst the complications recorded in the 2 years before the index date, fractures caused by injury were the most commonly observed overall (9.1%) followed by dysphagia (4.6%). Nervous system and sense organ diseases were the most frequent comorbidities (74.1%) with other motoneuron diseases excluding ALS accounting for 10%, followed by diseases of the circulatory system (32.5%). As reported in Table 2, the use of specific and symptomatic drug therapy was frequent in all the regions already at baseline. In detail, riluzole was used by about 20% of subjects in Latium and Umbria and by more than 35% of patients in Tuscany. Amongst

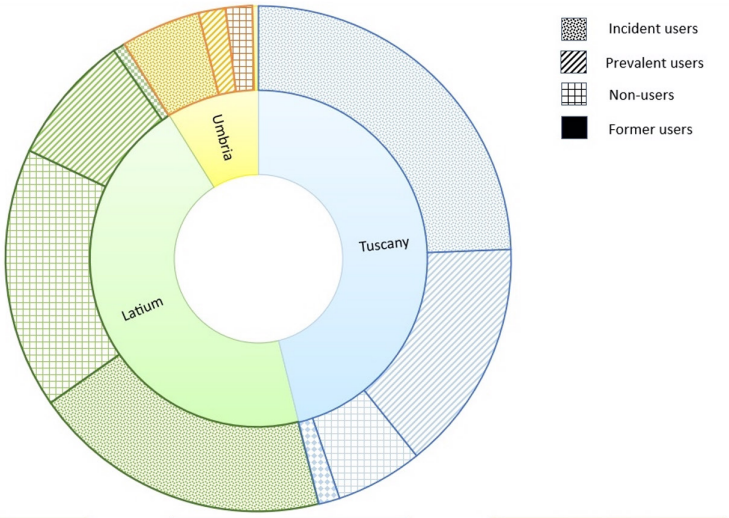
TABLE 2 Pharmacological and non-pharmacological therapy at baseline by region and overall.

	Latium		Tuscany		Umbria		Total		*p* value
	736		755		145		1636		
	n	%	*n*	%	*n*	%	*n*	%	
Drug therapy									
Riluzole[a]	149	20.2%	265	35.1%	34	23.4%	448	27.4%	<0.05
Psychoanaleptics	15	2.0%	105	13.9%	2	1.4%	122	7.5%	<0.05
Bronchial hypersecretion	176	23.9%	128	17.0%	22	15.2%	326	19.9%	<0.05
Constipation	6	0.8%	9	1.2%	4	2.8%	19	1.2%	0.136
Gastro-oesophageal reflux	448	60.9%	354	46.9%	71	49.0%	873	53.4%	<0.05
Cramps, spasms, fasciculation	189	25.7%	258	34.2%	16	11.0%	463	28.3%	<0.05
Baclofen	50	6.8%	41	5.4%	3	2.1%	94	5.7%	0.072
Gabapentin	61	8.3%	70	9.3%	2	1.4%	133	8.1%	<0.05
Pregabalin	88	12.0%	53	7.0%	5	3.4%	146	8.9%	<0.05
Anxiety/depression/emotional frailty	195	26.5%	251	33.2%	41	28.3%	487	29.8%	<0.05
Duloxetine	29	3.9%	21	2.8%	9	6.2%	59	3.6%	0.104
SSRI	141	19.2%	216	28.6%	30	20.7%	387	23.7%	<0.05
Amitriptyline	33	4.5%	35	4.6%	6	4.1%	74	4.5%	0.963
Dementia-related psychiatric disorders	29	3.9%	24	3.2%	5	3.4%	58	3.5%	0.728
Pain	329	44.7%	312	41.3%	42	29.0%	683	41.7%	<0.05
NSAIDs	307	41.7%	230	30.5%	35	24.1%	572	35.0%	<0.05
Opioids	80	10.9%	151	20.0%	10	6.9%	241	14.7%	<0.05
Thrombosis/embolism	368	50.0%	335	44.4%	61	42.1%	764	46.7%	<0.05
Heparinics	122	16.6%	131	17.4%	17	11.7%	270	16.5%	0.247
Other drugs (atc 4th level)[b]									
≤1	100	13.6%	147	19.5%	48	33.1%	295	18.0%	
2–5	318	43.2%	346	45.8%	51	35.2%	715	43.7%	<0.05
6+	318	43.2%	262	34.7%	46	31.7%	626	38.3%	
Non-pharmacological treatments[a]									
Non-invasive ventilation	55	7.5%	13	1.7%	3	2.1%	71	4.3%	<0.05
Invasive ventilation	38	5.2%	6	0.8%	3	2.1%	47	2.9%	<0.05
Percutaneous endoscopic gastrostomy (PEG)	25	3.4%	14	1.9%	4	2.8%	43	2.6%	0.176
Tracheostomy	13	1.8%	2	0.3%	2	1.4%	17	1.0%	<0.05

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitor.

[a]In the 2 years before the index date.

[b]Any fourth level ATC drug recorded in the 12 months before the index date (excluding the other drugs mentioned above).



LATIUM	
N=736	
	%
Non users	31.1
Ex users	1.8
Prevalent users	18.5
Incident users	42.7

TUSCANY	
N=755	
	%
Non users	12.1
Ex users	2.9
Prevalent users	32.2
Incident users	52.8

UMBRIA	
N=145	
	%
Non users	19.3
Ex users	4.1
Prevalent users	19.3
Incident users	57.2

FIGURE 2 Riluzole use in the first year after the index date (ALS diagnosis) by region and by category of riluzole use.

symptomatic medications prescribed to more than 40% of the overall study population there were drugs for gastro-oesophageal reflux, pain and thrombosis/embolism. Moreover, polytherapy with six or more other drugs was frequently observed ranging between 31.7% and 43.2% in the overall study population. Non-invasive ventilation was detected in 7.5% of the subjects in Latium, compared to only 1.7% in Tuscany and 2.1% in Umbria, invasive ventilation in 5.2% versus 0.8% and 2.1%. Recourse to PEG and tracheostomy was more similar amongst regions, varying between 3.4% and 1.9% and between 0.3% and 1.8%, respectively. For both, pharmacological and non-pharmacological therapy differences between regions were statistically significant for almost all treatments. Riluzole use steeply increased after the index date in all regions (Figure 2). Considering all users in Tuscany and Umbria, 85.0% and 76.5% received riluzole during the first year, whilst in Latium this percentage accounts for 61.2%. In all regions, about half of the subjects were newly prescribed with riluzole (Latium 42.7%, Tuscany 52.8% and Umbria 57.2%). Prevalent users were instead 32.3% in Tuscany and about 19% in the others. Latium registered a high portion of non-users (37.1%), approximately double those registered elsewhere. Observed differences between regions in prescribing riluzole were statistically significant for all categories ($p < 0.001$), also after stratifying by sex and age classes (results not shown). During the first year after the index date more than 50% of both prevalent and incident riluzole users were prescribed with drugs to treat gastro-oesophageal reflux, depression and cramps (Figure 3). Amongst former and non-users of riluzole, drugs for thrombosis and gastro-oesophageal reflux were most frequently prescribed, to over 50% of patients. Differences between user categories were statistically significant for some drug classes: psychoanaleptics, drugs for cramps, spasms, fasciculations, depression, anxiety, emotional fragility and opioids were more frequently prescribed to riluzole users, whilst drugs for thrombosis/embolism and gastro-oesophageal reflux were more frequently used by non-users. Regarding non-pharmacological therapy, over 10% of patients underwent at least one amongst non-invasive assisted ventilation, invasive assisted ventilation or PEG. Additionally, between 5% and 10% of patients needed tracheostomy. Invasive procedures were more frequent in former riluzole users. Results remained robust when stratifying by sex and age classes (results not shown). Region-specific results are reported in Figure S1. Figure 4 reports the results of the analysis of potential determinants of being prescribed with riluzole during the first year after the index date by region. Due to small numbers, most results do not reach statistical significance. Significant associations for not using riluzole were detected in Latium for gender with a significant odds ratio (OR) of 0.63, older ages (75+) (OR=0.49), presence of psychiatric disorders (OR=0.21) and initiation of PEG (OR=0.12) and invasive assisted ventilation (OR=0.09), in Tuscany for use of respiratory insufficiency drugs (OR=0.16) and in Umbria for the presence of tetraparesis or paraplegia (OR=0.01) and the use of drugs for cramps and spasms (OR=0.05).

DISCUSSION

This is the first pharmacoepidemiological study based on real-world data which provides insights into treatment patterns of a large sample of ALS patients particularly with respect to the use of riluzole, symptomatic drugs and non-pharmacological therapies. Furthermore, determinants associated with riluzole use were investigated. In this study, the index date was the best proxy of the clinical ALS diagnosis, considered as the disease incidence.

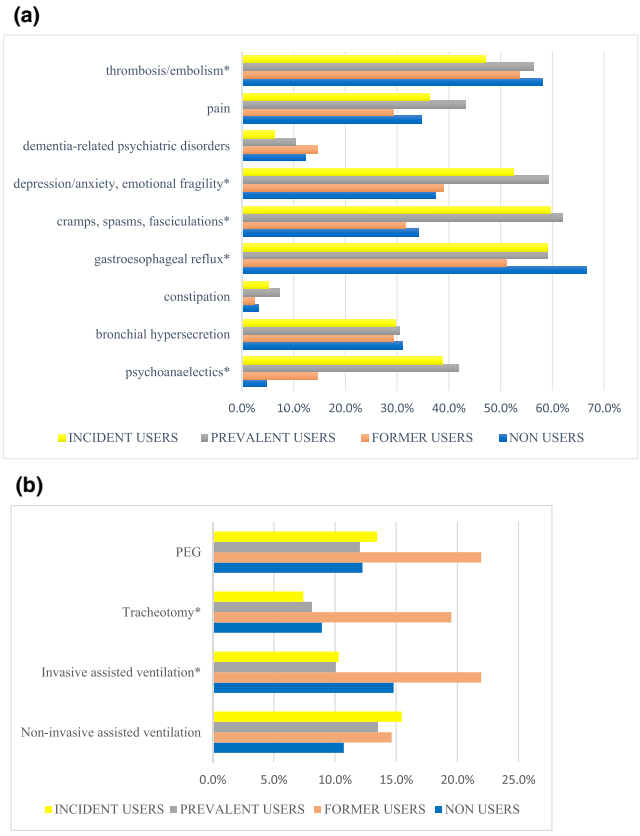


FIGURE 3 (a) Pharmacological therapy use during the first year after the index date, grouped for all the three regions and stratified by category of riluzole users. *Drug class for which the difference between the four categories of riluzole users was statistically significant. (b) Non-pharmacological therapy during the first year after the index date, grouped for all the three regions and stratified by the different category of riluzole users. *Procedure for which the difference between the four categories of riluzole users was statistically significant.

All three regional cohorts comprised slightly more male patients, the majority being over 65 years, many of whom were affected by comorbidities and complications typically associated with ALS. Fractures resulting from injuries were the most common major complication observed amongst newly diagnosed patients with ALS. The relationship between ALS and fractures has been extensively studied for several decades, with variations in study design and reported results [24–26]. Despite such variability, many of these studies reported a positive association between history of fractures and onset of ALS.

In Italy to date, riluzole remains the only disease-modifying drug approved for the treatment of ALS and fully reimbursed by the NHS for that indication. A similar percentage of ALS patients used riluzole in Latium and Umbria, whilst in Tuscany this percentage was higher. This finding may be an indicator of prescribing riluzole to patients during the complex diagnostic pathway and before a final clinical diagnosis. The differences observed amongst regions may be partly attributed to drug policies implemented at regional level, which regulate access to medicines and their reimbursement, or differences in clinical practice. Even within a single region, therapeutic choices may differ amongst health districts and hospitals [27]. In this regard, it should be noted that, although Italy has a national healthcare system, individual regions have autonomy in managing healthcare delivery. This regional autonomy allows each region to make decisions on the organization and management of health services, leading to variations in treatment protocols [28]. Observed differences may also depend on individual clinician's choices. Clinical trials have demonstrated that riluzole may extend both survival time and time to tracheostomy by approximately 2–3 months compared to placebo. However, its overall impact on other functional measures and muscle strength has been limited, leading some clinicians to opt against prescribing it due to the modest benefits considering also the risk of and potential side effects [9]. Apart from gastro-oesophageal reflux, pain and thrombosis/embolism medicines, observed in more than 40% of patients affected by ALS, the highest-ranking symptomatic drugs encompassed also agents for treating anxiety, depression, hypersalivation, cramps as well as bronchial hypersecretion, reflecting the complex diagnostic pathway typical of degenerative diseases.

This study focused on quantifying different categories of riluzole users (prevalent, incident, former users and non-users) amongst incident ALS patients within the three Italian regions participating in this study. Overall, incident users accounted for more than half of riluzole users with a 2:1 incident/prevalent user ratio in Latium and Tuscany and 3:1 in Umbria. Notably, Latium exhibited lower riluzole prescription rates, with a three-fold prevalence of non-users. Despite the European Federation of Neurological Societies (EFNS) recommends starting riluzole as early as possible after diagnosis, a notable proportion of patients received riluzole treatment already before the index date [22], with variations between regions. Part of these patients may have received off-label riluzole prescriptions for other motor neuron diseases than ALS mainly due to the lack of specific therapies [8] or may have been diagnosed with and treated for ALS before our index date; in this case the diagnosis was not performed within the public healthcare service or in the ambulatory setting and therefore was not traced in administrative healthcare data. In other cases, clinicians may have prescribed riluzole even before making the definite final diagnosis, as reported from a French cross-sectional study which revealed that riluzole was initiated before confirming the diagnosis in 13.0% of cases [29].

As expected, in the first year after the index date, riluzole and symptomatic drugs steeply increased. Patterns of riluzole treatment differ between regions, and in general the proportions of patients treated were highest in Tuscany. Common pharmacological therapies include antithrombotics, antidepressants and drugs for pain, spasticity, reflux and bronchial hypersecretion. Non-pharmacological interventions, like PEG, invasive and non-invasive ventilation, were administered to over 10% of various riluzole user categories. Regardless of the category of riluzole users, such findings align with the natural clinical progression of ALS [30–35] and comply with EFNS and National Institute for Health and Care Excellence (NICE) guidelines [22, 23]. Notably, approximately 20% of

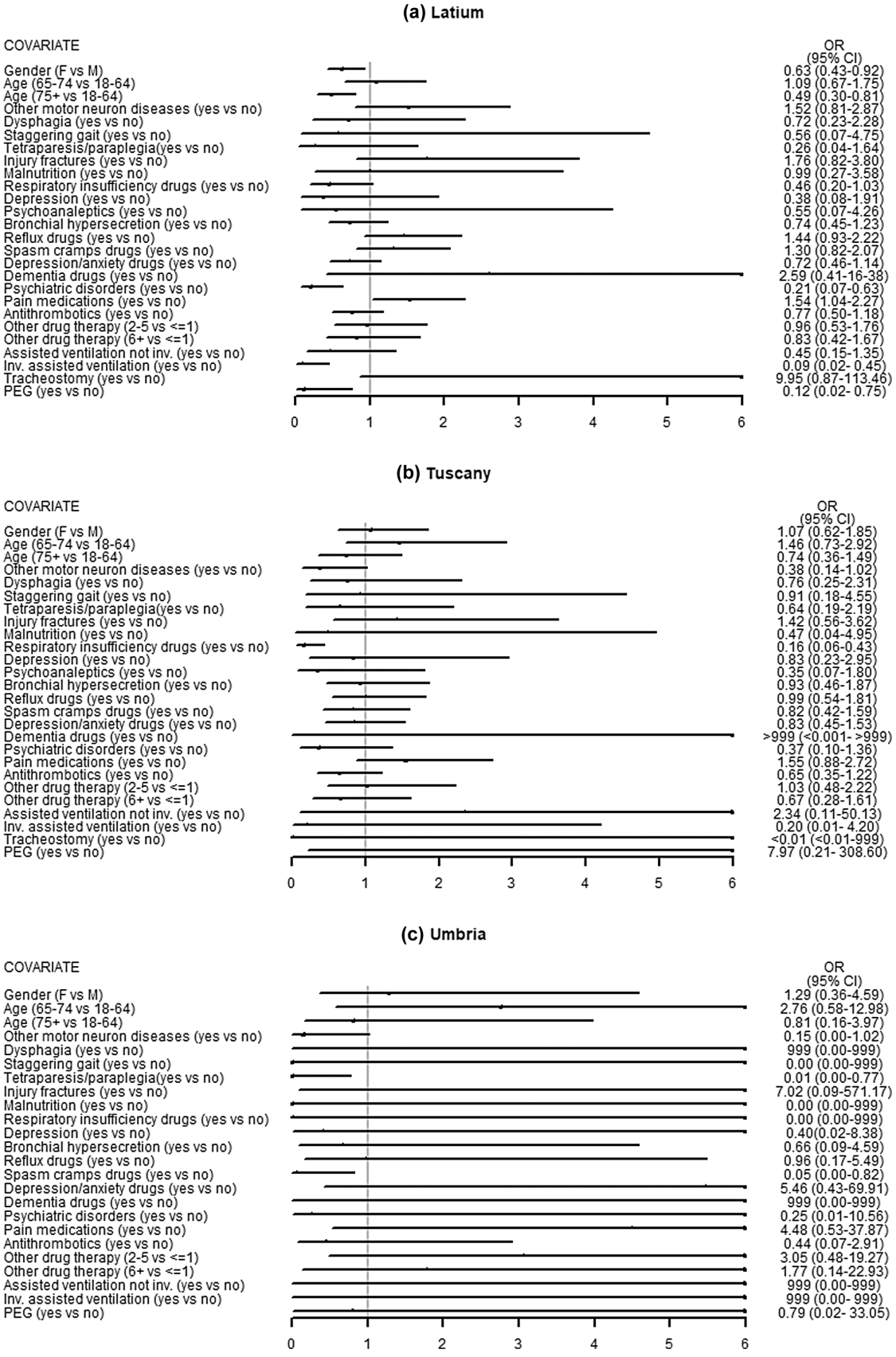


FIGURE 4 Potential determinants of incident ALS cases being prescribed with riluzole therapy during the first year after the index date by region. *All covariates without explicit categories specified in parentheses refer to the following comparison: yes versus no.

former riluzole users underwent procedures such as PEG placement, tracheotomy and invasive assisted ventilation, which is in line with riluzole contraindications.

Elderly patients, those with invasive assisted ventilation, PEG, respiratory medications, cramps, spasms, and those on more than six medications were less likely to use riluzole. Patients with psychiatric disorders, contrary to recent theories, were also more prone not to use riluzole, challenging the idea of dementia as an ALS symptom rather than a comorbidity [1, 36]. In the latter case, riluzole treatment might positively affect these symptoms, potentially reducing the need for symptomatic therapies. Based on these findings, patients less likely to be prescribed with riluzole fall into two groups. First, the more severe and advanced the disease (e.g., use of invasive assisted ventilation or PEG), the lower is the probability of using riluzole, suggesting that in the advanced stage of the disease the potential benefits of riluzole are limited, and physicians may consider alternative treatment options. This is in line with EFNS guidelines [22] and findings from several open-label non-randomized trials supporting that the most significant benefits of riluzole occur during the early stages of the disease [37–39]. Second, some patients, due to demographic characteristics, pre-existing medical conditions, contraindications or medications interacting with riluzole, may face increased vulnerability to adverse effects, prompting physicians to refrain from prescribing riluzole [40–42].

This study has several strengths. To the best of our knowledge, this is the first study that investigates, through an observational study, real-world drug utilization in ALS patients encompassing disease-modifying, symptomatic and non-pharmacological therapies. Moreover, this is a multicentre study based on administrative healthcare data extensively used for pharmacoepidemiological research over the past two decades [43, 44] providing evidence from three Italian regions accounting for about 17% of the overall Italian population. The three regions represent different settings characterized by different healthcare organizations. These regions feature distinct healthcare structures, fostering valuable insights into treatment variations. The observed differences offer a foundation for cross-disciplinary discussions amongst clinicians in various healthcare settings, promoting knowledge exchange and professional growth. However, some study limitations deserve to be mentioned, the first of which stems from the observational and administrative nature of the data. First, our algorithm may have missed patients not diagnosed or treated in public healthcare facilities, affecting the identification of the date of diagnosis, which was approximated through the index date. For instance, some of those prescribed with riluzole before the index date may have been diagnosed outside the public healthcare service in the early stage of the disease, or treated in an outpatient specialist ambulatory, for which our data do not provide diagnosis. This potential postponement of the real disease onset in our data may have contributed to the findings of complications typically present in ALS patients and use of non-pharmacological therapies already at baseline. In these cases, the index date may not represent the real disease onset. Second, drugs administered during hospitalization are not tracked at the patient level leading to potential underestimation of drug therapy utilization both at baseline and during the first year after ALS diagnosis. Moreover, data completeness can vary across the three Italian regions participating in this study due to changes in healthcare management and coding practices, which might be a stimulus for improvement. Finally, compliance with data protection regulations limit central-level processing and pooled analysis, resulting in inadequate sample sizes for robust regional comparisons of the determinants of riluzole use.

In conclusion, the present study showed regional variations in riluzole prescribing for ALS patients. Many patients started pharmacological therapy even before diagnosis and, in the first year after ALS diagnosis, use of both riluzole and symptomatic drugs steeply increased. Greater patient severity and complexity may lead to a lower likelihood of being treated with riluzole. This demonstrates the challenging nature of ALS therapeutic management, emphasizing the need for a multidisciplinary comprehensive approach. The observed differences between regions prompt discussions and knowledge exchange amongst professionals, aiding in clinical audits for appropriate riluzole prescribing and alignment between settings. The present data may also provide insights for future development and evaluation of alternative disease-modifying therapies for ALS. Future research should comprise a wider range of geographical areas, ideally going beyond the Italian context. This would allow for bigger numbers resulting in higher statistical power, thus allowing more robust results to be obtained. Furthermore, it would be interesting to compare patterns across regions and enlarge the external validity of the findings. In addition, the establishment of ALS registries with a nationwide coverage would offer an important opportunity to study this rare disease, both in terms of case ascertainment and collecting clinical details for each patient. In the context of the CAESAR project, studies regarding adherence to riluzole through trajectory analysis and riluzole use in the presence of contraindications in ALS and off-label use in other motor neuron diseases have been investigated and results have been published in open access [8, 45].

AUTHOR CONTRIBUTIONS

Olga Paoletti: Formal analysis; data curation; supervision; writing – original draft; writing – review and editing; conceptualization. **Giulia Hyeraci:** Writing – original draft; writing – review and editing; supervision; conceptualization. **Marco Finochietti:** Formal analysis; writing – review and editing; methodology; conceptualization. **Maria Grazia Celani:** Writing – review and editing; supervision; conceptualization. **Ilaria Bacigalupo:** Conceptualization; writing – review and editing. **Niccolò Lombardi:** Conceptualization; writing – review and editing. **Giada Crescioli:** Conceptualization; writing – review and editing. **Marco Tuccori:** Conceptualization; writing – review and editing. **Silvia Cascini:** Conceptualization; writing – review and editing. **Rosa Gini:** Conceptualization; writing – review and editing. **Antonio Addis:** Conceptualization; writing – review and editing. **Ursula Kirchmayer:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; writing – review and editing; project administration; data curation; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article. Giulia Hyeraci and Olga Paoletti are employed by/consultants of ARS, a public health agency that conducts or participates in pharmacoepidemiology studies compliant with the ENCePP Code of Conduct. The budget of ARS is partially sustained by such studies.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are not publicly available because of privacy reasons.

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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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