RASSEGNE E ARTICOLI

Incidence and prevalence of Amyotrophic Lateral Sclerosis in three Italian Regions: a study based on health administrative databases

Incidenza e prevalenza della sclerosi laterale amiotrofica in tre Regioni italiane: uno studio basato sugli archivi amministrativi sanitari

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Abstract

Objectives: to estimate Amyotrophic Lateral Sclerosis (ALS) incidence and prevalence in three Italian Regions (Lazio, Tuscany, and Umbria), using health administrative databases.
Design: retrospective population-based study.
Setting and participants: ALS patients residing in Lazio, Umbria, and Tuscany were identified through an algorithm based on three different administrative databases: hospital discharge records, exemptions from health care co-payment, and emergency departments (study period 2014-2019). Crude, age- and gender-specific prevalence were calculated on 31.12.2019 and incidence rates of ALS were standardised by region, year, and gender between 2014-2019. Using a clinical dataset available in the Lazio Region, the proportion of individuals residing in the region correctly identified as ALS cases by the algorithm were calculated.
Main outcomes measures: prevalence and incidence rates.
Results: a total of 1,031 ALS patients (≥18 years) were identified: 408 cases in Tuscany, 546 in Lazio, and 77 in Umbria. ALS standardised prevalence (per 100,000) was similar among regions: 12.31 in Tuscany, 11.52 in Lazio, and 9.90 in Umbria. The 5-year crude rates were higher in men, and in people aged 65-79 years. Among 310 patients included in the clinical dataset, 263 (84.8%) were correctly identified by the algorithm based on health administrative databases.
Conclusions: ALS prevalence and incidence in three Central Italy Regions are rather similar, but slightly higher than those previously reported. This finding is plausible, given that previous results relate to at least ten years ago and evidenced increasing trends. Overall, the results of this paper encourage the use of administrative data to produce occurrence estimates, useful to both epidemiological surveillance and research and healthcare policies.

Keywords: amyotrophic lateral sclerosis, incidence, prevalence, epidemiology, administrative data, algorithm

What is already known

- **Amyotrophic Lateral Sclerosis (ALS) is a rare, fatal neurodegenerative disease that imposes a great burden on the patient, the patient's family, and society.**
- **Occurrence estimates of ALS are available from different countries, but in Italy estimates of prevalence and incidence are based on single and locally limited disease registries.**

What this study adds

- **This study is part of a multi-regional project and uses a standardized methodology to measure the occurrence of ALS; the identification of cases is based on an algorithm, which accounts for access to hospital and emergency rooms and for disease specific co-payment exemption.**
- **Prevalence and incidence estimates are slightly higher than those reported by previous European studies and show some variation among regions.**
- **The results highlight the opportunity to support the use of health administrative data to produce ALS occurrence estimates, useful to both epidemiological surveillance and research and healthcare policies.**

Riassunto

Obiettivi: stimare l'incidenza e la prevalenza della sclerosi laterale amiotrofica (SLA) in tre Regioni italiane (Lazio, Toscana e Umbria), utilizzando banche dati amministrative sanitarie.

Disegno: studio di popolazione retrospettivo.
Setting e partecipanti: i pazienti affetti da SLA residenti in Lazio, Umbria e Toscana sono stati identificati attraverso un algoritmo basato su tre diverse banche dati amministrative: l'archivio dei ricoveri ospedalieri, l'archivio delle esenzioni e quello degli accessi in pronto soccorso (periodo di studio 2014-2019). Sono stati calcolati la prevalenza grezza e quella specifica per età e genere al 31.12.2019 e i tassi di incidenza standardizzati per regione, anno e genere tra il 2014 e il 2019. Utilizzando un set di dati clinici disponibili nella sola regione Lazio, è stata calcolata la proporzione di individui correttamente identificati come casi di SLA dall'algoritmo.
Principali misure di outcome: tasso di incidenza e prevalenza.
Risultati: sono stati identificati in totale 1.031 pazienti con SLA (età ≥18 anni): 408 casi in Toscana, 546 nel Lazio e 77 in Umbria. La prevalenza standardizzata (per 100.000) è risultata simile tra le regioni: 12,31 in Toscana, 11,52 nel Lazio e 9,90 in Umbria. I tassi grezzi a 5 anni erano più alti negli uomini e nelle persone di età compresa tra 65 e 79 anni. Tra i 310 pazienti inclusi nel dataset clinico, 263 (84,8%) sono stati corret-

tamente identificati come casi dall'algoritmo basato sui database amministrativi.
Conclusioni: la prevalenza e l'incidenza della SLA nelle tre regioni partecipanti allo studio sono piuttosto simili, sebbene leggermente superiori a quelle riportate in letteratura. Questo risultato è plausibile, dal momento che i dati dei precedenti studi si riferiscono ad almeno dieci anni fa e hanno messo in evidenza la tendenza a un incremento nel tempo dell'incidenza e della prevalenza di questa patologia neurodegenerativa. Nel complesso, i risultati qui presentati incoraggiano l'uso di dati amministrativi per produrre stime di occorrenza della SLA utili per la sorveglianza epidemiologica, la ricerca e la programmazione sanitaria.

Parole chiave: sclerosi laterale amiotrofica, incidenza, prevalenza, epidemiologia, dati amministrativi, algoritmo

Introduction

Motor neuron diseases (MND) are a group of neurodegenerative disorders that selectively affect motor neurons, the cells which control voluntary muscles of the body. They also include amyotrophic lateral sclerosis (ALS), which is classified as a very rare disease by the European Union.[1] ALS is a progressive neuromuscular disease characterized by the degeneration of upper to lower motor neurons, and leading to death within 3-5 years from symptoms onset.[2,3] Studies of the epidemiology of ALS are numerous, with incidence and prevalence estimates varying widely. In a meta-analysis conducted in 2017, pooled estimates of ALS incidences worldwide were 1.68 per 100,000 person-years, with heterogeneity in ALS standardized incidence between Northern Europe and Eastern Asia or Southern Asia.[4] On the contrary, homogeneous incidence rates were reported in populations from Europe, North America, and New Zealand (1.81 per 100,000 person years).[4] In a recent systematic review and meta-analysis, the overall crude worldwide incidence was 1.59 per 100,000 person-years, with higher estimates among males compared to females 1.91 vs 1.36.[5] Considering all new incident ALS cases registered in 6 population-based registries in 3 European countries including Italy, Logroscino et al. (2010)[6] estimated an average annual crude incidence rate of 2.16 per 100,000 person-years.
In Italy, a mean annual crude incidence rate of 2.90/100,000 was estimated in the period 1994-2005 (2.64/100,000 standardised rate) and a male/female rate ratio of 1.28:1 was reported.[7] In this study, incidence estimates were constantly higher among men with no relevant variation during the 10-year period. In a retrospective epidemiologic study, an annual incidence rate was 2.16/100,000.[8] Other studies, conducted with prospective regional registers, showed a standardized incidence rate of 2.09 or 2.51 per 100,000, with higher incidence ratio in males.[9,10] In a recent prospective based study in Italy, an age- and sex-adjusted incidence rate of 3.13/100,000 population was estimated.[11]
Significant heterogeneity within and between countries/geographic regions has also been observed for prevalence estimates. A recent study reported pooled prevalence rates (per 100,000) of 6.22 for Europe, 5.20 for North America, 3.41 for Latin America, 3.01 for Asian countries excluding Japan, and 7.96 for Japan, respectively.[12] In Italy, prevalence estimates have been produced using prospective registries, and range between 7.54/100,000, 7.89/100,000, and 11.2/100,000.[13-15]
Indeed, registries are considered the optimal approach to produce diseases occurrence measures, but known to be a very time-consuming and expensive methodology.[6] The ALS incidence estimates could be performed with a prospective study, with an important search in a defined area for ALS cases, but this methodology can be carried out in a specific area and for a limited period.[15] In recent years, health administrative data are increasingly used to retrieve information for case ascertainment in epidemiological studies, representing a convenient and easier-to-obtain source of data. From the public health view, administrative health records offer a new opportunity to study the epidemiology of diseases, since they represent an easily accessible, rapid, and inexpensive source of data.
Yet, since they are generated for administrative purposes, it is important to evaluate their accuracy before they are used for epidemiological analyses.[16]
A number of validation studies has been conducted in different countries where a single or two health administrative databases have been used to identify patients with ALS, with sensitivity values ranging from 44.1% to 93.9%.[15-20] Several authors recommend using mortality data in combination with other administrative data to create algorithms with higher accuracy performances.[18-20]
The performance of algorithms for case identification based on multiple health administrative databases has been tested for several diseases, such as multiple sclerosis[21], Parkinson[22], dementia[23,24], epilepsy[25].
The recent multicentre project 'Comparative Effectiveness and Safety of Drugs used in Rare Neuromuscular and Neurodegenerative Diseases (CAESAR)' funded by the Italian Medicines Agency, offers the opportunity to estimate occurrence of ALS at population level, taking advantage of the available administrative healthcare databases in three Italian regions (Lazio, Tuscany,

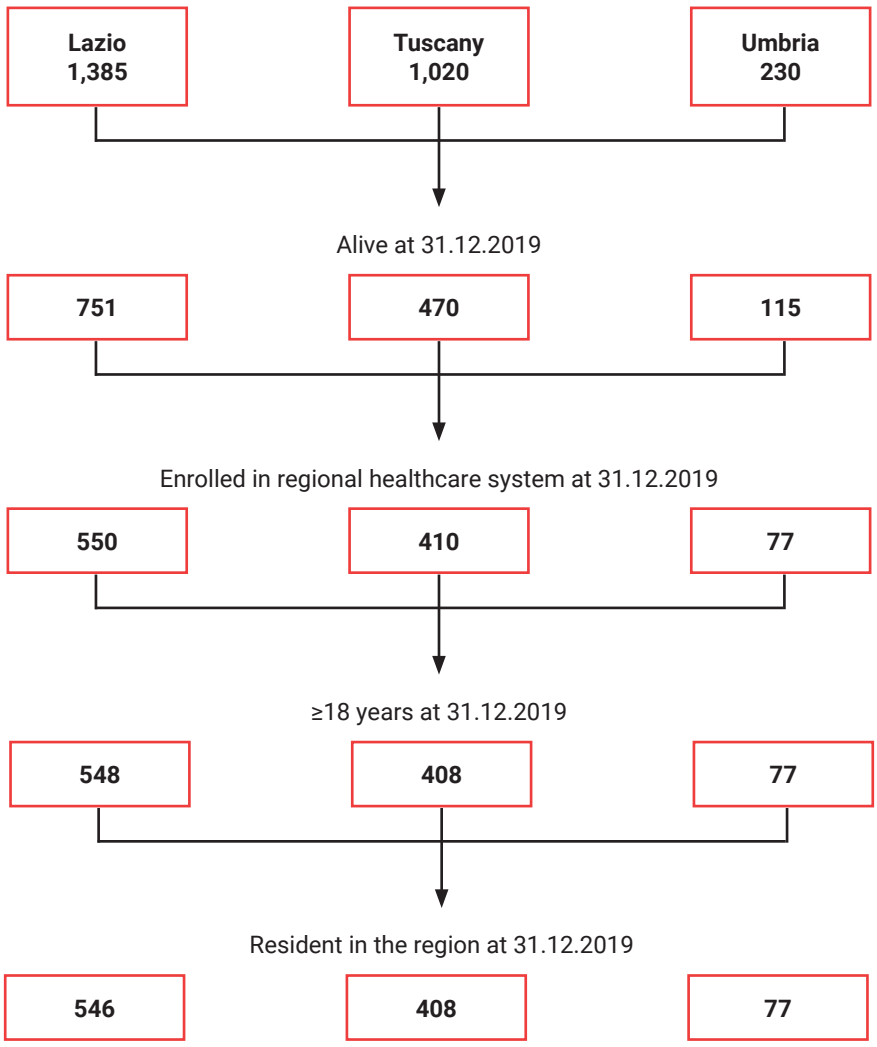

Figure 1. Patients diagnosed with amyotrophic lateral sclerosis in the years 2014-2019.
Figura 1. Pazienti con diagnosi di sclerosi laterale amiotrafica nel periodo 2014-2019.

and Umbria), accounting for approximately 10 million citizens. Moreover, the availability of disease-specific clinical dataset in the Lazio region,[12] allowed us to estimate the ability of the algorithm to identify ALS patients on the basis of administrative data.

Objectives

This study aimed to estimate the incidence and prevalence of ALS in three regions located in central Italy.

Methods

Study design and setting

This population-based study used an algorithm to identify ALS cases based on administrative healthcare data from three regions located in central Italy, namely Lazio, Tuscany, and Umbria. Lazio is the second most populated region of Italy, with 5,8 million inhabitants, and comprises Rome, which is the capital of Italy and the largest city in the country.[26] Populations in Tuscany and Umbria account for 3,7 and 0,9 million residents, respectively.[26]

In Italy, healthcare is tax funded and provides services to all residents who are enrolled in the National Health Service (NHS), covering around 95% of the resident population.[27] All healthcare services issued by public or affiliated providers are recorded at individual level. Data used in the present study are available in the regional health information systems of the participating regions and refer to the years 2014-2019, with a three-year look-back period. Data management and analysis were performed in agreement with the national and regional data protection rules.

Data sources

Different administrative databases were used, all available in the three regions. The Healthcare Assistance File collects demographic and residence information of people living in each of the participating region and

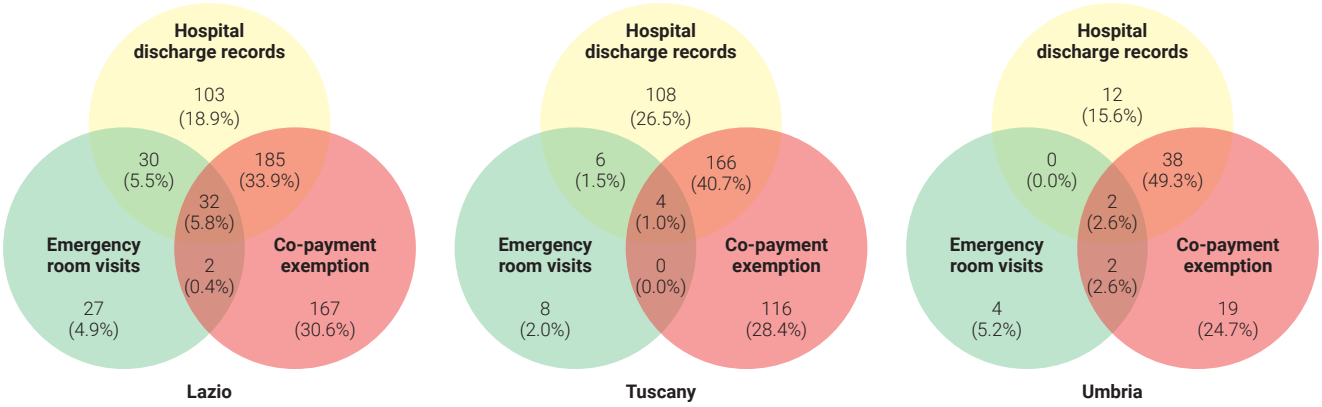

Figure 2. Contribution of regional health administrative databases to amyotrophic lateral sclerosis cases identification.
Figura 2. Contributo degli archivi dei dati amministrativi all'identificazione dei casi di sclerosi laterale amiotrofica

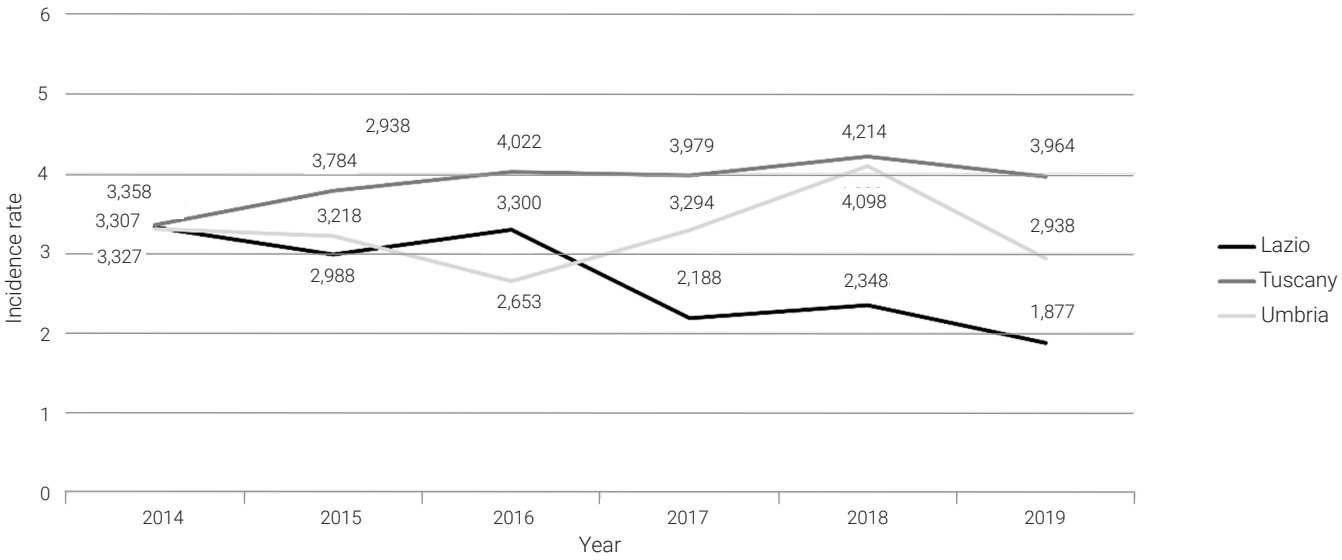

Figure 3. Standardized amyotrophic lateral sclerosis incidence rates from 2014 to 2019 in Tuscany, Latium, and Umbria.
Figura 3. Tassi standardizzati di incidenza della sclerosi laterale amiotrofica nel periodo 2014-2019 in Toscana, Umbria e Lazio.

registered in the Regional Health Service. Information about mortality (date, place, and cause of death coded by International Classification of Diseases 9 code, ICD-9) was retrieved from the regional Mortality Information System, while data on admissions to regional hospitals (e.g., primary and secondary diagnoses and procedures recorded at discharge, coded according to ICD-9-CM) were available from the Hospital Information System. Data about emergency room visits (diagnoses coded according to ICD-9-CM) were retrieved from the Healthcare Emergency Information System. The Regional Co-payment Exemptions Register collects information on patients who claim exemption from co-payments for medical services in case of high impact conditions. Exemption is authorised upon certified diagnosis and, therefore, this register allowed for the identification of patients with a confirmed diagnosis of ALS.

Data used in the present study were updated to the end of 2019. To create patient level records containing all information available in the different information systems and according to privacy legislation, all databases can be linked through an anonymous unique patient identifier.

Additionally, in the Lazio Region, a clinical dataset on ALS patients was established, in collaboration with 25 clinical centres[13] comprising 353 ALS patients diagnosed according to the El Escorial revised criteria[28] in the period 2010-2016.

Case ascertainment

To calculate the prevalence of adult resident ALS cases on 31.12.2019, patients were identified as affected by ALS if they met at least one of the following three criteria in the years 2014-2019 (Table 1):

1. discharge from hospital with a primary diagnosis of ALS (ICD-9-CM code: 335.20) or a secondary diagnosis in combination with discharge from a hospital neurology ward;

Data source	Selection criteria
INCIDENT CASES*	
Hospital information system	at least 1 discharge from hospital with a primary diagnosis of ALS (ICD-9-CM code 335.20)
	or
	at least 1 secondary diagnosis of ALS, only if discharge from neurological ward, or followed in the succeeding 12 months by start of disease specific co-payment exemption or hospital discharge with a primary diagnosis for ALS (ICD-9- CM code 335.20)
OR	
Healthcare emergency information system	at least 1 discharge from emergency room with a primary diagnosis of ALS (ICD-9-CM code 335.20)
OR	
Co-payment exemption registry	start of a disease specific co-payment exemption for ALS (code RF0100)
PREVALENT CASES	
Hospital information system	at least 1 discharge from hospital with a primary diagnosis of ALS (ICD-9-CM code 335.20)
	or
	at least 1 discharge from a hospital neurology ward with a secondary diagnosis of ASL (ICD-9- CM code 335.20)
OR	
Healthcare emergency information system	at least 1 discharge from emergency room with a primary diagnosis of ALS (ICD-9-CM code 335.20)
OR	
Co-payment exemption registry	current co-payment exemption for ALS (code RF0100)

***** Incident cases were identified considering a 3-year look-back period, to rule out any previous diagnosis / *I casi incidenti sono stati identificati considerando un periodo di riferimento di 3 anni, per escludere qualsiasi diagnosi precedente*

Table 1. Criteria for amyotrophic lateral sclerosis cases identification.
Tabella 1. Criteri per identificazione dei casi affetti da sclerosi laterale amiotrofica.

2. discharge from emergency room with a primary diagnosis of ALS (ICD-9-CM code: 335.20);
3. disease specific co-payment exemption for ALS (Italian specific code for certified diagnosis of ALS: RF0100).

All data sources were matched by a deterministic linkage procedure using the unique identifier. If an individual was present in more than one database and met the case identification criteria, then he/she was selected at the date of his/her first claim recorded in the administrative databases.

Patients not resident in the study area, not present in the healthcare assistance file (as a proxy for residence), younger than 18 years or not alive on 31.12.2019 were excluded.

The algorithm for identifying incident cases of ALS among adult residents required at least one of the following criteria:

1. hospital discharge with a primary diagnosis of ALS (ICD-9-CM code: 335.20); or hospital discharge with a secondary diagnosis of ALS, only if discharge from neurological ward, or if followed in the succeeding 12 months by start of disease specific co-payment exemption, or by an hospital discharge with a primary diagnosis for ALS;

2. emergency room visit with primary diagnosis for ALS discharge;

3. start of a disease specific co-payment exemption for ALS (RF0100).

The incident case was identified at the date of the first signal registered in the linked administrative databases (index date). Patients were excluded if they were younger than 18 years at index date, not resident and not present in the healthcare assistance file at index date, did not have a look-back of 3 years (wash-out period), or with any signal of ALS in the three years before the index date (prevalent cases).

Statistical analysis

For each region, age- and gender-specific prevalence rates per 100,000 residents were calculated, using the number of ALS patients that were alive on 31.12.2019 as numerator and the adult population living in the same region at the prevalence date as denominator. Standardized prevalence rates were calculated by sex and 5-year age groups, using the European adult population as a reference[29], with relative 95% CIs.

Incidence was calculated on December 31st of each single year between 2014 and 2019, with relative 95% CI. ALS patients identified by the algorithm were used

Region standardized rate (CI95%)	Age classes (years)	Male			Female			Total		
		ALS cases	Population	Prevalence (per 100,000)	ALS cases	Population	Prevalence (per 100,000)	ALS cases	Population	Prevalence (per 100,000)
Lazio 10.88 (10.01-11.84)	18-24	0	198,398	0.00	2	180,004	1.11	2	378,402	0.53
	25-29	0	150,453	0.00	1	142,128	0.70	1	292,581	0.34
	30-34	3	160,617	1.87	2	158,699	1.26	5	319,316	1.57
	35-39	3	181,335	1.65	1	182,057	0.55	4	363,392	1.10
	40-44	2	208,722	0.96	9	215,871	4.17	11	424,593	2.59
	45-49	12	234,004	5.13	10	247,731	4.04	22	481,735	4.57
	50-54	24	234,945	10.22	19	251,163	7.57	43	486,108	8.85
	55-59	41	214,454	19.12	17	232,268	7.32	58	446,722	12.98
	60-64	44	176,683	24.90	30	196,141	15.30	74	372,824	19.85
	65-69	47	151,574	31.01	45	172,691	26.06	92	324,265	28.37
	70-74	45	140,492	32.03	49	166,236	29.48	94	306,728	30.65
	75-79	40	107,403	37.24	35	137,876	25.39	75	245,279	30.58
	80+	26	150,267	17.30	39	250,338	15.58	65	400,605	16.23
	Total	287	2,309,347	12.43	259	2,533,203	10.22	546	4,842,550	11.28
Tuscany 11.60 (10.51-12.79)	18-24	0	121,081	0.00	0	109,446	0.00	0	230,527	0.00
	25-29	0	89,964	0.00	1	85,074	1.18	1	175,038	0.57
	30-34	1	95,067	1.05	2	94,969	2.11	3	190,036	1.58
	35-39	2	105,213	1.90	1	106,239	0.94	3	211,452	1.42
	40-44	4	127,146	3.15	4	130,442	3.07	8	257,588	3.11
	45-49	8	147,636	5.42	6	151,443	3.96	14	299,079	4.68
	50-54	10	149,375	6.70	7	155,169	4.51	17	304,544	5.58
	55-59	24	137,412	17.47	14	145,154	9.65	38	282,566	13.45
	60-64	25	116,308	21.50	22	127,257	17.29	47	243,565	19.30
	65-69	31	104,168	29.76	35	115,520	30.30	66	219,688	30.04
	70-74	49	106,257	46.12	47	121,980	38.53	96	228,237	42.06
	75-79	35	81,173	43.12	25	100,741	24.82	60	181,914	32.98
	80+	28	121,378	23.07	27	199,211	13.55	55	320,589	17.16
	Total	217	1,502,178	14.45	191	1,642,645	11.63	408	3,144,823	12.97
Umbria 9.35 (7.47-11.72)	18-24	1	28,846	3.47	1	26,001	3.85	2	54,847	3.65
	25-29	0	21,600	0.00	0	20,326	0.00	0	41,926	0.00
	30-34	0	23,020	0.00	0	22,947	0.00	0	45,967	0.00
	35-39	0	25,551	0.00	0	25,645	0.00	0	51,196	0.00
	40-44	1	29,683	3.37	0	30,488	0.00	1	60,171	1.66
	45-49	2	33,109	6.04	0	34,552	0.00	2	67,661	2.96
	50-54	0	33,553	0.00	1	35,602	2.81	1	69,155	1.45
	55-59	7	31,873	21.96	1	34,271	2.92	8	66,144	12.10
	60-64	6	27,586	21.75	1	30,064	3.33	7	57,650	12.14
	65-69	8	25,090	31.89	6	27,799	21.58	14	52,889	26.47
	70-74	11	24,535	44.83	9	27,443	32.80	20	51,978	38.48
	75-79	6	19,646	30.54	8	23,380	34.22	14	43,026	32.54
	80+	5	29,256	17.09	3	48,661	6.17	8	77,917	10.27
	Total	47	353,348	13.30	30	387,179	7.75	77	740,527	10.40

Table 2. Age- and gender-specific and standardized amyotrophic lateral sclerosis prevalence rates, per 100,000 inhabitants.
Tabella 2. Prevalenza specifica per età e genere e standardizzata della sclerosi laterale amiotrofica, per 100.000 abitanti.

as numerator; the resident population for each single year on January 1st was used as denominator.
The capability of the algorithm for the identification of patients affected by ALS from administrative data was investigated taking advantage of the clinical dataset available in the Lazio region for several years until 2016. To this end, the exclusion criteria used for the definition of ALS cases from administrative data (adult age, resident and enrolled in the healthcare system on 31.12.2016) were applied, obtaining 310 cases for whom traceability was checked through the algorithm.

Results

The recruitment of patients affected by ALS between 01.01.2014 and 31.12.2019 is shown for each region in Figure 1. A total of 2,635 persons affected by ALS were identified. After applying the inclusion and exclusion criteria, 546 ALS cases were identified in Lazio, 408 in Tuscany, and 77 in Umbria, which is in line with the dimension of the regional population. Mortality was high in these patients; in Lazio and in Umbria there was a considerable number of patients treated in the region, but who are not assisted, which is a proxy of not being resident.

Figure 2 shows the contribution of the three data sources considered for ALS identification in the three regions: diseases specific co-payment exemptions accounted for the biggest share, with an exclusive contribution which varied between 24.7% in Umbria, 28.4% in Tuscany, and 30.6% in Lazio. Hospital discharge records played an important role, with an exclusive contribution ranging from 15.6% in Umbria, to 18.9% in Lazio, and 26.5% in Tuscany, whereas emergency room visits played a minor role. The major difference was observed for the proportion of patients identified by both exemptions and hospital discharge, which was highest in Umbria (49.3%), followed by Tuscany (40.7%) and Lazio (33.9%).

Identifying ALS patients through the algorithm used in this study produced standardised overall ALS prevalence rates which are similar among the three regions, ranging 11.60/100,000 in Tuscany, 10.88/100,000 in Lazio, and 9.35/100,000 in Umbria (Table 2). The 5-year crude rates were higher in men and in people aged 65-79 years.

Standardised incidence rates over the years, stratified by sex for the three regions, are shown in Figure 3.

Looking at the time trend, differences were observed among regions. In Lazio, a decrease was observed, with overall standardised incidence rates dropping from 3.33 (95%CI 2.84-3.90) in 2014 to 1.88 (95%CI 1.53-2.30) in 2019. In Tuscany and Umbria, incidence was rather stable over time, with variations between 3.36 (95%CI 2.79-4.04) in 2014 and 3.96 (95%CI 3.36-4.68) in 2019 in Tuscany and 3.31 (95%CI 2.25-4.87) in 2014 and 2.94 (95%CI 1.96-4.40) in 2019 in Umbria.

Finally, comparing the cases in the clinical dataset with those identified through the algorithm used in this study, 263 out of 310 (84.8%) overlapped.

Discussion

This study found similar prevalence estimates of ALS in three regions located in Central Italy. Overall, ALS was more common among males and persons aged 60-79 years. The observed prevalence rates were slightly higher than those reported in previous studies both in Italy and in other countries.[7,13,14] Yet, the published data refer to more than a decade ago and national and international literature reported an increasing trend over the years,[14,30,31] which may be partly explained by earlier diagnosis of ALS along with an increasing life expectancy of ALS patients. Therefore, the results presented in this paper probably reflect an updated estimate of the phenomenon.

In line with prevalence, also the observed incidence was a little higher than values reported by other Authors,[2,16] but are similar to the results of a more recent study conducted in Emilia-Romagna.[11]

Differences among regions were detected in incidence rates over the years, but, unlike what other studies reported, there was no evidence of increasing incidence over time in any considered region.

The male-female ratio here found was comparable with previous results,[7] except for Umbria, where there was a stronger difference between men and women, with a rate ratio of 1.71. The comparison with the clinical dataset showed that the algorithm identified a high proportion of clinically confirmed ALS patients. Unfortunately, the available clinical data did not allow to perform a complete validation analysis due to major limitations. First, clinical data did not cover all centres treating ALS and cases are potentially underestimated. Second, the centres contributing to the clinical dataset did not notify individuals free from ALS, which hindered from enrolling a control population in this study.

Intraregional differences may partly be explained by different administrative procedures feeding the databases, and different regional organisation of the disease specific care pathways. Also, detection of ALS cases in administrative data are sensitive to changes in health policies, such as access to disease specific co-payment exemptions or redefinition of care pathways, which may have contributed to temporal variations.

The main strength of the present study is the availability of real-world data referring to the entire population of the three Italian regions, which account for about 10 million residents. This is also reflected in the considerable number of cases identified as ALS. Even if occurrence of ALS in the present study was partly higher than rates reported in the literature, it can be concluded that the algorithm might rather have underestimated the real number of ALS cases as confirmed by the comparison with the clinical data (15.2% not traced), probably due to the fact that patients not claiming disease specific co-payment exemption, not admitted to hospital, or accessing emergency rooms could not be identified.

While administrative databases offer a series of advantages, they also come along with several limitations, which may impact the generalisability of these

results. Just to mention two of them, only the patients treated by public services, or private providers authorised for public reimbursement were retrieved, and data referring to ambulatory services do not comprise information on diagnoses. Additionally, different level of completeness of administrative databases must be taken into account; for example, in Umbria, diagnostic codes were missing in a part of the emergency room visits; consequently, this part of the algorithm is potentially underestimated in that region. Moreover, the nature of the data does not offer information on genetics or other clinical details.

The major challenge in this study was the definition of the algorithm for ALS case identification from administrative databases. Given that this was the first step of a study which aims to evaluate efficacy and safety of drug treatments in ALS patients, specificity was paramount, because it was important to make sure that only true ALS cases are included in the cohort. Actually, while other authors also considered disease specific drug treatment (namely riluzole) for case identification,[32] in the present study this option was excluded, because a preliminary analysis showed a not negligible share of off-label riluzole use in patients affected by motoneuron diseases other than ALS.[33]

Conclusions

This study provides updated estimates of ALS prevalence and incidence in three Italian regions. The results are slightly higher than those previously reported. Yet, this is plausible, given that previous results relate to at least ten years ago and they evidenced increasing trends. The results of this study highlight the opportunity to use administrative data to produce occurrence estimates, useful to both epidemiological surveillance and research and healthcare policies. In future studies, the geographic distribution of patients within the single region could be analysed. This type of analysis could be useful in assessing possible environmental and genetic factors in ALS pathology. Furthermore, understanding in which area of the region ALS patients are present could be useful for regional healthcare policies in order to ensure patient care.

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References

1. European Commission. Rare diseases. Available from https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en (last accessed: 08.11.2022).
2. Beghi E, Logroscino G, Chiò A, et al. The epidemiology of ALS and the role of population-based registries. Biochim Biophys Acta 2006;1762(11-12):1150-57. doi: 10.1016/j.bbadis.2006.09.008
3. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. N Engl J Med 2001;344(22):1688-700. doi: 10.1056/NEJM200105313442207.
4. Marin B, Boumédiene F, Logroscino G, et al. Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. Int J Epidemiol 2017;46(1):57-74. doi:10.1093/ije/dyw06
5. Xu L, Liu T, Liu L, et al. Global variation in prevalence and incidence of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol 2020;267(4):944-53. doi: 10.1007/s00415-019-09652-y
6. Logroscino G, Traynor BJ, Hardiman O, et al. Incidence of amyotrophic lateral sclerosis in Europe. J Neurol Neurosurg Psychiatry 2010;81(4):385-90. doi: 10.1136/jnnp.2009.183525
7. Chiò A, Mora G, Calvo A, Mazzini L, Bottacchi E, Mutani R. Epidemiology of ALS in Italy: a 10-year prospective population-based study. Neurology 2009;72(8):725-31. doi:10.1212/01.wnl.0000343008.26874.d1
8. Mandrioli J, Faglioni P, Merelli E, Sola P. The epidemiology of ALS in Modena, Italy. Neurology 2003;60(4):683-89. doi:10.1212/01.wnl.0000048208.54755.78
9. Beghi E, Millul A, Micheli A, Vitelli E, Logroscino G; SLALOM Group. Incidence of ALS in Lombardy, Italy. Neurology 2007;68(2):141-5. doi: 10.1212/01.wnl.0000250339.14392.bb
10. Bandettini di Poggio M, Sormani MP, Truffelli R, et al. Clinical epidemiology of ALS in Liguria, Italy. Amyotroph Lateral Scler Frontotemporal Degener 2013;14(1):52-57. doi: 10.3109/17482968.2012.729062
11. Gianferrari G, Martinelli I, Zucchi E, et al. Epidemiological, Clinical and Genetic Features of ALS in the Last Decade: A Prospective Population-Based Study in the Emilia Romagna Region of Italy. Biomedicines 2022;10(4):819. doi: 10.3390/biomedicines10040819
12. Brown CA, Lally C, Kupelian V, Flanders WD. Estimated Prevalence and Incidence of Amyotrophic Lateral Sclerosis and SOD1 and C9orf72 Genetic Variants. Neuroepidemiology 2021;55(5):342-53. doi: 10.1159/000516752
13. Puopolo M, Bacigalupo I, Piscopo P, et al. Prevalence of amyotrophic lateral sclerosis in Latium region, Italy. Brain Behav 2021;11(12):e2378. doi: 10.1002/brb3.2378
14. Georgoulopoulou E, Vinceti M, Bonvicini F, et al. Changing incidence and subtypes of ALS in Modena, Italy: A 10-years prospective study. Amyotroph Lateral Scler 2011;12(6):451-57. doi: 10.3109/17482968.2011.593037
15. Chiò A, Ciccone G, Calvo A, et al. Validity of hospital morbidity records for amyotrophic lateral sclerosis. A population-based study. J Clin Epidemiol 2002;55(7):723-27. doi:10.1016/s0895-4356(02)00409-2
16. Vasta R, Boumédiene F, Couratier P, et al. Validity of medico-administrative data related to amyotrophic lateral sclerosis in France: A population-based study. Amyotroph Lateral Scler Frontotemporal Degener 2017;18(1-2):24-31. doi: 10.1080/21678421.2016.1241280
17. Beghi E, Logroscino G, Micheli A, et al. Validity of hospital discharge diagnoses for the assessment of the prevalence and incidence of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2001;2(2):99-104. doi:10.1080/146608201316949541
18. Stickler DE, Royer JA, Hardin JW. Accuracy and usefulness of ICD-10 death certificate coding for the identification of patients with ALS: results from the South Carolina ALS Surveillance Pilot Project. Amyotroph Lateral Scler 2012;13(1):69-73. doi:10.3109/17482968.2011.61425
19. Palese F, Pisa FE. Validation of discharge diagnosis coding for amyotrophic lateral sclerosis in an Italian regional healthcare database. Amyotroph Lateral Scler Frontotemporal Degener 2020;21(5-6):428-34. doi:10.1080/21678421.2020.1752245
20. Baldin E, Preux PM, Couratier P, Pugliatti M, Marin B; FRALIM Consortium. Validity of death certificates in the identification of cases of amyotrophic lateral sclerosis (ALS) in the Limousin region, France. A population-based study. Amyotroph Lateral Scler Frontotemporal Degener 2020;21(3-4):228-34. doi:10.1080/21678421.2020.1746811
21. Gnavi R, Picariello R, Alboini PE, et al. Validation of an Algorithm to Detect Multiple Sclerosis Cases in Administrative Health Databases in Piedmont (Italy): An Application to the Estimate of Prevalence by Age and Urbanization Level. Neuroepidemiology 2021;55(2):119-25. doi: 10.1159/000513763
22. Baldacci F, Policardo L, Rossi S, et al. Reliability of administrative data for the identification of Parkinson's disease cohorts. Neurol Sci 2015;36(5):783-86. doi: 10.1007/s10072-015-2062-z
23. Wilkinson T, Ly A, Schnier C, et al. Identifying dementia cases with routinely collected health data: A systematic review. Alzheimers Dement 2018;14(8):1038-51. doi:10.1016/j.jalz.2018.02.016
24. Bacigalupo I, Lombardo FL, Bargagli AM, et al. Identification of dementia and MCI cases in health information systems: An Italian validation study. Alzheimers Dement (N Y) 2022;8(1):e12327. doi: 10.1002/trc2.12327

25. Mbizvo GK, Bennett K, Simpson CR, Duncan SE, Chin RFM. Accuracy and utility of using administrative healthcare databases to identify people with epilepsy: a protocol for a systematic review and meta-analysis. BMJ Open 2018;8(6):e020824. doi:10.1136/bmjopen-2017-020824
26. Italian National Institute of Statistics. Istat data 2022. Available from: http://dati.istat.it/ (last accessed: 20.07.2022).
27. World Health Organization. State of Health in the EU. Italy: Country Health Profile 2019. Geneva WHO, 2019. Available from: https://eurohealthobservatory.who.int/publications/m/italy-country-health-profile-2019
28. Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000;1(5):293-99. doi: 10.1080/146608200300079536. PMID: 11464847
29. Eurostat. Population on 1 January by age and sex. 2023. Available from: https://ec.europa.eu/eurostat/databrowser/view/DEMO_PJAN__custom_6045640/default/table?lang=en (last accessed: 02.05.2023).
30. Arthur KC, Calvo A, Price TR, Geiger JT, Chiò A, Traynor BJ. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. Nat Commun 2016;7:12408. doi: 10.1038/ncomms12408
31. Chiò A, Mora G, Moglia C, et al. Secular Trends of Amyotrophic Lateral Sclerosis: The Piemonte and Valle d'Aosta Register. JAMA Neurol 2017;74(9):1097-104. doi: 10.1001/jamaneurol.2017.1387
32. Nelson LM, Topol B, Kaye W, et al. Estimation of the Prevalence of Amyotrophic Lateral Sclerosis in the United States Using National Administrative Healthcare Data from 2002 to 2004 and Capture-Recapture Methodology. Neuroepidemiology 2018;51(3-4):149-57. doi: 10.1159/000488798
33. Crescioli G, Finocchietti M, Cascini S, et al. Riluzole use in presence of contraindications in adults affected by amyotrophic lateral sclerosis and its off-label use in other motor neuron diseases: Findings from an Italian multicentre study (the CAESAR project). Front Drug Saf Regul 2022;2. doi: 10.3389/fdsfr.2022.1041275