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Amyotrophic Lateral Sclerosis in Latin America: Epidemiology, clinical features, and clinical practices on the diagnosis and management of ALS among neurologists

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“A mi querida madre Janet Aleman, quien siempre estuvo ahí

y me ayudo a cumplir todas mis metas”

“One never notices what has been done; one can only see what remains to be done”
Marie Curie

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Rights

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List of Abbreviations

ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
BMAA	B-Methylamino-L-Alanine
ECAS	Edinburgh Cognitive and Behavioral ALS Screen
FALS	Familial Amyotrophic Lateral Sclerosis
FDA	Food and Druga Administration
FVC	Forced Vital Capacity
GBD	Global Burden of Disease
ICD	International Classification of Diseases
LILACS	Latin American and Caribbean Center on Health Sciences Information
LMN	Lower Motor Neuron
MeSH	Medical Subject Headings
MND	Motor Neuron Disease
NIV	Non-Invasive Ventilation
PBP	Progressive Bulbar Palsy
PEG	Percutaneous Endoscopic Gastrostomy
PLS	Primary Lateral Sclerosis
PMA	Progressive Muscular Atrophy
PYFU	Person Years of Follow-Up
SALS	Sporadic Amyotrophic Lateral Sclerosis
SDI	Socio-Demographic Index
UMN	Upper Motor Neuron

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disease characterize by a progressive degeneration of motor neurons. ALS is a rare disease, but is the most frequent adult onset disease among motor neuron disorders with a worldwide age-and-sex standardized incidence of 1.68 per 100,000 PYFU follow up (PYFU) (1). ALS is an incurable disease with a poor survival due to respiratory insufficiency.

Recent scientific evidence have shown that ALS is heterogeneous among epidemiological indicators and clinical characteristics between geographical areas and populations. Homogenous incidence rates have been observed among countries in Northern Europe and North America with a common ancestral origin (1). Furthermore, studies performed in multi ethnics populations have reported significant differences among ethnics, with a higher occurrence among non-Hispanic populations compared to Hispanics (2,3). The variability of the disease could imply that certain populations could present a higher risk in developing the disease.

A lower ALS occurrence has been reported in Latin America compared to European and North American countries. Studies in the region have also reported differences among ethnic groups (4–6). Higher ALS mortality rates have been observed among White population compared to Admixed populations (4). Heterogeneity of ALS could be associated to ancestral origin, it is hypothesized that European population could share common “at risk” alleles increasing ALS susceptibility, while Admixed populations could present different combinations of this “at-risk” alleles leading to a low occurrence (4). Nevertheless, this variability could also be explained by differences in the methodology of the studies (study design, case ascertainment), socio-economic status, access to health care and environmental factors or genetic variants.

Most of ALS research has been performed in European countries, there is a lack of information from many regions in the world, more specifically in Latin America.

Latin America is a region shaped by continuous admixture throughout history among the European, African and Native American populations. The diversity of admixture in the Latin American population make this an interesting region for new research to improve our understanding in the pathology of ALS and how ancestral origin can play an important role in developing the disease. There is a need to provide reliable

epidemiological indicators using standardized methods to understand ALS heterogeneity.

The objective of this thesis is to describe ALS epidemiology, clinical characteristics, and the practices for diagnosis and management in Latin America.

To achieve this objective we have performed three scientific works:

Article 1: a systematic review of ALS literature in Latin America.

Article 2: a meta-analysis of ALS mortality in Latin America.

Article 3: a cross-sectional study describing the clinical practices of the diagnosis and management of ALS among neurologists in Latin America.

Chapter I. Amyotrophic Lateral Sclerosis: A general overview and variability among geographical areas and populations.

I.1. Amyotrophic Lateral Sclerosis: an overview

Amyotrophic Lateral Sclerosis is a rare neurodegenerative disease characterize by a progressive degeneration of motor neurons, which extends from the motor cortex in the brain, stem and to anterior horns of spinal cord (7). Since its discovery in the 19th century by Charcot, ALS remains an incurable disease, however advances in research have improve our understanding on ALS pathogeny, clinical presentation, and new therapies. Still, further research remains to be done to understand the full complexity of ALS.

I.1.1. Epidemiology

ALS is the most frequent adult-onset disease among motor neuron disorders. A recent meta-analysis estimated a worldwide crude ALS incidence rate of 1.75 (95% CI: 1.55 – 1.96) and an age-and sex-standardized incidence of 1.68 (95% CI: 1.50 – 1.85) per 100,000 PYFU follow up (PYFU) respectively (1). According to the Global Burden of Disease (GBD) study in 2016, worldwide all-age prevalence of motor neuron diseases was of 4.5 (95%CI: 4.1 – 5.0) per 100,000 people. ALS prevalence varies among areas, mainly because it is conditioned by the incidence and the survival of patients, ALS prevalence ranged from 4.1 to 8.4 per 100,000 persons (8).

I.1.1.1. Sex

A worldwide male predominance has been observed on ALS cases with a male to female sex ratio of 1.36 (95%CI: 1.28 – 1.45) (9).

Some studies have reported that there has been some changed over time, with an increasing number of ALS cases among women leading to a sex ratio approaching 1:1 nowadays(10–12). The apparent increase of female ALS cases in the recent decades could be explained by improvement of case ascertainment among women, better access to health, changes in the age structure of the population combined with a longer life expectancy among women. In addition, life style changes and an increase of occupational and environmental risk among women should not be dismissed (10–12).

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I.1.1.2. Age at onset and diagnosis

ALS exhibits a specific age-related pattern, characterized by an increasing incidence starting at 40 years followed by a peak in the 60s and 70s years and a sharp decrease thereafter (13). Median value of reported mean age at onset of ALS ranged between 63 and 65 years of age, variations among subcontinents have been observed, with regions showing more juvenile cases (8,9).

Mean or median age at diagnosis for ALS has been reported between 54 and 69 years (8). In some studies mean age at diagnosis has been reported to be older among women than men (8).

I.1.1.3. Sporadic and familial ALS

ALS is classified as either sporadic ALS (SALS) that represent 90% of cases and refers to patients with no known family history of the disease, or Familial ALS (FALS) that corresponds to 5-10% of cases. FALS cases are defined as the presence of history of ALS in family members.

I.1.1.4. Site of onset

ALS can also be classified depending on the site of the first clinical manifestation according to regions of muscles innervation. The most frequent categories are spinal onset and bulbar onset. Spinal onset is the most common site of onset with around 70% of cases; asymmetrical upper and lower motor neuron signs and symptoms on the limbs characterize it. Bulbar onset is associated to a poor prognosis and represent around 30% of cases, normally patients presents with speech and swallowing difficulties (14,15).

I.1.2. Etiology

Despite advances on research the cause of ALS remains unknown, different potential mechanisms has been proposed including abnormal RNA processing, mitochondrial dysfunction, protein toxicity, cytoskeletal function, SOD1-mediated toxicity by gain of function and protein misfolding (16).

Scientific literature has proposed several genetic variants that play a role in developing the disease. Different risk factors (life style and environmental) have also been assessed. The heterogeneity of the disease suggest that the combination of genetic variants and the accumulation of environmental risk factors in early time of life may

eventually lead to motor neuron degeneration (17). Other studies have proposed that ALS pathogenesis could incur a multistep process in which several sequential steps are needed to develop the disease. (18).

I.1.2.1. Genetic risk factors

Different studies through the decades have identified multiple ALS genes. Since the discovery of SOD1 in 1993 more than 120 genetic variants have been associated with a risk of ALS and at least 25 genes have been reproducibly implicated in FALS, SALS or both (7).

About 70% of FALS cases and 15% of SALS cases can be explained by a genetic factor (19). The most common pathogenic variants among FALS genes are C9orf72 (40%), SOD1 (20%) , TARDDBP (4%) and FUS (4%) (19,20). These same mutations have been also described in SALS cases. Indeed, C9orf72 has been also the most frequently mutation found in SALS cases (around 7% in European countries) (19,20).

Novel research have found seven new genes associated to ALS (MATR3, CHCHD10, TBK1, TUBA4A, C21orf2, and CCNF) (Figure 1) (21). The identification of these genes has been important in figuring out ALS molecular mechanism, that can provide important data for developing new therapies(21). Further genetic research is needed.

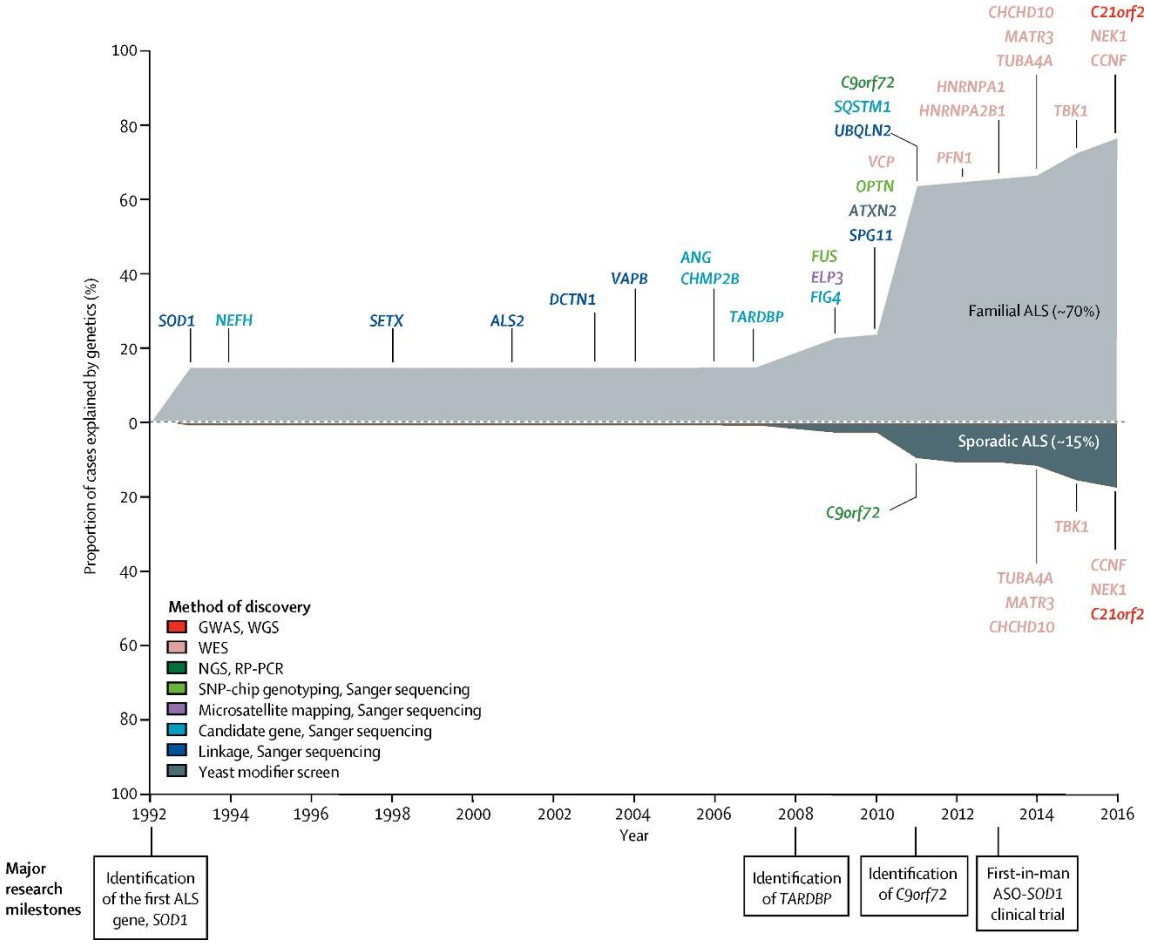

Figure 1. Genetic landscape of ALS

Source: (Chia et al 2018)

I.1.2.2. Non-genetic risk factors

Several non-genetic risk factors have been suggested in association to ALS. Some limitations have been identified in the assessment on the contribution of environmental risk exposures, which is difficult to evaluate due to the difficulty in assessing the amount of exposure and financing of studies (22). Until recently, the only established risk factors are older age, male sex and family history of ALS. Other risk factors have been suggested including life style factors such as, smoking (23,24), blood lipid levels (higher LDL levels) (25) and physical activity most specifically in football and soccer players or in people with a vigorous exercise (26).

Other studies have focused on dietary habits, a study in Italy showed that the consumption of some food and nutrients such as red meat, pork, processed meat, total protein, sodium, zinc and glutamic acid had a higher risk in developing the disease compared to the consumption of coffee, tea, raw vegetables and citrus fruits (27).

Epidemiological studies have also demonstrated potential associations to ALS among metals (28), viruses, electromagnetic fields (29) and b-methylamino-L-alanine (BMAA) (30), however scientific evidence in this area is inconclusive.

I.1.3. Clinical Features

Clinical manifestations of ALS demonstrate the lower and upper motor neuron progressive degeneration, characterize by a progressive weakness. Initial clinical manifestations could appear in any body region, bulbar, cervical, and thoracic or lumbosacral region. Depending on the affected regions, ALS can be categorized as spinal or bulbar as previously described.

ALS is a progressive disorder, symptoms will start normally in one limb with a spread to the contralateral limb and adjacent sites followed by other spinal and or bulbar areas (31,32). However, the rate of progression varies from patient to patient. Other non-contiguous symptom development has been reported, leg symptoms followed by bulbar onset and/or bulbar symptoms followed by leg onset (31).

I.1.3.1. Motor signs and symptoms

Upper motor neuron signs and symptoms

Loss of upper motor neuron will result in incoordination, stiffness, and slowness of movement. Patients with limb affectation will report difficulties in performing daily living activities and manipulation of small objects or writing, poor balance and falling. Dysarthria and dysphagia are the most common bulbar onset symptoms due to tongue and pharyngeal muscle incoordination, spastic and strained speech is characterized. At clinical evaluation, increased reflex such as Hoffman sign, distal spread of arm reflexes, jaw spasticity palm-mental sign, clonus and spastic tone can be present.

Lower motor neuron signs and symptoms

Weakness, atrophy, fasciculation’s and cramps are the main clinical features of lower motor neuron involvement. Dysarthria and dysphagia could result from tongue, lip or palate weakness. Other clinical manifestations include, difficulty holding up the head and maintaining an erect position, weakness of the diaphragm can produce progressive dyspnea and orthopnea and sleep disordered breathing. Examination could show poor palatal elevation, difficulty maintaining jaw closure, gait disorder such as steppage and waddling.

I.1.3.2. Extra motor signs and symptoms

Cognitive impairment

Observational studies have described that cognitive impairment is present in around 50 to 30% of ALS cases (33,34). A recent meta-analysis controlling bias due to motor impairment, reported that the cognitive profile of ALS consist of deficits in fluency, language, social cognitions, executive functions and verbal memory (35).

With the aim to evaluate the relationship of ALS disease stage (evaluated by the Kings clinical disease stage) and cognitive impairment (assessed by the Edinburgh Cognitive and Behavioral ALS Screen (ECAS)). A large multicenter cohort, of 161 ALS cases and 80 controls across Dublin, Edinburgh and London (36). Showed that cognitive deficit and behavioral impairment are more common with more severe disease stage (36). As the frequency of cognitive domains typically affected in ALS, the total ECAS performance and behavior impairment was higher among advancing disease stage (36).

Autonomic symptoms

Autonomic dysfunction is rare on early stages of the disease, however some studies have revealed autonomic manifestations. Among autonomic symptoms, the presence of constipation, urinary urgency, hyperhidrosis have been reported (37–39).

Parkinsonism

Extrapyramidal features may include bradykinesia, postural instability, tremor and rigidity (40).

An association between sporadic and familial Parkinson’s disease and ALS has been proposed as a syndrome defined by the presence of the two disorders without dementia or dysautonomia (32).

Focal endemic of ALS and Parkinsonism-dementia complex has been found in West New Guinea, the Mariana Islands and the Kii peninsula.

Sensory symptoms

Sensory symptoms have been reported among ALS patients. A study of a motor neuron disease registry reported that sensory symptoms were present in 22% of

patients. Numbness was reported as the most frequent, followed by neuropathic pain, tingling and diminished temperature (41) .

I.1.3.3. Phenotypes

The ALS spectrum includes different phenotypes which are dependent of the different degrees of involvement of UMN and LMN degeneration, the affected body regions, and the involvement of other extra motor systems (32).

Figure 2 shows the different phenotypes and the involvement of upper and lower motor neuron between each. In this section, we will describe the phenotypes based on the level of involvement of LMN and UMN (Progressive Muscular Atrophy (PMA) and Primary Lateral Sclerosis PLS), and those based on the body region involvement (Flail arm and Flail leg syndromes).

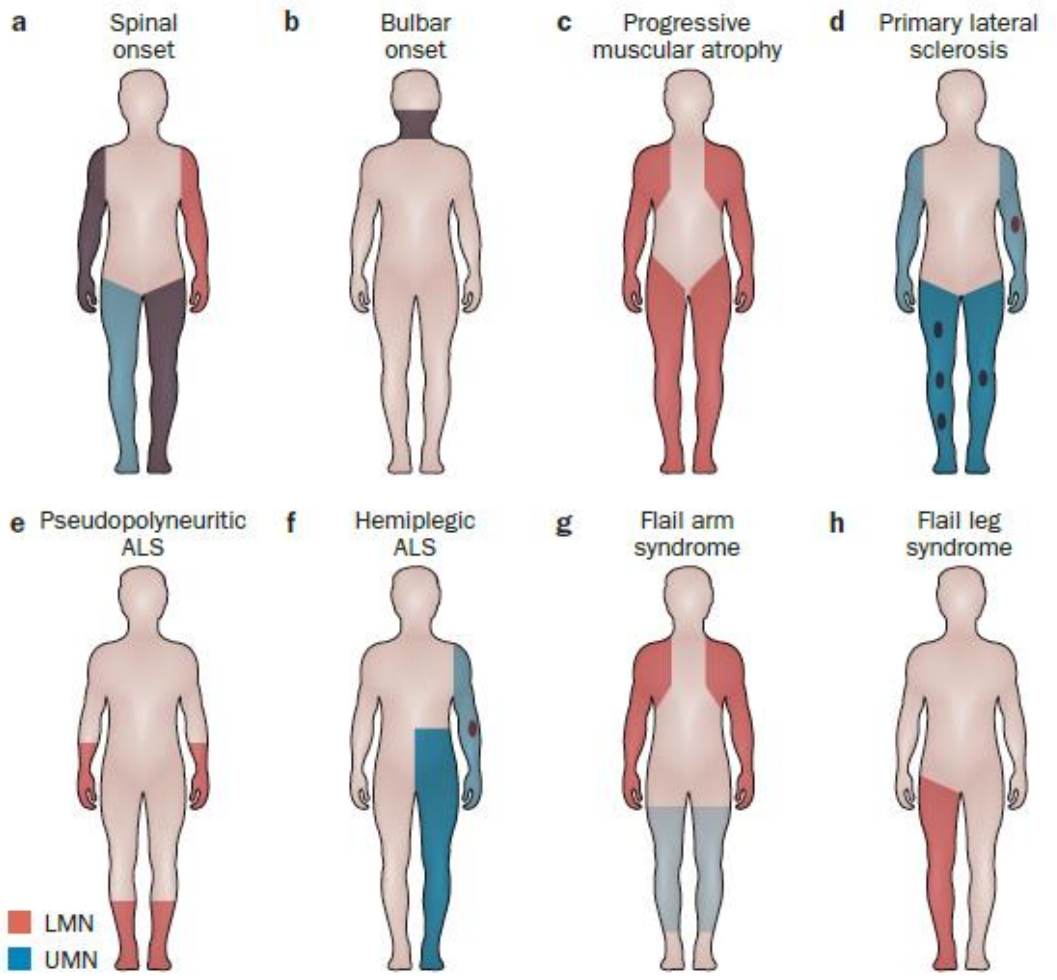

Figure 2. Pattern of motor involvement in different ALS phenotypes

Source: Swinnen et Robberecht, 2014.

Progressive muscular atrophy

Progressive muscular atrophy is characterized by signs of lower motor neuron dysfunction and comprises around 5% to 8% of all adult onset motor neuron disease (MND) (42) . This rare sporadic adult-onset disease involves LMN degeneration in the anterior horn cells and brainstem motor nuclei (32). According to the International Classification of Diseases, tenth revision (ICD-10) is classified as a motor neuron disorder. Some authors referred that it represents a form of ALS, as PMA is a progressive disorder where upper motor neuron dysfunction may occur and has been proved in imaging and post mortem studies (43). When PMA patients develop UMN signs in their clinical course the disease is known as lower motor neuron-onset ALS. However, a proportion of patients may never develop UMN dysfunction.

Clinical features of PMA include progressive flaccid weakness, muscle atrophy, fasciculation's and hyporeflexia, starting normally in distal limbs.

Primary lateral sclerosis

Primary lateral sclerosis is characterize by a progressive upper motor neuron degeneration, it represents around 5% of all cases of motor neuron disorders (44). Incidence rate is low around 0.12 in both sex, and median survival time is the longest among all ALS phenotypes with a 10 year survival rate of 71.1% (45).

Some patients with PLS may never develop LMN degeneration, however most of the patients develop LMN signs within 4 years of onset (46)

Flail leg syndrome

Flail leg syndrome also referred as pseudopolyneuritic variant, or Marie-Patrikio's type. It is characterized by progressive LMN weakness and wasting with onset in the distal leg. There no difference among sex, male to female ratio is 1.03:1 and mean age onset is around 65.0 years (45).

In a London cohort flail leg syndrome represented around 6% of all ALS cases, and around 3% in Melbourne Australia patients (47)

Flail arm syndrome

The flail arm syndrome also known as brachial amyotrophic diplegia or Vulpian-Bernhardts type. Clinical features include a progressive and symmetric weakness and wasting predominantly affecting the proximal arm while lower limbs and bulbar muscles

are spared (32). Is relative rare and is most frequent among men with a male to female ratio of 4:1 and a mean age at onset around 62.6 years (45).

In a London cohort flail arm syndrome cases represented around 11% of all cases, and 5.1% in Melbourne Australia patients (47).

I.1.4. Diagnosis

Diagnosis of ALS is based on the presence of upper and lower motor neuron signs and symptoms, progression of the disease and the absence or exclusion of other diseases that could explain the patient's situation (48,49).

In early stages of the disease, the wide variety of clinical features can make it difficult to establish ALS diagnosis, in an attempt to ensure appropriate patient inclusion for scientific studies and diagnostic precision, the El Escorial criteria was created in1994. However, research through the years has recognized the problems and weaknesses of this criteria most particularly the lack of sensitivity, leading to revisions of the Criteria in 2000 (Airlie house criteria), 2008 (Awaji criteria) and most recent in 2019, the Gold coast criteria. In spite of the changes in each revision, key features for the diagnosis of ALS have always include upper and lower motor neuron signs and disease progression over time.

In the following section, we described the different diagnostic criteria that have been used since the 90's.

I.1.4.1. Diagnostic criteria

El Escorial

In May 1994 a three-day workshop was assemble in El Escorial Spain by the World Federation of Neurology Subcommittee on Motor Neuron Disease, with the objective to develop a diagnostic criteria for ALS internationally accepted for patient inclusions in therapeutic trials and molecular genetic research studies. Even though at the beginning this criterion had a research purpose, it has been widely used in the clinical practice also.

El Escorial diagnostic criteria requires for the diagnosis of ALS the presence of LMN and UMN degeneration and progressive spread within a region to other regions. All together with the absence of electrophysiological and neuroimaging evidence of other diseases. Diagnosis of ALS is made by the identification of clinical findings through

clinical history and neurological examination, accompanied by electrophysiological, neuro-imaging and other laboratory examinations to exclude other diseases.

As shown in table 1, according to the clinical findings, four categories are proposed: definite, probable, possible and suspected.

Airlie house criteria

After eight years since the El Escorial meeting, different dilemmas have been faced by neurologist and researchers, more specifically the need to establish a definite diagnosis in early stages of the disease, so that can the patient has access to the qualified treatment. Neuroimaging and Electromyography are important in shortening ALS diagnosis (50). The revised version of El Escorial or Airlie house criteria was established on April 1998 at the Airlie conference center in Warrenton Virginia.

Airlie house criteria represents the clinical standard for the diagnosis of ALS for almost three decades (49). This revised version includes a new category that involves EMG evidence of motor neuron denervation, and the deletion of the suspected category (Table 1).

Awaji criteria

Different factors limited the clinical neurophysiology used of the laboratory supported category proposed by Airlie House criteria. To address these issues, the integration of electrophysiological criteria with clinical examination findings was proposed in the Awaji Island, Japan consensus conference in 2006. The aim of the Awaji criteria was to facilitate early diagnosis. These criteria eliminated the “Laboratory-supported” category and add the presence of fasciculation’s. As shown in table 1, the definite, probable and possible categories were maintained (51).

A systematic review by *Costa et al.*, of diagnostic studies that included an assessment of the diagnostic accuracy of the Airlie House criteria and the Awaji criteria in referred patients with a clinical suspicion of ALS, reported a higher pooled sensitivity of 81.1% (95%CI: 72.2 - 90.0) of the Awaji criteria compared to 62.2% (95%CI: 49.4 – 75.1) of the Airlie House criteria. While the diagnostic specificity was the same with both criteria. An increase of 23% was observed in the number of patients classified as definite/probable using the Awaji criteria compared to the Airlie house criteria (52).

Gold Coast criteria

A consensus conference sponsored by the International Federation of Clinical Neurophysiology, the WFN, the ALS association and the MND association was placed at Gold Coast, Australia on September 2019 (53). In spite, the Airlie house and Awaji criteria has been extensively used through the years, both criteria have shown different limitations and high complexity.

With the intension to simplify ALS diagnosis and take new information in to account, the Gold Coast proposal, diagnostic categories are reduced to: ALS or not ALS. This new proposition includes patients with progressive muscular atrophy and excludes patients with UMN signs in two regions without LMN signs, as these patients may never develop LMN involvement. Supportive evidence of LMN dysfunction can be derived from ultrasound detection of fasciculation's from multiple muscles, while UMN dysfunction can be evidence from transcranial magnetic stimulation, MRI and neurofilament levels. Finally, ALS may include cognitive, behavioral and/or psychiatric abnormalities (53,54).

A retrospective revision of 506 patients comparing the diagnostic accuracy of Gold Coast criteria to Awaji and Airlie house, reported that the sensitivity of Gold Coast (92%) was comparable to that of Awaji (90.3) and Airlie house (88.6%), recommending the Gold Coast Criteria for clinical practice and clinical trials (55).

Table 1. ALS diagnostic criteria

Diagnosis criteria	Categories	Definition
El Escorial criteria (Brooks, 1994)	Definite	Presence of UMN and LMN signs in the bulbar region and at least two of the other spinal regions; or the presence of UMN and LMN signs in three spinal regions.
	Probable	Presence of UMN and LMN signs in at least two regions. UMN signs must be above the LMN signs.
	Possible	UMN and LMN signs are in only one region, or the presence of only UMN signs in two or more regions; or LMN signs are rostral to UMN signs.
	Suspected	The presence of LMN signs alone in two or more regions.
El Escorial revised or Airlie House criteria (Brooks, 2000)	Clinically Definite	Clinical evidence alone of UMN and LMN signs in the bulbar region and at least two spinal regions; or UMN and LMN signs in three spinal regions.
	Clinically Probable	Clinical evidence alone of UMN and LMN signs in at least two region with UMN signs above the LMN signs.
	Clinically Probable-Laboratory supported	Clinical signs of UMN and LMN dysfunction in one region or UMN signs alone in one region and LMN signs by EMG criteria are found in at least two regions. Followed by exclusion of other causes by neuroimaging and clinical laboratory examination.
	Clinically Possible	Clinical signs of UMN and LMN dysfunction are present together in one region or UMN signs in two or more regions or LMN signs above to UMN signs, and the diagnosis of clinically probable-laboratory supported cannot be proven.
Awaji criteria (Carvalho, 2008)	Clinically definite	Clinical or electrophysiological evidence of UMN and LMN signs in the bulbar and at least two spinal regions, or the presence of LMN and UMN signs in three spinal regions.
	Clinically Probable	Clinical or electrophysiological evidence of UMN and LMN signs in at least two regions with some UMN signs above the LMN signs.
	Clinically Possible	Clinical or electrophysiological evidence signs of UMN and LMN dysfunction in one region, or UMN signs alone in two or more regions, or LMN signs are found above to UMN signs. With exclusion of other diagnosis.
Gold coast criteria (2019)	ALS	Progressive motor impairment and the presence of upper and lower motor neuron dysfunction in at least 1 body region or lower motor neuron dysfunction in at least two body regions and complementary exams (nerve conduction studies and needle EMG, MRI or other imaging studies) excluding other disease processes.

I.1.4.2. Complementary exams

Electro diagnostic studies

Electro diagnostic studies are a standard part of the evaluation of motor neuron disease as the evidence of motor neuron dysfunction supports ALS diagnosis. Studies have shown that electro diagnostic studies are a major help in identifying lower motor neuron abnormalities before clinical presentation, which can allow an early entry of ALS cases into clinical trials (52).

Needle electromyography and nerve conduction studies are the most important studies for neurophysiological data as both studies can assist in documenting the progression of lower motor neuron degeneration and minimizing early misdiagnosis (56).

Neuroimaging and laboratory studies

There are no known specific biomarkers for ALS diagnosis. Neuroimaging and laboratory studies are performed as the general evaluation of motor neuron disease to rule out other diseases. These studies include, computed tomography and magnetic resonance imaging (MRI) of the brain and spine. Laboratory testing of blood, urine and cerebrospinal fluid.

I.1.4.3. Differential diagnosis

Different diseases can present signs or symptoms of upper and lower motor neuron affection. A complete clinical evaluation combine with neuroimaging and laboratory testing should be aimed to rule out other disease, as some of the conditions are treatable if an early diagnosis is posed. Table 2 summarizes some diseases to take in consideration on the differential diagnosis of ALS.

Table 2. Differential diagnosis of ALS

Diseases to consider on ALS differential diagnosis	
Autoimmune syndromes	Multifocal motor neuropathy
	Multiple sclerosis
	Myasthenia gravis
Compression syndromes	Cervical meningioma
	Syringomyelia
Endocrine abnormalities	Hyper and Hypothyroidism with myopathy
	Hypokalemia
Infections	Acute and post poliomyelitis
	HIV-1
	Brucellosis
	Prion disorders
Myopathies	Inflammatory myopathies
	Polymyositis

Modified from the European guidelines on the clinical management of ALS (57).

I.1.5. Prognosis and survival

ALS is a fatal disease with a median survival time since onset around 25 to 35 months and around 15 to 20 months since diagnosis (9). There is a poor prognosis of ALS mainly due to the respiratory and nutritional complications. However, several factors have been associated to improve prognosis, including sociodemographic characteristics (younger age at onset), clinical features (spinal onset, longer diagnostic delay) and management (use of Riluzole, PEG and multidisciplinary care) (58) .

I.1.5.1. Prognostic factors

Sociodemographic factors

Age has been considered an independent as prognostic predictor in ALS. Older age at onset or diagnosis of ALS has been associated to a shorter survival (59,60). A study performed in a French ALS registry reported the shortest median survival time since onset (26.2 months) and since diagnosis (15.6 months), which was probably due to the age structure of patients(median age at diagnosis of ALS cases 70.3 years) and the old age structure of the population under consideration (30% of subjects older than 60 years) (61).

Clinical factors

Bulbar onset has been showed to have a poor survival compare to spinal onset (59,60). Worse prognosis has been observed in patients with respiratory involvement in early stages of the disease (22).

Better survival has been associated to patients that had a longer delay of diagnosis (time from symptoms onset to diagnosis)(62,63). Shorter diagnostic delay is likely to indicate a more aggressive disease or a more progressive disease which leads the patient to seek medical attention.

The rate of progression of ALS has been analyzed as a predictor for prognosis. The ALS Functional Rating Scale-Revised (ALSFRS-R) is a rating scale that measures physical function on daily living activities. This scale has been related to prognosis (64,65). A Danish cohort evaluated the ALSFRS-R score at initial assessment in association with duration of symptoms (time from onset to initial assessment) defined as ΔFS (progression rate). This study showed that a ΔFS ≥ 0.68 was a poor predictor for survival with a hazard ratio of 3.3 (95%CI: 1.91-5.69) (66). A recent meta-analysis showed that patients with a rapid functional deterioration assessed as a ALSFRS-R change rate of 1/month, tended to have a shorter survival with a hazard ratio of 1.48 (95%CI: 1.13 - 1.95) (67).

Respiratory status is also related to ALS outcome. Studies have shown that a lower force vital capacity at diagnosis is a poor predictor of survival (68), a meta-analysis estimated that a FVC lower than 85% increases the risk of death by 0.86 times (67).

Management

Riluzole: it was the first drug therapy approved by the U.S. Food and Drug Administration (FDA) in the treatment of ALS. Evidence of the benefits or Riluzole was observed from four randomized controlled trials. Results showed that Riluzole 100 mg per day improved survival around two or three months on ALS patients (69).

Multidisciplinary care: Studies have shown that patients who are followed on multidisciplinary clinics with specialized teams consisting of multidisciplinary disciplines have presented longer survival and improvement on quality of life compared to patients that are normally followed by general neurology only (70–73). A study from four European registries showed that patients that attended ALS centers have a longer survival (11% to 15%) than the entire ALS population, but referral bias needed to take in consideration as patients that attended ALS centers were younger and more likely to have a spinal onset (70).

Non-invasive ventilation*:* Non-invasive positive-pressure ventilation is the standard of care for ALS patients and respiratory insufficiency, a considerable increased in survival and an improve in quality of life has been observed among patients using NIV than controls (74–76). The aim of NIV is to compensate diaphragm weakness, and alleviate symptoms of respiratory insufficiency (74). It is not clear when to initiate NIV, recent studies have showed that an early intervention increased survival (77) and patients that started earlier showed a slower subsequent decline of FVC compared with placebo (78).

I.1.6. Management

I.1.6.1. Clinical management guidelines

There is a lack of a specific therapy and until date there is no cure for the disease but a number of different therapies are available.

With the aim of establishing evidence-based guidelines on the diagnosis and management of ALS and identifying areas where further research is needed, and create a consensus among neurologist, European and American neurology task force performed systematic reviews of relevant and updated citations on ALS diagnosis and management (57,79). The American Academy of Neurology guidelines were published in 2009, while the European Federation of Neurological Societies guidelines were published two years later (2011).

Both guidelines recommend several key points according to ALS diagnosis (communication of diagnosis), symptomatic treatment, disease modifying treatment, nutritional and respiratory aspects, diagnosis of cognitive impairment, follow up of patients and quality of life at the end of life. Some key recommendations include the following:

- Early diagnosis should be pursued. Patients should receive diagnosis by a consultant with good knowledge of the patient situation and he should provide sufficient information of the disease.
- Patients with ALS should receive a multidisciplinary approach among different disciplines, including neurologist, pneumologist, nutritionist, gastroenterologist, rehabilitation medicine physician, speech therapist, specialized nurse and palliative care physician.
- Symptoms such as sialorrhea, pseudobulbar affect, spasticity and pain should be controlled.
- Riluzole should be initiated as early as possible.
- Percutaneous endoscopic gastrostomy (PEG) and Non-invasive ventilation (NIV) have shown to improved quality of life and survival. Symptoms or signs of respiratory insufficiency and deglutition problems should be checked at each visit for an early intervention.
- Directives and decisions of palliative care and end of life should be discussed with time.

I.2. Epidemiology of ALS among geographical areas and populations

Current research has demonstrated that ALS varies among geographical areas and populations. ALS heterogeneity has been observed among: i) epidemiological indicators including incidence and mortality rates, ii) variations of clinical features such as age at onset, proportion of bulbar cases and survival among others iii) and frequency of genetic mutations. The variability of the disease could imply that certain population's presents a risk in developing the disease or a protective factor, as ALS incidence has been showed to be lower in specific regions in the world.

In this chapter, we present a detailed description of ALS epidemiology and heterogeneity.

I.2.1. Epidemiological variability among geographical areas

Different studies have provide important clues that the worldwide distribution of ALS is not uniform. A systematic review by *Cronin et al*. that searched for all incidence, prevalence and mortality studies on ALS from 1966 to 2006, found that the crude incidence rates among Europe and North America (0.6 to 2.4 per 100,000 PYFU) were the highest compare to other studies outside Europe and North America (80). Age and sex adjusted to the 2000 US population incidence rates showed that incidence of ALS appear to be uniform in Europe as population-based prospective studies from Ireland, Scotland and Italy reported an age- and sex-adjusted incidence in the 45 to 74 age band of 3.8 – 5.7 per 100,000 PYFU. Prospective studies from North America reported a similar adjusted incidence to Europe studies, while a study in Japan reported the lowest adjusted incidence of 2.0 per 100,000 PYFU. In this systematic review, most of the studies were performed in Europe, and in studies performed outside Europe showed a broad methodological heterogeneity, which make it difficult to draw firm conclusions (80).

Chio et al., performed an update of worldwide ALS epidemiology, in 2013. In this review in order to decrease the methodological heterogeneity, only observational population-based studies that were conducted after the publication of the El Escorial criteria, and that reported quantitative data of incidence and prevalence rates were included. There was an underrepresentation of major regions of the world, as most of the studies were from Europe (n=25) followed by 6 studies in Asia and the Pacific and 5 from North America and only one study from South America (Uruguay). The median incidence

was of 1.90 (95%CI: 1.37 – 2.40) per 100,000 PYFU. Incidence and prevalence rates varied among studies. In Europe, crude incidences ranged from 0.5/100,000 in Yugoslavia (81) to 3.6/100,000 in the Faroe Islands (82). In Asia and the pacific region, China reported the lowest crude incidence rates of 0.3 per 100,000 PYFU (83), while New Zealand crude incidence was of 3.3 per 100,000 PYFU (84). Median incidence rates from the different geographical areas varied, Europe reported the highest median ALS incidence of 2.08/100,000 PYFU, followed by North America (1.80/100,000 PYFU), while studies from Asia reported the lowest median incidence of 0.60/100,000 PYFU. These findings helped established the wide variability of ALS occurrence, however the methodological differences among the studies more specifically, the differences in data collection or the use of sources for case ascertainment could conduct to an underestimation of cases in areas were only one source was used (85).

To further, clarify the global ALS epidemiology a meta-analysis was performed to control potential biases and explore potential factors of heterogeneity. The authors included studies that followed specific criteria: population-based studies of newly diagnosed ALS cases using multiple types of sources for case ascertainment, a clear description of the study population and diagnostic criteria for ALS cases and neurological confirmation of the diagnosis. To provide accurate comparisons between studies, age and sex direct standardization was performed. Overall, 45 geographical areas and 11 subcontinents were covered, once again most of the studies found were from Europe (53.3%), and followed by the American continent (31.1%) from which, most were from North America. While Asia was only represented by 5 studies, North Africa and Oceania by one study each. Subgroup analysis according to subcontinent classification by the United Nations Statistics Division showed statistically difference on ALS standardized incidence between Northern Europe 1.89 (95%CI: 1.46- 2.32) and Eastern Asia 0.83 (95%CI: 0.42 – 1.24) and Southern Asia 0.73 (95%CI: 0.58 – 0.89). Metaregression was performed to explore sources of heterogeneity, different variables were taken in consideration such as life expectancy after 50 years, study design, diagnosis criteria and PYFU of follow up (PYFU). Subcontinent was identified as significant source of heterogeneity (1). Figure 3 shows the standardized worldwide ALS distribution.

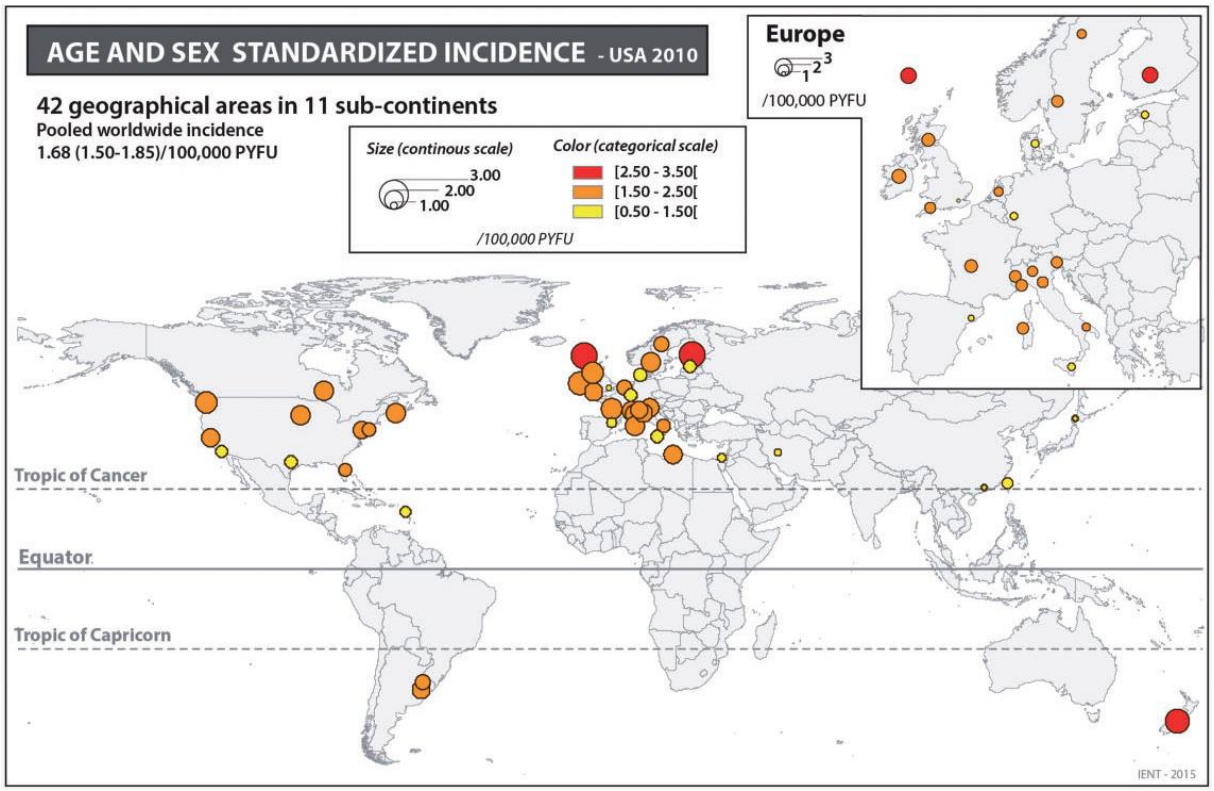

Figure 3. ALS worldwide distribution, age- and sex-standardized incidence rates. Source: Marin et al 2016.

The Global burden of disease study 2016 of motor neuron disease was a study that covered195 countries and territories from 1990 to 2016. They found that the highest age-standardized prevalence per 100,000 population was observed in high-income North America 16.8 (95%CI: 15.8 -17.9), followed by Australasia 14.7 (95%CI: 13.5-16.1) and Western Europe 12.9 (95%CI: 11.7-14.1). While the lowest were reported in Central Sub-Saharan Africa 1.2 (95%CI: 1.1 -1.4) and in Eastern Sub-Saharan Africa 1.3 (95%CI: 1.1 -1.4). Similar results were also observed among age-standardized incidence, Australasia (2.77/100,000), North America (2.30/100,000) and Western Europe (2.00/100,000) reported the highest rates while the lowest were observed in Sub-Saharan Africa (0.36-039/100,000) and Central Asia (0.39/100,000) (86). In this study, an assessment of the relationship between age-standardized rates with Socio-demographic Index (SDI) was performed, high incidence and prevalence of ALS were observed among countries with a high SDI (European countries), nevertheless other countries with a high SDI lower ALS occurrence was observed (Asian and some South American countries). This is discussed in further detail in the following chapters.

The data presented in these studies confirms the heterogeneous distribution of ALS occurrence. However, it also emphasizes the lack of information on major regions of the world.

I.2.2. Epidemiological variability among populations

Observation on whether ALS occurrence varies among ethnic groups, have been proposed since the 90's, as genetic polymorphism studies have suggested that ethnic background could indeed modify predisposition in developing ALS (80). Recent epidemiological descriptive studies have helped established this scientific query and confirm the heterogeneity of ALS distribution among ethnic groups.

Caucasian populations from Europe and North America have presented homogenous rates and they have been higher when compared to Asian and African populations. These observations were first reported in a systematic review by *Cronin et al*. This theory was strengthened by *Marin et al.*, who reported homogenous rates for geographical areas with a common ancestral origin in Europe, North America and New Zealand of 1.81 (95%CI: 1.66 – 1.97) per 100,000 PYFU. This study also reported significant differences between North Europe and Asia as previously discussed (1,80).

Studies in multiethnic populations have identified a lower ALS frequency (incidence, prevalence and mortality) among non-Whites populations (Hispanics, Asian and African American) compared to White populations in the same region.

Two studies in United States that covered large metropolitan areas, collected ALS cases between 2009 and 2011 and found significant differences between ethnic groups. A population-based study conducted in the San Francisco Bay area (SFBA) and Los Angeles (LA) California, reported higher age-adjusted incidence estimates in SFBA (2.0 95%CI: 1.8 – 2.3) compared to LA (1.2 95%CI: 1.0 – 1.3) per 100,000 PYFU respectively. In both areas incidence was higher among Whites (SFBA: 2.5; LA: 1.4) compared to Asians (SFBA: 1.0; LA: 0.7) and Blacks (SFBA: 1.4; LA: 1.0) per 100,000 PYFU respectively. Differences were also found between Hispanics and Non-Hispanics in both areas, a slightly lower rate was found in Hispanics (SFBA: 1.6; LA: 0.7) versus non-Hispanics (SFBA: 1.9; LA: 1.0) per 100,000 PYFU respectively (87).

Another study that covered three states and eight metropolitan areas with an important representation of Asians, African Americans and Hispanics. In this study, an overall of 5883 cases were collected, from which 74.8% were White, 9.3% were African

American, 3.6% were Asian, 12% were of unknown race and 0.3% were categorized as other race (American Indian, Caribbean and multiple races). According to ethnicity, 10.8% were Hispanic and 77.5% were non-Hispanic. Age-adjusted average annual incidence rate was 1.44 per 100,000 PYFU. Differences among race were observed, higher age-adjusted average incidence rates were found among Whites (1.48) compared to African American (0.89) and Asians (0.78) per 100,000 PYFU respectively, regarding ethnicity higher rates were observed in non-Hispanics 1.36 versus Hispanics 0.84 per 100,000 PYFU respectively(88).

Lower incidence has been reported in African Americans and Hispanics, however, studies assessing worldwide epidemiology have been geographically limited (mostly in Europe) and in the studies performed in United States both populations are represented as minorities.

A recent four-year prospective study in South Africa, reported a crude incidence rate of 1.09 (95%CI: 0.94 – 1.24) per 100,000 person-years and an estimated incidence rate by capture-recapture analysis of 1.11 (95%CI: 1.01-1.22). Age- and sex- adjusted incidence rates was of 1.67 (95%CI: 1.09 – 2.26) which are similar to the rates reported in studies in United States for African American populations. Furthermore, when comparing adjusted incidence rates among different population groups, highest adjusted incidence rates were observed among the European ancestry group (2.62 95%CI: 2.49 – 2.75) compared to mixed ancestry (1.09 95%CI: 0.80 – 1.37) and African ancestry group (0.56, 95%CI: 0.0 - 1.23) (89).

Studies performed in Latin America have reported lower incidence and mortality rates compared to other regions, however information of ALS in this region is limited. In the following chapters we present a description of ALS in Latin America and the possible factors of these differences.

I.2.3. Clinical variability

ALS appears to be a predominantly disease among males characterize by an age specific incidence with an age peak between 60 and 70 years, a more frequent spinal onset and a poor median survival after diagnosis. Variations of ALS clinical presentation have been observed in European countries, but also differences have been reported when compared to other geographical areas.

A meta-analysis of population-based studies with multiple sources for case ascertainment found significant differences on the sex ratio, age at onset, type of ALS and Bulbar form at onset between subcontinents of different regions and within the same continent (9).

ALS clinical characteristic difference within Europe

In Europe, in spite of presenting uniform incidence rates, some differences were observed, the proportion of FALS appear to be lower in Southern Europe (3.33%) compared to Northern Europe (5.18%), and Western Europe (5.42%). The proportion of bulbar onset was significantly higher in Northern Europe (45.4%) than in Western (34.9%) and Southern Europe (34.2%), the crude incidence of bulbar onset was also higher in Northern Europe (0.86, 95%CI: 0.81-0.91) than Eastern (0.73, 95%CI: 049 – 0.96) and Southern Europe (0.68, 95%CI: 0.48 -0.88). Differences were also observed in median survival time since onset, Northern Europe reported a shorter survival around 25 months, while in Western Europe was around 30 months and between 26.6 - 49.0 months in Southern Europe (9).

Difference across Europe were also observed in a study of six population-based registries. After adjustment to the 2000 European population, highest incidence rates of spinal ALS was observed in Piemonte, while the lowest was observed in England. Bulbar adjusted incidence rates were highest in Ireland than in Puglia and Scotland, the authors explained this differences to regional differences of case classification (90).

ALS clinical characteristic difference between Europe and other regions

Clinical characteristics varied for other geographical regions compared to Europe. FALS proportion was higher for North America (6.69%) but lower for, Hong Kong (1.2%) and Israel (0.6%) (9).

Sex ratio has varied among subcontinents, in Europe, North America and New Zealand has ranged from 1.22 to 1.33, while in some regions sex ratio seems to be higher, for instance in East (1.53) and West Asia (1.72) and higher than 2 for Iran, Uruguay and Libya (9).

Median value of the mean age at onset varied between subcontinents an older age at onset was observed in Europe and New Zealand (63 and 65 years), while it was around 59 years for North America and East Asia and even lower in Israel, Iran and Libya (9).

Crude incidence of bulbar onset was 0.43 (95%CI 0.21 – 0.66) for North America and 0.15 (95%CI: 0.12 -0.18) in East Asia (9).

A recent study that compared two hospital-based registries in Germany and China showed significant differences among prognostic factors. Age at onset was younger in patients from China (51 years) compared to Germany (61 years) ($p<0.0001$), proportion of PLS and PMA was higher in Germany than China ($p<0.0001$). The use of Riluzole, NIV and percutaneous gastrostomy was higher in German patients compare to China ($p<0.0001$). Disease progression was slower in China than in Germany (loss of ALSFRS-R score between onset and first visit divided by the number of months between both time points) ($p<0.0001$). However, no survival differences were found between the two cohorts. The authors explained that the natural course of the disease could be more benign in China, but there could be a higher standard medical care in Germany (91).

Reports from Africa are limited; a systematic review of ALS literature in Africa reported a higher proportion of juvenile form and younger age at onset for classic ALS, and a median sex ratio of 2.75 which is higher than the one reported in Europe. (92). These results were once again found in an original contribution in a multicenter hospital-based cohort, the TROPALS study, which is the first cohort of ALS in Africa(93). A male to female ratio of 2.9 was reported, and a median age at onset of 53.0 years was found. Median survival time since diagnosis was 14.0 months, and significant differences were found among centers, which could be related to differences in the use of Riluzole (93).

I.2.4. Genetic variability

Recent evidence shows that this heterogeneity is observed among ALS genetic mutations.

A large hexanucleotide repeat expansion in the first intron of C9ORF72 located on chromosome 9p21 is the most common mutation detected in FALS patients; however, the frequency of this mutation varies between regions. This mutation is highly prevalent in Europe, a study in Finland reported a proportion among FALS patients of 46% and 21.1% in SALS patients (94). Samples from a DNA bank in Ireland from 49 FALS cases and 386 SALS cases, 41% of FALS cases and 5% of SALS cases presented the C9orf72 expansion (95). A study in Piemonte Italy, from 475 ALS patients 32 cases

(6.7%) carried the C9orf72 repeat expansion, from these cases 75% were FALS cases and 25% SALS (96). On the contrary, in Asia a study of 563 Japanese patients this repeat expansion was found in only 0.4% of SALS cases and in none FALS cases (97).

A cross sectional study with a large sample of ALS cases, including cases from Europe, United States, middle Eastern, Indian, Asia and Australia (98). In overall, C9orf72 was found in 6.3% of SALS cases and 37.6% of FALS cases. Among the European sample 7.8% of SALS and 40.6% of FALS carried C9orf72. Similar proportions were observed in the United States cases (5.5% in SALS and 36.2% in FALS) (98). While in other regions, C9orf72 was only found in 5.3% of Australian SALS patients, in 21.4% of the Israel and 5% of Asian FALS cases (98).

A meta-analysis of original articles reporting C9ORF72, SOD1, TARDB and FUS mutations in ALS included 111 studies from which 81 studies were from European population and 30 studies from Asian population. Significant differences were reported for European and Asian patients. C9ORF72 repeat expansion was most common among European populations (FALS 33.7%, SALS: 5.1%) compared than Asian populations (FALS: 2.3%, SALS: 0.3%). SOD1 mutation was most frequent in the Asian population (FALS 30.0%, SALS: 1.5%) compare to the European (FALS: 14.8%, SALS: 1.2%). TARDBP and FUS mutations were less frequent in both populations, however TARDBP proportion was higher in the European population (FALS: 4.2%, SALS: 0.8%) and FUS was higher in the Asian population (FALS: 6.4%, SALS: 0.9%) and more higher than C9ORF72 repeat expansion in the same population (99).

These results support the heterogeneity in the frequency of ALS genetic mutations across geographical areas and populations. Nevertheless, most of the studies have been performed in European and Asian countries. There is an important lack of information concerning genetic mutations in other parts of the countries.

I.2.5. Potential factors of ALS variability

The epidemiological evidence of ALS in different geographical areas have lead researchers to postulate the heterogeneity of ALS in terms of epidemiology and clinical presentations. It is unclear the factors involved to explain this variability. ALS differences could be explained in part by under ascertainment of ALS cases and selection bias due to methodological issues, health care access and socio-economic factors between populations. But also, other determinants such as genetic predisposition, environmental factors and genetic ancestral origin could also explain ALS variability.

Differences of ALS occurrence and clinical characteristics across populations could imply that some populations are more at risk in developing the disease.

The epidemiological evidence presented in the previous sections has stated the worldwide heterogeneity of ALS, reporting lower ALS occurrence outside Europe and North American countries (that have reported homogenous rates).

Furthermore, studies in United States have continuously reported a lower occurrence of ALS compare to non-Hispanics populations. Which has lead researchers to postulate that Caucasian populations could have an increase risk in developing ALS compare to Admixed populations. Nevertheless, ALS research is limited in different regions of the world more specifically in Latin America a region with a predominantly Admixed population.

New evidence is needed among under represented regions to determine the true ALS spectrum. Providing new information of ALS features in Admixed populations will provide important insights of ALS variability among populations, improving our understanding of the potential implications of ancestral origin.

Initially, an ALS research project was planned in Ecuador which included a retrospective study using multiple sources of case ascertainment to perform a population-based approach, in order to estimate ALS incidence and describe clinical characteristics and survival in Ecuador. In addition a cross-sectional study in Ecuador was also planned to describe the clinical practices of the diagnosis and management of ALS among the neurologists in Ecuador. However, this project was highly impacted by, i) a political crisis in Ecuador and ii) Covid-19 pandemic.

For these reasons this project could not be finished and a new approach to study ALS in Latin America was performed, using mainly information available online.

This Thesis focus on ALS in Latin America, we have performed a systematic review of ALS in this region, followed by two original research in Latin America.

I.3. Regional overview: Latin America

I.3.1. Geography

Latin America and the Caribbean is a region in the Americas composed of 52 countries scattered across the Caribbean, Central and South America according to the United Nations Statistics divisions. Most of the region is located between the tropics of Cancer and Capricorn, where a tropical weather is predominant. However, the climate can be heterogeneous as the region includes areas along the Equator and the South Pole. Latin America geographical variation can be divided into physical regions: mountains and highlands, coastal plains and river basins. It is home of the world's driest dessert, largest rainforest, biggest river and the longest and second highest mountains range.

I.3.2. Population characteristics

According to the World Bank, Latin America and the Caribbean total population in 2020 was of 652,276,325 inhabitants (100). A younger population characterizes the age structure with 67.15% representing the 15-64 years age group, and 23.9 % of the 0-14 years age group. There has been a demographic age transition in Latin America, before the age pyramid had a broad base with the majority of the population among the 0-14 years age groups, but in recent years there has been a shift with a narrow base and an expanded center. In addition, there has been a growth among the 65 and above years age group since 2010 to 2020, this age group increase from 6.87% to 8.97% of the total population (101). Life expectancy at birth is of 75.60 in 2019 but this differs from country to country. Life expectancy in the region has been increasing over the years, gaining around 4 years since 2000 (102).

I.3.3. Socio economic characteristics

Economy varies among Latin American and the Caribbean countries, with a higher percentage of countries in the lower and upper middle-income classification. This inequality and poverty could conduct to major consequences for health.

I.3.4. Healthcare system

Latin American health systems are characterized by a fragmented system in three parts: the public sector, the private and the social security.

The organization of health systems varies from country to country. For instance, in Brazil public systems is divided in two segments, one that provides free universal

access and another that is restricted to government employees (103). Cuba National health system on the contrary, is the only health system operating in the country, characterized by being regionalized and decentralized based on the principles of free services and universal access to care (104).

Universal health is a fundamental aspiration for the Americas (105).The fragmentation and segmentation of health systems in Latin America conducts to a major inequality in access to health (106,107). Among the world regions, Latin America and the Caribbean is considered to have the highest levels of social and health inequality which could be the result of the inequalities in income distribution.

I.3.4.1. Access to health care

Latin American health systems present many challenges. Even though significant progress has been reached among health indicators in the region poverty and inequities continue to be a serious problem. Differences in access to health are highlighted among economic differences and ethnic groups more specifically among indigenous populations(107,108).

I.3.4.1.1. Number of health care resources

Health care resources including infrastructure, material and human resources are fundamental for measuring quality of health care (108). The World Health Organization considers having fewer than 23 health care professional for every 10,000 inhabitants insufficient to provide adequate attention(108). Latin American and the Caribbean region shown significant deficiencies when compared to Europe or other high income regions.

Health workers are the fundamental pillar in providing health services and improving health outcomes. The demand and supply of health works have increase over time. There are still important gaps among Latin American countries. According to the OECD, on average, there are two doctors per 1000 population (109).

There are important deficiencies in health care resources in Latin American countries, the number of hospital beds per capita is of 2.1 which is lower than the OECD average of 4.7.

I.3.4.2. Double burden of disease

Another challenge in Latin America and the Caribbean region is the epidemiological transition. As the aging population continue to growth, and the changes on the region's socioeconomic profiles, life style adaptation from other cultures have conduct to a change on the epidemiological profiles of countries. Chronic diseases such as cardiovascular diseases, cancer, mental illness and disability represent the leading health problems. Communicable diseases are still prevalent among Latin American countries, and death by injuries continue to be a major concern.

I.3.5. Ethnic population

Latin Americans represent the largest Admixed population in the world. Admixed populations are a result when moderate to large-scale movements of individuals from two or more previously isolate populations allows the exchange of genes, creating populations with ancestors from multiple sources. The previous isolated populations are referred to as ancestral or parental and the new formed population as admixed (110,111).

A result of continuous admixture mostly from European and African populations with Native Americans. This process goes back in time since approximately 15,000-18,000 years ago, as populations originating from Asia colonize America and originated Native Americans (112). However, the origins of these populations are not yet clear. One of the most accepted discussions is that Asians populations entered America after a stage in Beringia through coastal routes (113). Admixture in Latin America was marked by historical events, the Spanish colonization in 1492, the Portuguese colonization, and the subsequent slave trade from Africa. As well by an important immigration from other European countries in the 19th and 20th century (16).

Admixtures in the initial stages of colonization was marked by a strong sex bias, which involved European men and Native-American women. Studies have found that Latin Americans commonly present an increase of Native American ancestry on the X-chromosome compared to the autosome, and they trace their paternal ancestry to Europeans and the maternal ancestry to Native Americans (114,115).

Homburger et al. performed ancestry-specific PCA analysis to explore the European origins from samples of South American countries. They found that most of the European ancestry is from the Iberian Peninsula and Southern Europe (114).

Even though, admixture in the beginning was mostly between European men and Native American women, it right away expanded to include European men descendants born in America (Criollo) and Admixed women. Followed by African men and Native-American women or Admixed women, or African-descendant women with European or Criollo men (112).

African population was introduce in Latin America because of the transatlantic slave trade. Brazil, Colombia and the Caribbean ports received a greater number of enslaved people compared to other ports in America, mostly due because of mines and the production of sugar (116,117).

Migration from other populations to Latin America has continue throughout the years. Recent studies have found individuals in Peru with >25% proportion of East Asian probably due to an important immigration from China to Peru between 1859 and 1874. In Argentina individuals showed the highest number of European haplotypes that cluster in the Italian peninsula, due to recent migration events from Italy into Argentina, as well haploid genomes that cluster near individuals from Germany, Hungary and Poland have been found (114).

Research objectives

General objective

To describe ALS epidemiology, clinical characteristics, practices for diagnosis and management in Latin America.

Specific objectives

To describe epidemiological indicators, frequency of genetic mutations, clinical characteristics and survival of ALS patients in Latin America.

To describe ALS mortality rates in Latin America.

To describe clinical practices for the diagnosis and management of ALS patients among neurologists in Latin America.

To describe the clinical characteristics of ALS patients in Cuenca, Ecuador.

Chapter II. : Epidemiology, clinical features and genetics of ALS in Latin America

II.1. Rationale of studying ALS in Latin America

Research studies on ALS epidemiology have reported that there is a variability of ALS occurrence between geographic areas and populations (1,80). In the last decade, Latin America has drawn the attention of different ALS researchers because of reports describing a low risk in developing the disease. This lower risk is supported by research studies comparing ALS characteristics between Latin American and other regions that have showed: i) a lower ALS occurrence in Latin America, ii) differences in ALS clinical characteristics, and iii) differences in ALS genetic mutations.

Furthermore, several publications suggest a higher risk in developing the disease among Caucasian populations with a European ancestral origin, and a lower risk for Admixed populations.

Latin America is under represented on the ALS literature, the predominantly Admixed population make it an interesting region to performed ALS research.

In this chapter we present the evidence based data that suggest there is a lower risk of ALS in Latin America, followed by our systematic review of ALS literature covering different subjects of ALS (epidemiology, genetic mutations, clinical characteristics and survival) in Latin America.

II.1.1. Lower occurrence of ALS in Latin America?

First clues of a lower ALS occurrence in Latin America were reported in 1972 a first publication in Mexico stated a “resistance” to ALS for the Mexican community as one of the lowest ALS mortality (0.28 per 100,000 population) was reported compared to other regions where mortality ranged from 0.06 to 1.54 per 100,000 population (United States and European countries) (118). According to this study, the only populations that reported a mortality lower than 0.4 per 100,000 were, Union of South Africa, non-White population in the United States, and other Latin American countries (Chile and Uruguay) (118).

This lower occurrence was also reported in the 2000s by *Dietrich neto et al*. Studies in Brazil from 1980-2000, showed incidence rates that ranged between 0.3-0.4 per 100,000 population which was considerable low compared to studies in the same

period in Europe (incidence rates that ranged from 0.68 to 2.24) and North America (0.4 to 2.1) (119).

ALS research was rarely performed in Latin America before 2000. For instance in a global systematic review by *Cronin et al.* low incidence was reported in South America, but this region was under represented as only four studies were included from Central and South America compared to 27 studies in Europe. In this study methodological heterogeneity was highlighted (80).

More recent scientific publications have continue to report lower ALS rates in Latin America, a study in Costa Rica (1998 – 2001) reported a crude incidence of 0.97 (95%CI: 0.8 – 1.2) (120) and another in Guadeloupe (1996 – 2011) reported a crude incidence of 0.93 (95%CI: 0.71 -1.19) (121). Contrary to studies in Europe and North America in similar time periods which reported higher rates, for example, France (2000 – 2011) reported a crude incidence of 3.19 (95%CI: 2.81 – 3.56) (122), Netherlands (2006 – 2009) crude incidence 1.85 (95%CI: 1.74 – 1.95) (123) and United States 1.12 (95%CI: 1.0 – 1.24) and 2.14 (1.89 – 2.38) (87). Then again the methodological differences such as the design of the study, the sources of case ascertainment make it difficult to draw firm conclusions.

A recent worldwide meta-analysis using only population based studies assuring case ascertainment from multiple sources, reported an age standardized incidence for Southern America of 1.59 per 100,000 PYFU and 1.19 per 100,000 PYFU in the Caribbean. Both estimates were relatively lower compare to Northern (189; 95%CI: 1.46 – 2.32) , Western (1.71; 95%CI: 1.33 – 2.10) and Southern Europe (1.75; 95%CI: 1.44-2.06) and North America (1.79; 95%CI: 1.56 – 2.01) (1).However, only two studies from South America and one study from the Caribbean were included in this analysis.

This results suggest a lower ALS occurrence in Latin America, but also showed the limited data showed in this region.

II.1.2. Differences of ALS clinical characteristics and survival

Few studies have assessed the clinical characteristics and survival between Latin American countries and other regions. Two studies that have compared ALS characteristics between Latin American countries and European countries have showed some differences of ALS.

Reports of a younger age at onset has been observed in Latin America and the Caribbean compared to Europe and North America. This was reported by *Ryan et al*. a study that compared demographic and clinical information of 115 Cuban, 220 Uruguayan and 1038 Irish ALS cases. ALS referral clinics and tertiary referral centers were used as sources for case identification. In this study, a younger mean age of onset was observed for Cuba (53.0 years (95%CI: 50.4 – 55.6)) and Uruguay cases (58.2 years, (95%CI: 56.5 -60.0)) compared to Irish cases (61.6 (95%CI: 60.9 – 62.4)) and was statistically significant (p<0.001). A younger mean age of diagnosis was also observed for Cuban and Uruguayan cases compared to Irish (124). This younger age was also supported by *Gil et al.* a study that compared clinical features and survival between Uruguay and Limousin region in France. Median age at onset and diagnosis was younger for Uruguay (61 and 62 years respectively) than cases from Limousin (66 and 67 years respectively), statistical significance was also reached p=0.010 and p=0.023) respectively(125). In this latter study diagnostic delay was longer for Uruguay cases (10 months) than Limousin cases (9 months) (125).

Survival on ALS cases have been variable, for instance the study by *Ryan et al*. showed longer mean survival from onset and diagnosis for Cuba (39.0; 95%CI:24.0-70.0), and Uruguay (36.9; 95%CI: 22.9 – 71.4) than Ireland (35.0 95%CI: 23.0 – 63.0) but these were not statistical significance (124). On the contrary in the study by Gil et al. longer median survival from diagnosis was observed for Limousin cases (28 months) than Uruguayan (19 months) p=0.030. A higher proportion of bulbar cases, longer diagnostic delay and a higher proportion of definite EEDC cases in Uurguay were identified as poor prognostic factors (p<0.001) (125).

Other differences of clinical characteristics were reported in a meta-analysis of newly diagnosed ALS cases (9). Pooled sex ratio ranged from 1.24 to 1.29 in Europe, and 1.33 in North America. Conversely, in Asia sex ratio ranged from 1.53 to 1.72, and was higher than 2 in Iran, Uruguay and Libya. Reports of a lower bulbar onset was also observed in Latin American compared to Europe, crude incidence of bulbar onset

ranged from 0.68 (95%CI: 0.48 -0.88) to 0.86 (95%CI: 0.81 -0.91) in Europe, while it was 0.46 (95%CI: 0.31 – 0.66) in Uruguay p=0.08 (9). However, in this meta-analysis Latin America was only represented by one study in Uruguay (as this was the only study that fulfilled the methodological inclusion criteria of the meta-analysis).

The limited studies of ALS clinical characteristics in Latin America make it difficult to draw a firm conclusion.

II.1.3. Genetic mutations in Latin America

As described in chapter one, several studies have observed that the frequency of known ALS genetic mutations varies among geographical areas. This type of studies are limited due to the difficulties and high costs of genetic studies. *The study by Ryan et al.* found that from the 115 Cuban cases only 5.2% (5 cases) carried a already described disease variant: ANG and CHCHD10 were found in two cases and DCTN1 was found in 3 cases. When assessing the C9orf72 repeat expansion, a lower proportion was found in Cuba cases (1.7% (95%CI: 0.6 -4.1) compared to the Irish population (9.9% (95%CI: 7.8 -12.0) (124). Furthermore this repeat expansion was only found in the White population of Cuba and both were sporadic cases. No known SOD1, TARDBP or FUS mutations were found in Cuban (124).

Little is known of the genetic mutations of ALS in Latin America and due to the already known differences among countries, this rise different questions as: what is the frequency of genetic mutations in the region? Does these differs from other countries? Or are there other genetic mutations associated to Latin American populations?

The study by *Ryan et al.* provide important clues about ALS genetic differences among populations, further studies are needed in this matter as this evidence can help us add our understanding of ALS variability.

II.1.4. ALS among ethnic groups in Latin America

Studies performed in United States have reported lower rates in Hispanics populations compared to non-Hispanics populations (2,87,88). According to the National Institutes of Health (NIH), Hispanics or Latino populations is defined as a person of Cuban, Puerto Rican, Mexican, South or Central American or other Spanish culture or origin regardless of race (126).

Studies performed in Latin America from Cuba and Ecuador have shown significant differences among ethnic groups. In Cuba, mortality data was lower among the Admixed population (standardized mortality 0.55; 95%CI: 0.4-0.72) compared to the White population (standardized mortality 0.93; 95%CI: 0.83 – 1.03) p<0.001 (4). In Ecuador, a country with a predominantly admixed population reported lower mortality rate (standardized mortality 0.33; 95%CI: 0.30-0.36) compared to other regions, in addition significant differences among Admixed populations (standardized mortality 0.49; 95%CI: 0.43 – 0.55) and other ethnics (standardized mortality 0.19; 95%CI: 0.05-0.34) were observed p=0.015 (5).

II.1.5. Potential factors of variability

Difference in ALS occurrence and clinical characteristics could be related to different potential factors, as differences in case ascertainment, low access to health, lower life expectancy, socio economic status (SES) and methodological issues beneath the studies (85).

Life expectancy in Latin America is lower than European and North American countries; this could make us think that potentially ALS cases could die before developing the disease, this can also explain differences of age at onset.

As stated in chapter 1, there is an important inequality in access to health in Latin America and the Caribbean region, which is highly associated to the differences in socio economic factors, this difficulties could lead to an under estimation of ALS cases as only the part of the population that has the economic resources to specialized care could be diagnose leading to the no identification of cases in certain populations as the elderly or poor.

Heterogeneity of ALS could also be related to genetic ancestral origin. Current research have demonstrated homogenous incidence rates among countries with a predominant European population (1,80,85). Difference researchers have suggested a lower occurrence among populations of admixed genetic ancestral origin. It is hypothesized that European populations with a high proportion of Caucasian ancestral origin could share common at risk alleles leading to a higher susceptibility in developing the diseases, while in admixed populations, the combination of this alleles could produce a protective factor (4) .

II.1.6. Latin America an interesting region for ALS research

Latin America is a region shaped by continuous admixture throughout history among the European, African and Native American populations. The diversity of admixture in the Latin American population make this an interesting region for new research to improve our understanding in the pathology of ALS and how ancestral origin can play an important role in developing the disease.

However, variations of ALS could be also the result of differences in terms of determinants of incidence and phenotype such as environmental risk factors and type of frequency of ALS genetic mutations.

There is an important lack of information in different regions of the world more specifically in Latin America. For instance, in meta-analysis that assessed worldwide ALS incidence using only studies that followed specific methodology (population-based studies, multiple sources for case ascertainment) (1,9,85). Only three studies were found representing the Latin America and the Caribbean region. Two studies were from Southern America, (Uruguay and Argentina) (127,128) both high-income countries and with a predominantly European population, and another study from Guadeloupe which is a French overseas region (121).

There is an underrepresentation of ALS literature in Latin America, we are unaware of the disease characteristics in other countries of South and Central America. The existing literature of ALS in Latin America is limited to ALS incidence and mortality, there is not specific literature concerning frequency of genetic mutations and phenotype characteristics in the region.

We consider that is pertinent to acknowledge the ALS scientific production in Latin America, a clear description of ALS across geographic areas could offer the opportunity to gain more insight into the heterogeneity of ALS and the potential factors of heterogeneity.

II.2. Article 1: Epidemiological and genetic features of ALS in Latin America and the Caribbean: a systematic review

With the aim to established evidence-based research in Latin America and the Caribbean, as well to identify areas where further research is needed we performed a systematic review to describe ALS epidemiology, frequency of genetic mutations, clinical characteristics and survival in the region.

II.2.1. Methodology

To accomplish our objective, we performed a systematic search in four different databases: Medline/PubMed, Scopus, Scielo and the Latin American and Caribbean Center on Health Sciences Information (LILACS) until April 2020 without time or language restriction. To identify ALS studies in the region we used the following Medical Subject Headings (MeSH) terms *and Boolean operators* : “amyotrophic lateral sclerosis” OR “motor neuron disease” in combination with the list of countries of Latin America and the Caribbean according to the United Nations Statistics Division (129).

The disease under consideration was ALS, including also ALS subtypes such as Progressive Muscular Atrophy (PMA), Progressive Bulbar Palsy (PBP) and Primary Lateral Sclerosis (PLS). The population of interest was ALS patients in Latin America and the Caribbean. Ethnic groups were defined as the participant self-identification as Caucasians, Admixed or Mulatto and African American or Blacks as reported on the original studies.

All observational studies and case series reporting more than 10 patients that were carried out in Latin American and the Caribbean were included. When several articles reported ALS cases in the same population under study over the same time period, only studies with the larger sample or longer time of follow up were taken into consideration. We extracted only the information of Latin American countries, for the studies that compared different countries in different subcontinents. We excluded, pre-clinical studies, editorials, letters to the editor, case reports, conference proceedings and clinical trials. Systematics reviews and meta-analyses were not included but their references were manually examined.

All the identified articles were retrieved and exported into the software Rayyan QCRI (Qatar Computing Research Institute, Data Analytics Medical) (130). Two researchers performed data selection. All articles were examined independently. Initially, screening

of titles and abstracts was carried out in search for relevant studies. Secondly, a full text examination was performed to assess study eligibility. Discrepancies were discussed and agreement was reached between the two researchers in both steps.

Studies were classified in four main domains (1) epidemiology, (2) genetics, (3) clinical characteristics, (4) survival and prognosis. When articles reported information of different domain, we classified the study according to their main objective. Data extraction was recorded independently using an ad hoc created database. The information gathered for all the domains included: first author, year of publication, study period, design, sources of case ascertainment, diagnosis criteria, number of patients, and population under study. Specific data was collected by domains: i) Epidemiology: prevalence, crude and standardized incidence and mortality, population of reference (standardization) and sex ratio. ii) Genetics: type and frequency of mutations and familiar ALS (FALS) proportion, iii) Clinical characteristics: sex ratio, age at onset, age at diagnosis, diagnostic delay, FALS proportion and bulbar proportion. iv) Survival and prognosis: survival time since onset and diagnosis, use of Riluzole, gastrostomy and noninvasive ventilation.

A methodological overview was performed to evaluate the quality of the studies. We used an ad-hoc list considering the basic principles of descriptive epidemiology. For all studies we retrieved the following information: Country and study area, years of duration, study design, sources for case ascertainment; and the diagnosis criteria describing the selected patients. In addition to this information for studies that reported epidemiological information such as ALS incidence, mortality or prevalence, we reported whether standardization was performed, the population of reference and whether standardization was performed by sex and age including the standardization group. This information is available in appendix 1 (supplementary S2- S5).

II.2.2. Results

In this section we have summarized the principal findings of this publication. The complete article is presented in the following sections. All figures and tables are shown on the article.

We included 36 articles from 1364 publications. We covered 13 countries from Latin America and the Caribbean. Epidemiology and clinical characteristics of ALS were the most common domains (12 publications respectively), followed by survival and

prognosis (8 publications) and the least common genetics (4 publications). Brazil reported most of the studies in the region (14 publications), followed by Mexico and Argentina (5 and 4 publications respectively). While other countries like Ecuador, Colombia and Chile only had one or two publications.

Principal findings are reported as follow according to each domain:

Epidemiology of ALS in Latin America

ALS Incidence

ALS epidemiological indicators in Latin America varied among countries. ALS incidence was available in seven countries (Mexico, Costa Rica, Guadeloupe, Uruguay, Argentina, Ecuador and Colombia). Crude rates remain low for most of the studies ranging from 0.2 to 0.97 per 100,000 PYFU, in Mexico, Costa Rica, Guadeloupe and Ecuador. Conversely, crude rates ranged from 1.4 to 3.17 per 100,000 PYFU in Uruguay, Argentina and Colombia.

For countries where standardization was available (five of seven), a difference persisted between countries, Uruguay and Argentina continue to had higher incidence (3.6 and 4.34 per 100,000 PYFU respectively) than Ecuador and Guadeloupe (0.29 and 1.13 per 100,000 PYFU).

From the seven publications that reported incidence, only one study was performed in a prospective design. Four publications use more than one source for case ascertainment, and Hospital data was the most common source. One study from Mexico that was performed before 1994 used information of medical records for diagnosis criteria and another study from Costa Rica in 2006 used clinical files. Most of the studies used El Escorial diagnostic criteria, and the most recent study from Colombia in 2019 used Airlie house criteria.

ALS mortality

Mortality rates were reported in four countries. Crude mortality rates were low and ranged from 0.16 to 1.13/100,000 PYFU, Chile reported the highest mortality rate. After standardization mortality rates remain low, Cuba and Brazil reported the highest rates (0.83/100,000 PYFU and 0.89/100,000 PYFU respectively).

Standardization was not performed for all the studies, and different populations of reference were used in each original study. All mortality studies used a retrospective

design and death certificates and the International disease classification as case ascertainment.

A detailed description of ALS incidence and mortality studies in Latin America is showed in table 1 on the article.

Genetic features in Latin America

There was a limited number assessing the genetic variants among the studies. Five studies were identified that reported genetic mutations in Latin America. Most of the studies were from Brazil (3 publications), and two other studies were from Argentina and Cuba.

C9orf72 repeat expansion was the most frequent genetic mutation studied. The expansion was most frequent among the FALS patients in Argentina (33%) and Brazil (12.8%) compared to the SALS patients were the proportion ranged from 1.7% to 3.6%.

SOD1 and TARDBP mutations were not frequent. Other mutations such as VAPB and ATXN2 were also observed.

ALS clinical characteristics in Latin America

ALS clinical characteristics varied among countries.

A predominance of ALS cases among males was observed, with a male to female sex ratio that ranged from 1.5 to 2.8.

Age at onset was around 50 and 60 years of age and age at diagnosis was lower than 55 years for most of the studies.

Bulbar onset was found around 20% to 40%. In Brazil this proportion was lower than 20%.

Mean survival time since onset was heterogeneous among countries. In Mexico, Brazil, Argentina and Colombia it ranged from 40 to 68.6 months. The Caribbean reported a lower survival time around 39 and 34 months in Cuba and Guadeloupe respectively. While two studies in Uruguay reported different survival time since onset of 36.9 (mean) and 19 months (median).

ALS clinical characteristics are describe in table 3 on the article presented in the next section.

ALS among ethnic groups in Latin America

Epidemiological ALS differences among ethnic groups was assessed by four countries in Latin American and the Caribbean.

A study in Cuba reported a statistical significant difference of adjusted mortality rates ($p<0.001$) between Admixed population (0.55, 95%CI: 0.4-0.72), White population (0.93, 95%CI: 0.83 – 1.03) and Black population (0.87, 95%CI: 0.62 – 1.17).

In Chile, the Austral area with a larger population of European origin reported a high mortality rate compare to the national average.

In Ecuador, a statistical difference ($p=0.015$) was showed in admixed populations when compare to other ethnics (Indigenous, Asians and Arabs) 0.49, 95% CI: 0.43–0.55 to 0.19, 95% CI: 0.05–0.34 respectively.

In Brazil, a higher ALS risk of death was observed in the Caucasian population (OR: 2.92, 95% CI: 2.78–3.07). While a lower risk was found in Black populations (OR: 0.04, 95% CI: 0.03–0.04) Admixed populations (OR: 0.05, 95%CI: 0.04–0.07) and Indigenous population (OR: 0.02, 95%CI: 0.01-0.004) compared to the general population.

Methodological quality of the studies

Retrospective studies were predominantly, we only found seven studies that were performed in a prospective design. Regarding the years of study, less than two years were study for prospective publications, a longer period was observed for retrospective publications. For data collection, Hospital data and medical files were the most frequently used sources. Diagnosis was normally based on the EEDC and Airlie house criteria but in some studies only patients with a definite or probable diagnosis were selected.

The methodological characteristics for each study is showed in appendix one (S2-S5).

II.2.3. Discussion

Principal Findings

This systematic review provides important clues of ALS in Latin America and the Caribbean. The different studies among Latin American countries suggest that ALS occurrence, clinical presentation, genetic mutations and survival is heterogeneous

among countries in the region. This heterogeneity is also observed when comparing Latin America to other regions such as Europe and North America.

Regarding each subject important insights were found: i) lower rates are observed in Latin America compared to Europe and North America (1). ii) Studies assessing genetic mutations in ALS were geographically limited as most of the studies were performed in Brazil. In comparisons to European countries the frequency of the C9orf72 repeat expansion in Latin American countries is low (99). iii) As for clinical characteristics, differences among countries in the region were observed, including a lower bulbar onset in Brazil compare to other Latin American countries. When comparing to other regions, , Latin America ALS cases exhibited a younger age at onset than Europe (9). iv) Longer survival with a mean higher than 45 months since onset was observed among some countries (Mexico, Colombia and Brazil).

Furthermore, studies within the region reported, variations of ALS occurrence among ethnic groups, lower mortality rates were observed among Admixed groups compared to Caucasian groups from the same country.

This systematic review also provided key insights of potential factors to explain ALS heterogeneity.

Potential factors of heterogeneity

Methodological issues

It is difficult to draw firm conclusion as different methodological issues were found. Regarding epidemiological studies, different methodological aspects should be discussed, including sources of case ascertainment, study design, diagnostic criteria, time of the study and population at risk.

Using multiple independent sources for case ascertainment has been considered the gold standard to provide accurate estimations of ALS occurrence in a population (12,80,122). Prospective design are preferred than retrospective design, as these allow to collect unified information. If we observe our results, we can observe that the highest ALS incidence rate was reported in Uruguay (crude incidence of 1.42 (95%CI: 1.13 – 1.72) and a standardized incidence of 3.6 (95%CI: 2.7 - 4.5)), the only study using multiple sources and following a prospective design (127). Other countries that used multiple sources for case ascertainment such as Costa Rica and Guadeloupe reported also a high crude incidence, 0.97 and 0.93 respectively (120,121). On the

contrary, the study from Ecuador that only used Hospital data reported one of the lowest crude and standardized incidence rates (0.2 and 0.29 per 100,000 PYFU respectively). Hospital based studies are unrepresentative of the general population, and are known for presenting selection bias which includes, patients with younger age and less likely to present a bulbar onset resulting in a more favorable prognosis (11). Adding to this issue, the difficulties in access to health in Latin America, may further affect the representativeness of hospital based studies in the region.

Some studies have observed an increase over time of ALS occurrence (3,5,131), however this is a controversial subject as other studies have found stable rates over time (132,133). Increase over time of ALS occurrence could be party explained by improvements on ALS diagnosis. Before the introduction of El Escorial Diagnosis criteria, clinicians and researchers relied on clinical judgement leading to differences among other countries. We can observe in our results that ALS research in Latin America was vaguely performed before 2006. For instance, the study in Mexico which reported a low incidence compare to other countries, was performed in 1972 before the Escorial Diagnostic Criteria publication, this could result in an under ascertainment of cases as compare to other studies that used El Escorial Diagnostic criteria. However, when compare to other countries in the same period, the rates found in Mexico are still lower (80,85).

One of the main characteristics of population-based registries in Europe, is the ability of these registries to identify cases in a well geographically defined population (10). The study reporting incidences in Argentina reported an elevated crude and standardized rate 3.17 (95%CI: 2.24 – 4.48) and 4.34 (95%CI: 2.31 – 6.39), in this study the population studied was the affiliates to the Italian Medical Care program which is a prepaid Health Maintenance Organization (128). To estimate the incidence rate only the population that was affiliated to this network during the study period was considered as population at risk, which do not represent the entire population of Buenos Aires, Argentina. Furthermore, after standardization to the Argentinian 2010 population, incidence rate was 1.43 per 100,000 person-years. ALS standardized incidence rate to the 1990 United States in this study was high 4.34 (95%CI: 2.31 – 6.39), however standardization was only performed within the 45-74 years age group. When standardized to the entire 2010 US population ALS standardized incidence was 1.84 (95%CI: 1.17 – 2.52) (1).

A similar issue was observed in the study by *Zapata et al*., ALS cases were identified in different neurological centers and private neuromuscular centers in Medellin, Capital city of Antioquia, new cases were estimated for 2013, and the population at risk used was the 2014 population of Antioquia according to the national census. It is not clear if only patients residents from Medellin or all Antioquia were considered for this estimation (134).

Mortality studies in the region seems to present an almost homogenous methodology, as most of the studies used death certificates and ICD codes and were performed in similar time periods (before 2000). Still some methodological differences were observed for example different reference populations for standardized rates. The variations reported among these studies could be partly explained by the differences on health systems among countries but also due to ancestral origin.

Genetic studies in Latin America, presented selection bias, most of the studies have a high percentage of FALS patients, and some included members of the same family, which could incur to a greater percentage of genetic mutation due to the Mendelian inheritance.

Most of the publications describing clinical characteristics and survival in Latin America were hospital-based studies, which present referral bias, as younger patients tend to seek more specialized care compare to elderly (70). Patients with bulbar onset which is known to have a poor prognosis and tends to be more frequent in older ages, this patients can have more difficulties in access to health and prefer not to go to hospitals. Younger age at onset and lower proportion of bulbar onset have been observed as good prognostic factors, which could explain the longer survival observed in some Latin American countries.

Socio-economic factors

We need to highlight that socio economic factors should be taken in consideration, as the countries that reported the higher rates are classified as high income countries such as Uruguay, Chile and Argentina. However, the study performed in Cuba, a country where we can assume all the population has free health-care and no income differences, reported a lower mortality rate compared to Uruguay, Chile and Argentina and more over reported a higher mortality among the Caucasian population compared to the Admixed population in the same country (4).

Ancestral origin

Studies in Latin American reported difference on ALS distribution among ethnic groups (Ecuador, Brazil and Cuba) (4–6)Heterogeneity among Latin American countries could also be explained by ancestral origin. As homogenous incidence rates have been observed in countries that have showed a common ancestral origin (1).

As previously discussed, Admixture is predominantly in the region. Genome-wide studies have showed that the level of Admixture varies among countries in the region. For instance, Uruguay, Argentina, Chile and Costa Rica have showed a greater percentage of European ancestry compare to Mexico and Ecuador where Native American ancestry is predominantly (114). Higher ALS incidence rates have been observed in European countries, regarding our results countries with a higher level of European ancestral origin (Uruguay, Chile, Argentina and Costa Rica) have reported the highest AL occurrence compared to Mexico and Ecuador with a higher level of Native American ancestry.

A further explication of ancestral origin in Latin America countries is discussed in chapter 3.

Areas for further research

ALS research is limited in Latin American, as we reported publications from only 13 countries from all the region. Most of the countries were performed in South America, mostly by Brazil, and only one study was found from Central America. Regarding time of publication, in Mexico the first and only study reporting epidemiological indicators was performed in 1972, while the following publications in the same country were reported almost 40 years later in 2011 and 2019.

As previously discussed this systematic review have provide us important clues to explain ALS heterogeneity. However, many questions remain to be answered, there is a need to performed further epidemiological studies in more countries of the region following a homogenous methodology to provide reliable information. Comparisons among countries and populations could provide important insights to explain the potential role of ancestral origin in ALS pathogenesis.

There is a need of prospective population-based studies, using a standard methodology to further clarify important questions of ALS in this region such as: i) Is there a lower ALS occurrence? ii) Does ALS cases present a younger age at onset?

iii) Which are the common genetic mutations? iv) Does ALS differ among ethnic groups?

Novel research focusing on ALS heterogeneity due to ancestral origin in this region should take in consideration all the potential factors of ALS variability including, socio-economic status and environmental factors.

Conclusion

This review supports the hypothesis of ALS heterogeneity among geographical areas and populations. It also supports the evidence of a lower ALS occurrence in Admixed populations and a higher risk among the Caucasian population.

This systematic review have helped us showed the methodological issues in this region and the areas for further improvement. Further studies are needed, establishing accurate epidemiological indicators in this region to performed reliable comparisons can provide to the scientific community important insights of whether some populations showed a higher risk or not to ALS.

In the following section, we present the publication associated to this work.

II.2.4. Article presentation

Journal:

Amyotrophic Lateral Sclerosis and Fronto-temporal Degeneration Journal

Impact Factor (IF): 2.78

Title: Epidemiological and genetic features of amyotrophic lateral sclerosis in Latin America and the Caribbean: a systematic review

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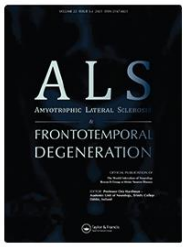

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REVIEW ARTICLE

Epidemiological and genetic features of amyotrophic lateral sclerosis in Latin America and the Caribbean: a systematic review

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Abstract

Introduction: Heterogeneity of amyotrophic lateral sclerosis (ALS) has been suggested in terms of epidemiology, phenotypes and genetics between geographic areas and populations. However, there is limited information in Latin America. We conducted a systematic review that aimed to describe the epidemiology, frequency of genetic mutations, clinical characteristics and survival of ALS patients in this region. *Methods*: We reviewed Medline, Scopus, Scielo and LILACS databases up to April 2020. The search terms "Amyotrophic Lateral Sclerosis" or "Motor Neuron Disease" were used in combination with the list of Latin American countries from the United Nations. All observational studies were included. A methodological overview was performed using the principles of descriptive epidemiology. *Results*: Overall, 1364 publications were identified and 36 studies were selected, covering 13 Latin American countries. According to the original reports, ALS occurrence varied among countries with a standardized incidence ranging from 0.3 per 100,000 person-years follow up (PYFU) in Ecuador to 3.6 per 100,000 PYFU in Uruguay. A low proportion of the C9orf72 repeat expansion was reported in Cuba and Brazil. We identified age at onset between 50 and 60 years. Survival time was higher than 40 months in half of the studies. Data from multiethnic populations reported a higher risk of developing ALS in Caucasians compared to admixed and Black populations. *Conclusion*: This review provides a perspective of ALS variability across Latin America and highlights specific differences when comparing to Europe and North America. However, we cannot draw firm conclusions because of different methodological concerns within the studies.

Keywords: *Amyotrophic lateral sclerosis, epidemiology, clinical characteristics, genetics, survival, Latin America*

Introduction

ALS is the most common form of motor neuron disease in adults showing a standardized worldwide incidence of 1.68 (95%CI 1.50–1.85)/100000 PYFU (1). Several studies have suggested heterogeneity of epidemiological indicators, clinical phenotypes and genetic mutations between geographic areas and populations (1–3). However, there is an important lack of information about ALS in several parts of the world. Latin America is a multiethnic region shaped of continuous admixture among European, Native Amerindian, and African populations (4). Latin America has drawn ALS scientific community attention because of reports describing a low risk of developing the disease in certain populations (5,6). The variability of risk could be associated with the ancestral origin (7). It is hypothesized that European populations share common "at-risk" alleles, which may increase ALS susceptibility. Conversely, admixed populations might have different combinations of "at-risk" alleles that lead to a low risk of developing ALS (6). Heterogeneity could be also related to differences in the frequency of genetic mutations and environmental risk factors. However, methodological issues related to study design, biases and underestimation of cases due to difficulties for case ascertainment and lack of health care access cannot be excluded.

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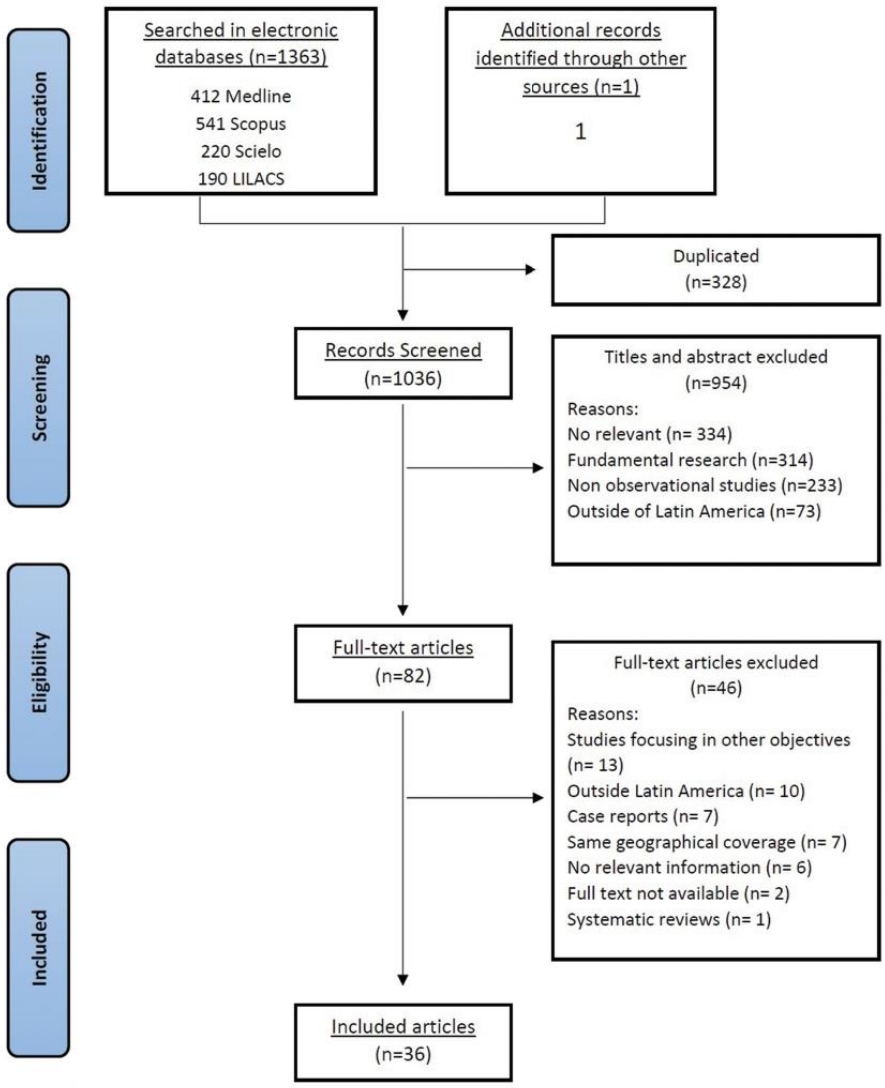

Figure 1. Flowchart of included ALS studies in Latin America and the Caribbean.

A clear description of ALS across geographic areas could offer the opportunity to gain more insights into the heterogeneity of ALS. In this context, we conducted a systematic review that aimed to describe the epidemiology, frequency of genetic mutations, clinical characteristics and survival of ALS patients in this region.

Methods

The protocol was submitted on the International Prospective Register of Systematics Reviews (PROSPERO) under the number CRD42020153187. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was followed (8).

Search strategy

We searched in four electronic databases: Medline/PubMed, Scopus, Scielo and the Latin American and Caribbean Center on Health Sciences Information (LILACS) without time restriction until April 2020. We used the following Medical Subject Headings (MeSH) terms and Boolean operators: "Amyotrophic Lateral Sclerosis" OR "Motor Neuron Disease" in combination with the list of countries of Latin America and the Caribbean according to the United Nations

Statistics Division (9). The search strategy is described on Supplementary data (S1).

Inclusion and exclusion criteria

We included all observational studies and case series with more than 10 patients carried out in Latin America and the Caribbean. Pre-clinical studies, editorials, letters to the editor, case reports, and clinical trials were excluded. Systematic reviews and meta-analyses were not included, but their references were manually examined. When several articles reported ALS cases in the same population under study over the same time period, only studies with the larger sample or longer time of follow up were taken into account. We extracted only the information from Latin America in studies comparing different countries in different subcontinents.

Data extraction

All the identified articles were retrieved and exported into the software Rayyan QCRI (Qatar Computing Research Institute, Data Analytics Medical) (10).

Two authors (DE and JL) independently examined all the studies, after removing duplicate records. Titles and abstracts were screened for relevant studies, followed by a full-text examination to assess eligibility. Discrepancies were discussed and an agreement was reached between the two authors in both steps.

Data extraction was recorded independently using an *ad hoc* created database. The included articles were classified into four main domains according to their objective: (1) epidemiology, (incidence, mortality and prevalence), (2) genetics, (3) clinical characteristics (site of onset, diagnostic delay, age at onset and diagnosis), (4) survival and prognosis. When articles reported information of different domains, we classified the study according to their main objective, and all data were retrieved.

A methodological overview was performed to evaluate the quality of the studies. We used an *ad-hoc* list considering the basic principles of descriptive epidemiology.

Results

Included studies

We identified 1364 publications from our literature search. After the exclusion of duplicates, 1036 publications were considered. Following the screening of titles and abstracts, 82 articles were selected. Subsequent to a full-text comprehensive examination, 36 articles were included for analysis in this review. A PRISMA flowchart describing the selection process is shown in Figure 1.

Geographical coverage

We covered 13 countries from Latin America and the Caribbean. Brazil reported most studies in the region ($n = 14$). The most frequent domains investigated were descriptive epidemiology ($n = 12$), clinical characteristics ($n = 12$), survival and prognosis ($n = 8$), and genetics ($n = 4$) (Figure 2).

Epidemiology of ALS in Latin America and the Caribbean

Incidence. As shown in Table 1, the crude incidence varied from 0.2 to 0.97/100,000 PYFU in Mexico, Costa Rica, Guadeloupe and Ecuador (5,11–13) and from 1.4 to 3.17/100,000 PYFU in Uruguay, Argentina and Colombia (14–16). After standardization, differences remain among countries. Nevertheless, standardization was only performed in five studies (5,12–15). The highest standardized incidence was observed in Argentina (4.34/100,000 PYFU (15)) and Uruguay (3.6/100,000 PYFU (14)), while the lowest was reported in Ecuador (0.29/100,000 PYFU (12)). However, we need to take into account that standardization was conducted using different populations of reference in each original study (Table 1(a)).

Prevalence. Prevalence was reported in four studies (Uruguay, Argentina, Colombia and Brazil) ranging from 2.01 to 8.86/100,000 inhabitants (14–17).

Mortality. Six countries reported ALS mortality rates (Table 1(b)). The crude mortality ranged from 0.16 to 1.13/100,000 PYFU (5,6,18–20). After standardization, mortality rates remained low varying from 0.33 to 0.89 per 100,000 PYFU in Cuba, Ecuador and Brazil.

ALS genetic variants

We identified five studies reporting the frequency of ALS genetic mutations in Latin America. Three studies were performed in Brazil (21–23), one in Argentina (24) and another in Cuba (25). The proportion of Familial Amyotrophic Lateral Sclerosis (FALS) was reported between 16 and 19% (21–23,25). The type and frequency of genetic variants associated with ALS in Latin America are shown in Table 2.

C9orf72. C9orf72 repeat expansion was assessed in four studies (21,23–25). Over the FALS population, the percentage of C9orf72 mutations was 33.3% in Argentina and 12.8% in Brazil, while the repeat expansion was not found in Cuba. Over the Sporadic Amyotrophic Lateral Sclerosis (SALS) patients, C9orf72 proportion ranged from 1.7% to 3.6%.

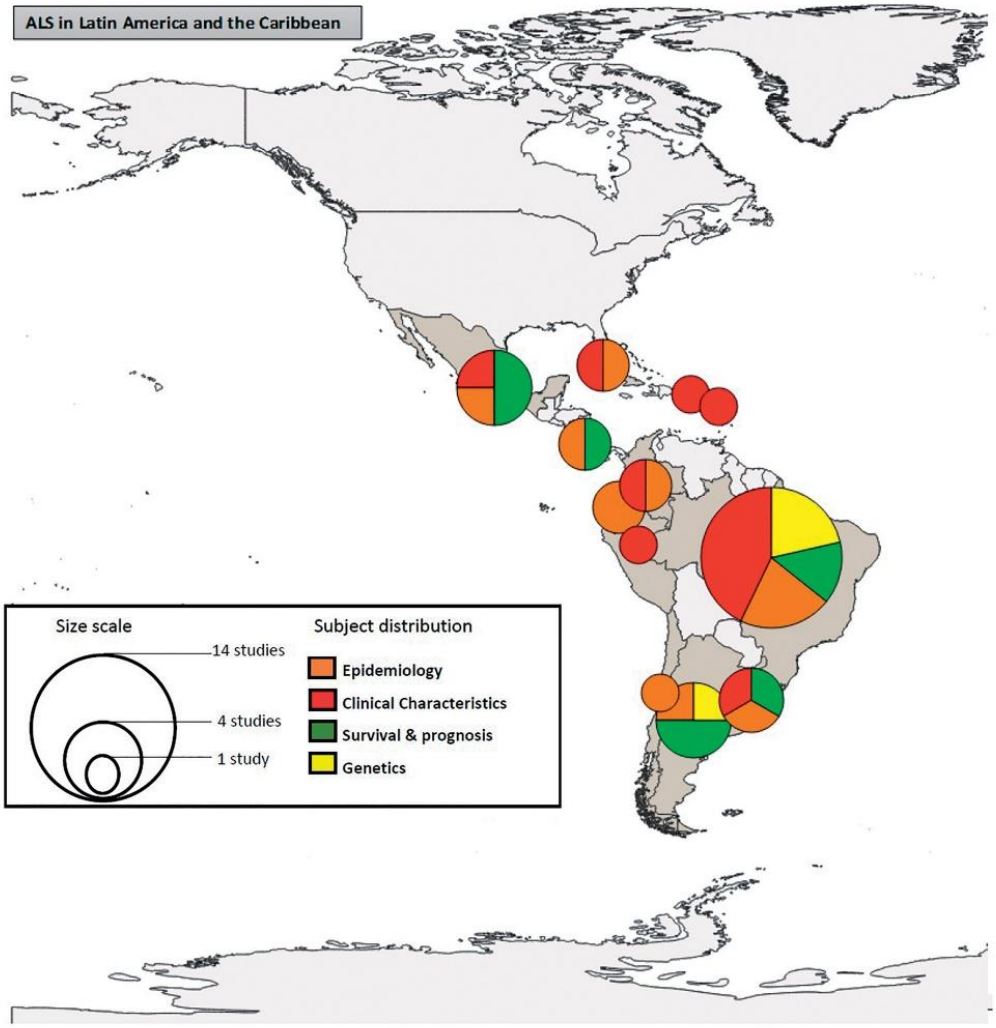

Figure 2. Geographical coverage of ALS studies and subjects distribution according to their primary objective by country in Latin America.

SOD1, TARDBP and other mutations. Two studies in Brazil and Cuba screened for SOD1 and TARDBP mutations (21,25). In Brazil, SOD1 proportion was reported only in FALS patients (7.7%), while TARDBP only in SALS patients (2.64%). The study also showed a high frequency of VAPB mutation in FALS patients (43.6%) but 9 of 17 participants were family-related (21). In Cuba, SOD1 and TARDBP mutations were not found. ATXN2 was another mutation found in another study from Brazil (22).

ALS clinical characteristics in Latin America

Sex ratio. There was a predominance of ALS male cases in Latin America. The male-to-female sex ratio ranged from 1.5 to 2.8 for most of the studies (11,14,26–35).

Age at onset. The mean age at onset was around 50 and 60 years (11–14,16,21,25,31,32,34,36–39). Younger age was only reported in Mexico (26,40) and Brazil (37,38).

Age at diagnosis and diagnostic delay. The mean age at diagnosis was lower than 55 years (11,12,21,25,26,28,33,34,37–40), while only two studies reported an age higher than 60 years (15,31). Diagnostic delay ranged from 9.2 to 23.5 months (12,14,16,27,29,32,34,35,37–40).

Familial ALS. The proportion of FALS was lower than 5% in most of the clinical studies

Table 1. ALS incidence and mortality in Latin America.

Subcontinent	Author	Year	Country	Period	Design	Sources for case ascertainment: H	N	Sp	DC	RDC	PA	HI	Diagnostic criteria	Number of ALS patients	Crude incidence (95% CI)	Standardized incidence (95% CI)	Reference population	Age standardization (age group)
(a) Incidence																		
North and central America	Olivares et al.	1972	Mexico	1962–1969	R	X	X						Cd	16	0.40	0.40	US 1960	No specified
	Rodriguez et al.	2006	Costa Rica	1998–2001	R	X				X	X	X	Cd	76	0.97 (0.8–1.2)			
The Caribbean	Lannuzel et al.	2015	Guadeloupe	1996–2011	R	X		X					AH	63	0.93 (0.71–1.19)	1.13 (0.84–1.42)	EU 2000	No specified
South America	Vasquez et al.	2008	Uruguay	2002–2003	P	X	X	X	X	X			EEDC	143	1.42 (1.13–1.72)[#]	3.6 (2.7–4.5)	US 1990	45–74 years
	Bettini et al.	2013	Argentina	2003–2010	R	X							EEDC	32	3.17 (2.24–4.48)	4.34 (2.31–6.39)	US 1990	45–74 years
	Bucheli et al.	2013	Ecuador	2000–2012	R	X							EEDC	116	0.2 (0.22–0.12) 0.6 (0.71–0.45)[h]	0.29 (0.35– 0.24)	US 1990	Over15 years
	Zapata et al.	2019	Colombia	2013	R	X	X	X					Awaji and AH	88	1.4 (0.5–2.2)			

Subcontinent	Author	Year	Country	Period	Design	Sources for case ascertainment: H	N	Sp	DC	RDC	PA	HI	Diagnostic criteria	Number of ALS patients	Crude mortality (95% CI)	Standardized mortality (95% CI)	Reference Population	Age standardization (Age group)
(b) Mortality																		
North America	Olivares et al.	1972	Mexico	1962–1969	R	X	X						Cd	16	0.28			
The Caribbean	Zaldivar et al.	2009	Cuba	2001–2006	R				X				ICD codes	432	0.67 (0.6–0.72)	0.83 (0.72–0.8)	US 2000	Over 15 years
South America	Matos et al.	2011	Brazil	2002–2006	R				X				ICD codes	326	R:0.44–0.76	0.44–0.78	No specified	No specified
	Valenzuela et al.	2015	Chile	1994–2010	R				X				ICD codes	1671	1.13			
	Moura et al.	2016	Brazil	2004-2013	R				X				ICD codes	8942	R:0.36–0.58	0.61–0.89	US 2010	Over 20 years
	Luna et al.	2019	Ecuador	1990–2016	R				X				ICD codes	570	0.16 (0.15–0.18)	0.33 (0.30–0.36)	US 2010	All ages

H: Hospital discharge data; N: Neurologist; Sp: Specialist; DC: Death certificates; RDC: Riluzole dispense centers; PA: Patients association; HI: Health Insurance; Cd: Clinical diagnosis based on clinical files; EEDC: El Escorial diagnostic criteria; AH: Airlie House; h: incidence reported for each hospital; R: range; US: United States; EU: European Union; ICD codes: International Classification of Diseases.

[#]Capture recaptured method.

Table 2.. ALS genetic variants frequencies in Latin America

Author	Year	Country	Study period	Number of ALS patients	FALS (%)		Percentage (%) of participants with positive genetic mutation			
							C9orf72	SOD1	TARDB	Other mutations
Chadi et al.	2016	Brazil	2010 -2015	228	17.1	FALS	12.8	7.7		43.6 (VAPB)[a]
						SALS	2.6			
Itzcovich et al.	2016	Argentina	No specified	50	6.0	FALS	33.3		2.64	
						SALS	2.1			
Cintra et al.	2018	Brazil	1998-2016	377	18.0	FALS	11.8			
						SALS	3.6			
Tavares de Andrade et al.	2018	Brazil	2011-2017	459	18.9	FALS				8.0 (AXTN2)
						SALS				5.9 (AXTN2)
Ryan et al.	2019	Cuba	1996-2017	115	15.8	FALS				5.2 (ANG, CHCHD10, DCTN1)
						SALS	1.7			

Proportion of positive mutations is according the proportion of FALS and SALS patients respectively. FALS: Familial ALS; SALS: Sporadic ALS.
[a]Patients were family-related.

(12–16,24,26–32,36,40–42). However, four studies described a proportion between 10.0 and 17.1% (21,25,33,37).

Site of onset. Bulbar onset ranged between 20 and 40% (11,13–16,25–27,31,35,36,39,41). However, bulbar onset was lower than 20% in most of the studies from Brazil (21,29,32, 33,37,38).

Survival

The mean survival time since onset was around 40 to 68.6 months in Mexico, Brazil, Argentina and Colombia (16,26,27,30,32,33,36,38). Cuba and Guadeloupe reported a mean survival time since onset of 39 months (25) and 34 months (13), respectively. In Uruguay, the mean survival time since onset was 36.9 months according to Ryan et al. (25) while Gil et al. reported a median survival since diagnosis of 19 months (31).

The clinical characteristics including the number of cases, sex ratio, age at onset, age at diagnosis, FALS proportion, type of onset and survival time are shown in Table 3.

ALS among ethnic groups in Latin America

Epidemiology among ethnic groups. Four mortality studies assessed ALS occurrence between ethnic populations (6,19,20,43). Two studies compared adjusted mortality rates per 100,000 PYFU among ethnic groups. In Cuba, admixed population (0.55, 95%CI: 0.4–0.72) was compared to White population (0.93, 95%CI: 0.83–1.03) and Black population (0.87, 95%CI: 0.62–1.17) showing a statistically significant difference (6). In Ecuador, a significant difference between admixed populations and other ethnics groups (Indigenous, Asians and Arabs) (0.49, 95%CI: 0.43–0.55 vs. 0.19, 95%CI: 0.05–0.34, $p = 0.015$) was found (20). Table 4 shows ALS mortality rates between ethnic groups in Latin America.

In Brazil, a higher risk of ALS death was observed in Caucasian population (OR = 2.92, 95% CI: 2.78–3.07) while Indigenous population reported a lower risk (OR = 0.02, 95%CI: 0.01–0.04) compared to the general population (19). A geographical distribution analysis in Chile found that the highest mortality rate was observed in the Austral area (1.47/100,000), an area presenting a large population of European origin (43).

Ethnic groups proportion across ALS cases. Several studies reported the proportion of ethnic groups across ALS cases (11,13,20,21,25, 29,30, 32,33,42). As shown in Figure 3, a predominant number of cases were self-identified as Caucasians in Brazil, Cuba and Costa Rica (11,21,29,30, 32,33,42), while most cases were admixed and

Table 3.. ALS clinical characteristics and survival time in Latin America and the Caribbean.

Subcontinent	Country	Author	Year	Study period	Design	Diagnostic criteria	Number of ALS patients	Sex ratio	Mean age at onset (SD) or (95%CI)	Mean age of diagnosis (SD) or (95%CI)	FALS (%)	Bulbar onset (%)	Diagnostic delay mean (SD) or (95%CI)	Survival time since onset mean or median (SD) or (95%CI)
North and Central America	Mexico	Otero-Siliceo et al.	1997	1965–1995	R	EEDC	248	1.2[b]	47.8 (14.5)		3.2[b]		23.1 (21.7)	
		Martinez et al.	2011	2005–2010	R	AH	61	1.8	47.5 (10.6)	48.3 (10.6)	3.3	34.4	12.0 (8.0–16.0)[c]	68.6 (57.2–79.9)
		Sanchez et al.	2019	2000–2015	R	Awaji; AH	45	0.8	58.1	58.9	4.4	46.6		64.7 (34.8)
	Costa Rica	Rodriguez et al.	2007	1998–2001	R	EEDC	76	1.7	53.1[M] 54.4[F]			36.8		
		Abadia-Cubillo et al.	2015	2009–2014	R	EEDC	235	1.9[b]			0.8[b]	31.9[b]	16.2 (10.0–22.5)	25.0 (19.8–30.5)[c]
The Caribbean	Cuba	Ryan et al.[a]	2019	1996–2017	R	AH	115	1.2[b]	53.0 (50.4–55.6)	54.4 (51.9–56.9)	15.8	39.1	12.0 (7.0–17.0)	39.0 (24.0–70.0)
	Guadeloupe	Lannuzel et al.	2015	1996–2011	R	AH	63	1.4	58.4 (14.2)		6.4	20.6	12.0 (0.0–19.0)[c]	34.0 (17.0)
	Puerto Rico	Marco et al.	1983	No specified	R	Clinical	76	1.7	50.0 [M] 48.3 [F]				15.6 / 39.1[c]	
		Deliz et al.	2018	2004–2014	R	AH	76	0.9[b]		57.2 (11.1)	4.0	31.6		
South America	Argentina	Garguilo- Monachelli et al.	2011	2003–2009	R	AH	215	1.7		55.0	0.0	24.0	20.5	42.4
		Bettini et al.	2013	2003–2010	R	EEDC	32	1.2	72.0 (8.6)	72.3 (8.5)	0.0	43.7[b]	9.2 (6.1)	
		Itzcovich et al.	2016	No specified	P	No specified	50	1.0			6.0	14.0[b]		
South America	Brazil	Castro- Costa et al.	2000	1980–1998	R	EEDC	78	1.8	42.0 (15.5)		2.5			
		Dietrich- Neto et al.	2000	1998	R	EEDC	443	1.4	52.0 (13.0)		5.9	18.5	18.0 (28.0)	42.0 (37.0)
		Werneck et al.	2007	1977–2004	R	EEDC	251	1.7		54.4 (12.3)	2.8	9.6	17.9 (15.7)	
		Loureiro et al.	2012	2000–2007	R	AH	227	1.7				30.4		49.0 (42.5–55.5)[c]
		Adry et al.	2012	1996–2007	R	AH	70	2.8	49.7		10.0	11.4		64.1[d]
		Moura et al.	2015	2005–2014	R	EEDC	218	1.5	57.2 (12.3)		5.0	19.7	22.7[M] 23.5[F]	45.7 (47.0)[M] 39.3 (29.8)[F]
		Chadi et al.	2016	2010–2015	P	AH	228	1.3	50.3 (12.4)		17.1[b]	13.2		
		Prado et al.	2016	2013–2014	P	Awaji	68	1.5[b]	SALS: 54.9(11.4) FALS 42.7 (4.4)	SALS:56.3 (11.1) FALS:44.5 (4.1)	10.3	9.8	20.0	
	Colombia	Zapata et al.	2019	2010–2014	R	Awaji; AH	159	1.0[b]	57.9 (13.3)	59.1 (13.2)	2.2	27.0	16.6 (16.4)	48 (38–53)[c,e]
	Ecuador	Bucheli et al.	2013	2000–2012	R	AH	116	1.4	54.3 (15.1)	54.7 (15.8)	5.0	18.1[b]	15.9 (12.3)	
	Peru	Torres et al.	2009	1985–2007	R	AH	85	0.5[b]	51.0			37.6	20.0	
	Uruguay	Vasquez et al.	2008	2002–2003	P	EEDC	143	2.0	58.7 (12.0)		4.2	31.5	16.8	
		Gil et al.	2009	2002–2004	P	EEDC	103	1.9[b]	61.0 (52.0–68.0)[c]	62.0 (53.0–70.0)[c]	4.0	37.0	10.0 (6.0–20.0)	19.0[c,d]
		Ryan et al.[a]	2019	1996–2017	R	AH	220	1.6[b]	58.2 (56.5–60.0)	59.5 (57.8–60.3)	5.0	34.6	10.0 (5.1–18.8)	36.9(22.9–71.4)

[a]Ryan et al.: Populations of Cuba and Uruguay were reported separately in this table.
P: Prospective; R: Retrospective; EEDC: El Escorial diagnostic criteria; AH: Airlie House; M: data reported for male; F: data reported for female; FALS: Familial ALS.
[b]Calculated by author (D.E.).
[c]Median.
[d]Survival time since diagnosis.
[e]Data was reported on years on the original study.

Table 4. ALS mortality rates by ethnic groups.

Author	Year	Country	Standardized mortality rate (CI 95%) by ethnic groups				Reference population
			Caucasians	Admixed	Black	Other ethnics	
Zaldivar et al.	2009	Cuba	0.93** (0.83–1.03)	0.55** (0.4–0.72)	0.87** (0.62–1.17)		US 2000
Luna et al.	2019	Ecuador	0.37 (0.20–0.53)	0.49* (0.43–0.55)	0.26 (0.05–0.47)	0.19*(0.05–0.34)	US 2010

**Statistically significant difference Admixed vs. Caucasian ($p < 0.001$) and Admixed vs Black ($p < 0.001$).
*Statistically significant difference Admixed vs. other ethnics ($p = 0.015$).

African–Caribbean in Ecuador (20) and Guadeloupe (13), respectively.

Genetic mutations among ethnic groups. The C9orf72 repeat expansion was mostly found in Caucasian cases. In Brazil, eight of nine cases with C9orf72 were self-identified as Caucasians (21). Similarly, only two cases exhibited the repeat expansion in Cuba and both were Caucasians (25).

Clinical features among ethnic groups. One study in Cuba showed no statistical differences when comparing age at onset, sex ratio, site of onset, FALS proportion and survival among White, Black and Mulatto populations (25).

Methodological overview

There was a predominance of hospital-based studies with a retrospective design. Clinical characteristics were mostly collected from medical records. The El Escorial diagnostic criteria and Arlie House were the diagnostic criteria of choice, and for some of the studies, only patients with definite or probable forms were selected. A detailed description of the methodological overview is shown in Supplementary Tables S2–S5.

Discussion

This review provides a wide description of ALS in Latin America to gain more insights into disease heterogeneity. Epidemiological studies showed a low ALS occurrence in some countries. Genetic studies suggested that the proportion of known genetic variants are less frequent (e.g., C9orf72, SOD1). Variability was observed between ethnic groups in terms of risk to develop the disease and genetic variants. However, it is difficult to draw meaningful conclusions because of methodological issues.

Epidemiology

Lower incidence and mortality rates were observed in most countries of Latin America compared to Europe, North America and New Zealand (1,44–47). ALS epidemiological variability has been observed among subcontinents. A meta-analysis considering only population-based studies found differences in ALS standardized incidence between North Europe (1.89/100,000 PYFU) and East Asia (0.83/100,000 PYFU), and South Asia (0.73/100,000 PYFU) (1). The Global Burden of Disease study 2016 (GBD 2016) assessed the relationship between age-standardized rates and the socio-demographic index (SDI) showing that age-standardized rates changed in each SDI level. A lower age-standardized prevalence was observed among regions with high SDI values such as Asia Pacific, southern Latin America, eastern Europe and central Europe (48).

Population-based studies have contributed to a better understanding of ALS. This methodology is the gold standard for addressing ALS epidemiology because they provide an accurate representation of the ALS population relying on multiple sources for case ascertainment (2,7). In contrast, hospital-based studies could lead to selection bias and underestimation of incidence rates (49). Furthermore, population-based registers have played an important role in describing ALS clinical features, survival and prognostic factors (50).

In this review, eight studies used a population-based approach (6,11,14,16,18–20,43), from which the majority were mortality studies using nationwide death registers. Death certificates are a valuable source of information, it is assuming that all cases could be identified, as ALS is consistently lethal (7,51). However, specific epidemiological criteria need to be fulfilled to obtain reliable mortality data (52). Only three incidence studies used several sources for case ascertainment (11,14,16) and only one performed a prospective design (14). In the latter study, the incidence rate was one of the highest in the region.

Standardization using the same reference population is essential to compare epidemiological data among countries (7). In Latin America, the lowest rates were observed in Ecuador and Cuba where the entire population or the population over 15 years were taking into account for the analysis (6,12,20). The highest incidence rates were reported in Uruguay and Argentina considering the specific group age of 45–74 years (14,15). However, a meta-analysis using the same data from the original publications found age and sex-adjusted incidence of 1.53 for Uruguay (14) and 1.84 for Argentina (15) using the entire United

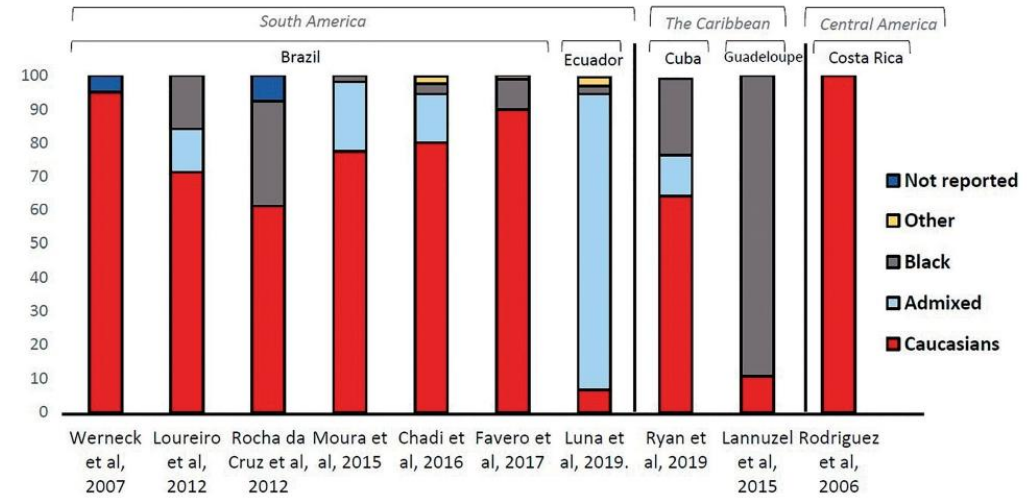

Figure 3. Proportion of ethnic groups across ALS cases in Latin America.

States 2010 population as standardization reference (1).

Latin American population presents a complex genomic structure that reflects admixture from different genetic contributions from Native American, European and African populations, because of important historical events such as colonization (53). By applying ancestry-specific PCA analyses in the Latin American population, Homburger et al. found that most of European origin comes from the Iberian peninsula and that there is a strong gradient in the Native American ancestry component associated with the geography of local indigenous populations (4). The ancestral origin could explain the epidemiological heterogeneity of ALS (54). Using genome-wide SNP data, Argentina showed a higher proportion of European origin (4) and reported an ALS incidence that is consistent with those of European countries. Populations with a higher Native American origin like Ecuador, Peru, Colombia and Mexico (4,53) showed low ALS incidence rates. Another study showed that the Caribbean region has shown a higher proportion of African origin (53). Nevertheless, these epidemiological differences could also be related to methodological issues.

According to reliable population-based registries, ALS incidence is homogeneous in Caucasian populations from Europe and North America (1,2). Multiple studies in the United States have reported lower occurrence in Hispanics and African American populations compared to Whites (55,56). In South Africa, the age-adjusted incidence rate in African ancestry populations (0.56, 95%CI: 0.00–1.23) was lower compared to European ancestry populations (2.62, 95%CI: 2.49–2.75) (57). These multiethnic studies support the findings in Cuba, Brazil and Ecuador (6,19,20). One of the main limitations addressing ethnicity is the variability of the terminology and the lack of international consensus. Another factor to take into consideration is the social-economic status (SES) as differences among ethnic groups could be explained by it. To control this factor, Roberts et al. conducted an adjusted model for SES factors (education, household income, type of health insurance, immigrant status) showing a higher mortality rate of ALS in Whites compared to non-Hispanics Black and Hispanics (58). The mortality rates in Cuba were higher in Caucasians compared to Admixed and Black populations (6), a country where we might assume that there are universal and free health-care access and no differences in terms of socio-economic aspects among ethnic groups.

The modern approach for ALS research encourages well designed longitudinal population-based studies with a complete follow-up of a population including diverse ethnicities of a defined territory. The comparisons of differences could lead to a better understanding of ALS (59,60).

Genetic mutations

Studies assessing genetic mutations in Latin America were limited and presented selection bias. None of these assessed the proportion of genetic mutations in the general population. The proportion of C9orf72 repeat expansion is around 5% in SALS and 34% in FALS in Europe (61), while lower proportions were found for both FALS and SALS patients in Cuba and Brazil.

In Brazil, SOD1 proportion was lower than in Europe (FALS: 14.8%) and Asia (FALS: 30.0%). VAPBN was a common mutation reported in FALS patients from Brazil. However, the study

reported participants from the same family. SOD1 and TARDBP were not found in Cuba.

Clinical characteristics in Latin America

Younger age at onset was reported in Latin America (50–60 years) compared to Europe and New Zealand (63 and 65 years) (3). The age structure of the population could explain this observation. Differences in age at onset could also be related to life expectancy (62). Another factor to take into account is that most of the studies describing ALS clinical features were hospital-based studies, which can imply referral bias as younger patients tend to seek specialized care compared to elderly patients (49,63). Additionally, older patients present more difficulties in access to healthcare.

FALS and bulbar onset were highly variable among Latin American countries. This clinical heterogeneity could be related to limitations in the data collection from medical files. The clinical examination could vary among physicians as neurologists in specialized centers may be more aware of specific clinical features (3,49,64). Interestingly, heterogeneity of bulbar onset proportion has been shown among subcontinents. Bulbar onset was significantly higher in Northern Europe compared to other European subcontinents, North America and Asia (3).

Survival in Latin America

A longer survival time since onset was reported in Latin America (40–68 months), while the median survival times were shorter in Europe (Northern Europe: 25 months, Western and Southern Europe: 30 months) and North America (32 months) (3). This apparent longer survival in Latin America could be partly explained by a younger age at onset and long diagnostic delay (50). However, there are several limitations among the studies assessing survival in Latin America. Some studies did not include all the patients in the analysis. Studies that reported more than 60 months of survival had a small sample size (around 45 to 70 patients) (26,33,36). Only one prospective population-based study reported a median survival of 19 months since diagnosis (31). Two studies using the same methodology compared survival among Latin America and European countries. No statistical differences were found in survival time since onset in Cuba (39 months), Uruguay (36.9 months) and Ireland (35 months) (25). In contrast, a significantly shorter median survival time since diagnosis was found in Uruguay (19 months) compared to France (28 months), $p = 0.030$ (31).

Latin America challenges on ALS research

In 2040, ALS is projected to increase by 73% in South America (65). Therefore, it is necessary to improve health care policies and resources. Further research is essential to estimate the real burden of the disease in these countries. Latin America's health care system faces several challenges including important social inequalities and scarce medical resources. In 2017, the World Health Organization (WHO) reported that the median number of adult neurologists per 100,000 inhabitants was 0.70 for the American region with a particular deficiency in low-income (0.03) and lower-middle-income countries (0.13) (66). There is an important double burden of disease (infectious disease and chronic diseases) in Latin America. Rare diseases such as ALS draw less government attention (67). The challenge imposed by the privatization of the health sector in Latin America implies a greater difficulty to health care access. Specialized physicians and multidisciplinary centers are mostly located in the private sector (66,68), which could lead to a lack of diagnosis and specialized management in patients with limited economic resources.

Strengths and limitations

Some limitations need to be considered. There was a broad methodological heterogeneity between studies, which makes it challenging to compare among countries. Another limitation was the lack of standard classification concerning ethnic groups. Our main strengths were the use of specific databases for Latin American countries and the wide selection of topics about ALS to provide a large perspective on the subject.

Conclusion

This review supports ALS heterogeneity among geographical areas and populations. Methodological issues on ALS research in Latin America are highlighted. A lower incidence and mortality was reported in Latin America compared to Europe and North America. Admixed population showed a lower occurrence compared to Caucasian population. The frequency of C9orf72 repeat expansion was low. Patients exhibited a younger age of onset. Population-based studies using multiple sources for case ascertainment, prospective design, and uniform diagnostic criteria are encouraged to provide reliable data.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Chapter III. ALS mortality rates in Latin America

III.1. Mortality of ALS as a proxy of incidence

Gold standard methodology for ALS research implies a population based study with a prospective design, a uniform diagnostic criteria and multiple sources for case ascertainment to assure exhaustiveness with a long follow up period (12,80).

Population based registries have play a critical role in ALS descriptive epidemiology due to the: (i) complete case ascertainment because of the multiple sources for case identification, (ii) accuracy of diagnosis with a uniform diagnosis criteria and (iii) a complete follow up of patients that allows diagnosis confirmation (135). Since their creation in Europe, incidence of ALS in Europe appears to be homogenous. An analysis of six population based registries in Europe reported an average crude incidence rate of 2.16 per 100,000 PYFU and a crude incidence of 2.7 per 100,000 person-years for the European population over 18 years (90).

These population-based registries are geographically limited to Europe and North America. Before 2004 European population-based registries were located in Italy, Scotland and England (10). Other novel population-based ALS registries have been created, in Europe, there are the population-based registries from Limoges (France) (122), Germany (136), Switzerland and Sweden (137). Outside Europe, we have identified population-based registries in United States(138) and China (139).

Population-based registers have helped provided valid incidence data, the success of this registries relies on the capacity of identifying cases in a well-defined geographical area, for instance in Europe ALS registries used data from ALS centers, data from neurologists, neurophysiologist, hospital discharge and administrative data, ALS associations and death certificates (10). In United States, another methodology for recruitment of cases is performed, which consist in a search among medical databases and a self-identification registration available in the registry web portal (138).

ALS is a rare disease, population-based registries need to assure a long population surveillance to assure a sufficient number of cases, which leads to a need of specific funding's and resources to keep them running. Mortality data could be used as a proxy of incidence, due to the fact that ALS is a mortal disease with no cure, which is why we can hope to identify all ALS cases using mortality data. This information is valuable more specifically in countries where population based registries are not available or

not feasible. Good accuracy with regard to incidence rates can be accomplished if high-quality criteria is followed (140). For instance, mortality rates in Hong Kong and England were consistent with incidence rates for the same time periods (83,141) .

Mortality data can be used for many research perspectives, for example, mortality data can helped investigators to evaluate time trends in countries assuming a homogenous systems (140). Also, it could be used as a case-finding algorithms to identify ALS patients(10,142), and can also provide information to investigate changes in age and sex mortality, which can help identify risk factors for an specific age or sex.

Most importantly, death certificates can provided population-based data as every person who dies is obligated to be notify by them. Most of countries followed a specific methodology for case notification and mortality coding following the guidelines of the World health Organization for morbidity and mortality coding (143).

In the following sections, we present the epidemiological variability of ALS mortality among countries, followed by differences of ALS mortality among populations and the important clues of ALS mortality in Latin America. At the end of this chapter we present our original publication of ALS mortality in Latin America.

III.2. Worldwide ALS mortality rates

Mortality studies of ALS have also shown that ALS occurrence is heterogeneous. Higher mortality rates have been observed in Europe, while countries from the Asian continent have reported lower rates. Table 3, shows different ALS mortality studies among subcontinents, we can observed that mortality rates in Europe have ranged from 0.91 to 5.35, in North America from 0.69 to 2.9 and in Asia mortality rates have been low as 0.33 to 1.10 per 100,000 persons. Differences among the same continent can also been observed, in Europe crude mortality rates seems to be higher in Northern Europe (0.91 to 5.35 per 100,000 persons) compared to Southern Europe (0.95 to 1.83 per 100,000 persons) (Table 3).

Methodological aspects of the mortality studies described in table 3 should be discussed, such as the differences in time periods which lead to the use of different editions of the International classification of diseases (ICD). The ICD-7th edition code 356, indicated motor neuron disease and muscular atrophy, the latter disease has been separated from MND. The codes 356.1 and 348.0 from the 7th and 8th edition respectively, only consider the specific subtype of ALS excluding PMA, PBP and PLS

which are included in codes 335.2 and G12.2 of the 9th and 10th edition. Which could be misleading, as a higher rate could be showed in more recent studies using the 9th and 10th edition suggesting an increase of ALS according to time. In order to follow consistent ICD codes among different ICD editions, recent publications recommend the use of the following codes: 356.0 and 356.1 for ICD-7th, 348.0, 348.1 and 348.2 for ICD-8th, and 335.2 for ICD-9th (140).

Regarding the ALS mortality studies summarize in table 3, they suggest higher mortality rates in Northern Europe and North America and lower mortality rates in West and East Asia. This observation is consistent with the results of a worldwide meta-analyses of prospective population-based studies that reported significant differences among subcontinents, higher and homogenous incidence rates were reported in North Europe and North America and lower rates in Eastern Asia (1).

Table 3. Worldwide ALS mortality studies

Sub-continent	Country	Authors	Study period	Sources of case ascertainment				Diagnostic criteria	Crude mortality rate per 100,000 persons	Standardized mortality rate per 100,000 persons
				H	DC	N	PA			
North Europe	Finland (144)	Jokelainen et al.,1976	1963 -1972		X			ICD 6 &7	0.91	
	Sweden (145)	Gunnarson et al., 1990	1961- 1985		X				r: 1.4 -2.3	r: 1.3 -1.8
	England (141)	Dean et al., 1993	1975- 1985		X			ICD 7 to 9	M: 2.3; F: 1.8	
	Norway (146)	Seljeseth et al.,2000	1961- 1994		X			ICD 7 to 9	r: 1.38 - 2.54	r: 1.52- 2.54
	Finland (147)	Maasilta et al., 2011	1986- 1995		X				r: 1.54 – 2.27	
	Sweden (148)	Bostörm I et al.,2012	1990- 2010		X			ICD 9 & 10		2.98
	Denmark(149)	Seals et al.,2013	1970- 2009		X			ICD 8 & 10	5.35	
	Norway(150)	Nakken et al.,2016	1951- 2014		X			ICD 6 to 10	r: 1.00- 2.80	r: 1.30 - 2.80
West Europe	France(151)	Gordon et al.,2011	1968- 2007		X			ICD 8 to 10	1.74	
South Europe	Italy (152)	Guidetti et al.,1996	1983- 1992	X	X	X		ICD 9	1.30	
	Italy(153)	Mandrioli et al., 2003	1990- 1999	X	X	X	X	EEDC	1.69	
	Italy (154)	Palese et al., 2018	2002- 2014	X		X	X	ICD 9 EEDC		1.11
	Spain (155)	Veiga-Cabo et al.,1997	1951- 1990		X			ICD 6 to 9	1.53	1.49
	Spain(156)	Alonso et al.,2011	1990-2005		X			ICD 9 & 10	r: 0.95 -1.83	
North America	United States (3,157–161)	Matsumoto et al., 1972	1952- 1969		X			ICD 7 & 8	0.69	0.98
		Sejvar et al., 2005	1979- 2001		X			ICD 9 &10	1.84	
		Noonan et al., 2005	1969- 1998		X			ICD 8 & 9		r: 1.25 -1.82
		Mehal et al., 2013	1999- 2009		X			ICD 10		2.17
		Caller et al. 2015	2005- 2010		X			ICD 10		2.9
		Larson et al., 2018	2011- 2014		X			ICD 10		1.70
West Asia	Israel (162)	Kahana et al., 1975	1960- 1970	X	X			EEDC	0.58	
East Asia	Chine (83)	Fong et al., 1996	1989 -1992		X			ICD 9	0.33	
	Japan (163)	Okamoto et al., 2005	1995- 2001		X			ICD 10	r: 1.00 – 1.10	r: 0.79 – 0.74
	Japan (132)	Doi et al., 2010	1995- 2004		X			ICD 10	r: 0.82 -1.07	

All studies use a retrospective design
H: Hospital; DC: Death certificates; N: Neurologist; PA: Patients association; M: Male; F: Female
ICD: International Classification of Diseases; EEDC: El Escorial Diagnostic criteria; r: range from the first year of study to the last year.

III.3. Mortality rates among ethnic groups

Studies conducted in multi-ethnic populations in United States have also led to the hypothesis of ALS heterogeneity among ethnic groups. Differences among ethnic groups could suggest that genetic and environmental factors could play a key role in ALS pathogenesis. As shown in table 4, the publications performed in United States in different time periods have repeatedly shown that ALS mortality rates are higher among White populations compare to Black and Hispanic populations.

Prior to demonstrating the difference of ALS mortality among populations in the United States, we consider that it is relevant to describe the classification of population according to the US census bureau. In United States the census bureau consider race and ethnicity two different concepts. The information of Race and Ethnic are based on self-identification. Racial categories reflect a social definition of race recognized in the country and not an attempt to define race biologically, anthropologically or genetically. The categories can also include national origin or sociocultural groups, people may choose to report more than one race. Ethnicity in United States determines whether a person considers itself as Hispanic origin or not (164).

The racial categories in the US census are: (i) White: an individual that has origins in any of the original peoples of Europe, Middle East or North Africa. (ii) Black or African American: a person having origins in any of the Black racial groups of Africa. (iii) American Indian or Alaska Native: a person belonging to any of the original peoples of North and South America and who maintains tribal affiliation or community attachment. (iv) Asian: a person having origins from the Far East, South East Asia or the Indian subcontinent. (v) Native Hawaiian or Other Pacific Islander: a person having origins from Hawaii, Guam, Samoa or other Pacific Islands (164).

The study by *Sejvar et al.* found that risk ratios in Blacks (RR= 0.62; 95%CI: 0.60-0.64) and other races (RR= 0.42; 95%CI: 0.40–0.46) were lower compare to Whites (158). A significant result was observed in the study by *Larson et al*, when comparing to other races, risk ratio was higher for Whites (RR= 2.64; 95%CI: 2.42-2.89) and Blacks (RR=1.48; 95%CI: 1.34-1.64) compare to other races. Furthermore non-Hispanic ethnics showed a higher risk (RR: 1.85; 95%CI: 1.74-1.96) compare to Hispanics population (161).

Blacks and other races represent minority groups in United States, the variability of risk could also be explained by differences in case ascertainment, access to health and socio economic status. To address this issues the National Longitudinal Mortality study used adjusted models for SES indicators (household income, educational attainment and home ownership) type of health insurance coverage and indicators of immigrant status (birthplace and presence or not of social security number) to estimate ALS mortality risk in different ethnic groups (2). After adjustment, significant differences were found with a higher risk in non-Hispanic Whites compare to other groups, non-Hispanic Blacks (HR: 0.61; 95%CI: 0.48-0.78), Hispanic (HR: 0.64; 95%CI: 0.46–0.88), and other races non-Hispanic (HR: 0.52; 95%CI: 0.31-0.86) (2).

The epidemiological evidence in United States suggest that Hispanic populations showed a lower risk in ALS occurrence. However, this ethnic group remains a minority, studies in Latin America could provide key information to further clarify this hypothesis.

Table 4. ALS mortality rates among ethnic groups in United States.

Country	Authors	Study period	Race or ethnic group	Standardized mortality (95%CI) per 100,000 population
USA (157)	Matsumoto et al., 1972	1952 - 1969	Caucasian	0.61
			Filipino	1.08
			Japanese	0.44
			Other	1.74
USA (158)	Sejvar et al., 2005	1999-2001	White	2.51
			Black	1.29
			Other	0.96
USA (3)	Noonan et al., 2005	1992- 1998	Hispanics	0.92 (0.75 – 1.08)
			Non-Hispanic White	1.96 (1.89 – 2.02)
			Non-Hispanic African American	1.06 (0.95 – 1.18)
USA (159)	Mehal et al., 2013	1999-2009	White	2.33
			Black	1.18
			Other	0.93
USA (161)	Larson et al., 2018	2011 - 2014	White	1.84 (0.64 – 0.76)
			Black	1.03 (0.98 – 1.09)
			Other	0.70 (0.64 – 0.76)
			Hispanic	0.96 (0.91 – 1.02)
			Non-Hispanic	1.78 (1.76 – 1.80)

III.4. Mortality rates in Latin America

In our previous systematic review of ALS studies in Latin American and the Caribbean presented in chapter 2, we identified six mortality studies from five different countries (Brazil, Mexico, Chile, Ecuador and Cuba). These studies have reported lower rates compare to other regions such as North America and Europe with standardized mortality rates that ranged from 0.33 to 0.89 per 100,000 population.

The results found in Chile, Cuba and Brazil (165,4,6) are consistent to the reports in Hispanic populations from studies in United States. Moreover, studies in Latin America also found significant differences among ethnic groups, suggesting that there was a higher risk in Caucasian or White population compared to Admixed and Black populations.

ALS mortality rates were also heterogeneous within Latin American countries. This differences could be explained in part by differences in methodological issues. For instance, the study from Brazil used the underlying and secondary cause of death as case ascertainment, while in the studies from Chile and Cuba and other study in Brazil this is not clear and in Ecuador only the principal cause of death was used. Which could impact the results showing a higher rate for studies that used underlying and secondary causes (140). All studies used the ICD 9th code 335.2 or 10th edition code G12.2 according to the period of study, but in the Study from *Matos et al.* in Sao Paulo, Brazil PLS, PSA and PBP were excluded. The population at risk for each study was only specified in three studies from six, in Brazil and Chile annual projections from the country census data were used, while in Ecuador the annual demographic yearbook of the United Nations was used which is based on the country census. Standardization was performed only in some countries and the reference population was different in each study.

Differences of ALS mortality in the region can also be explained by ancestral origin. The studies performed in United States showed that ALS mortality was higher among White population which are consistent with ALS rates in European countries and a lower mortality was observed among Hispanics populations compared to non-Hispanic. Latin Americans show a complex genetic variation between African, European and Native-American ancestry, the proportions of ancestry varies among countries. Which suggest that countries in Latin America that presents a high proportion of European ancestry could present a high ALS occurrence.

III.4.1. Geographic variation of ancestry

The variations of ancestry proportion in Latin American countries are the result of the historical demographic events. Genome-wide ancestry studies have shown that there is an extensive variation of ancestry patterns among Latin American populations.

Native-American ancestry has been predominantly in areas, that according to history had an important settlement of native populations such as the Andean regions (Western part of South America) and Meso-America (Mexico and Central America) where major pre-Columbian civilizations developed (166).

As shown in table 5, Peru (0.64 – 0.80), Ecuador (0.39 – 0.50) and Mexico (0.50 – 0.56) have reported the highest levels of Native American ancestry. In contrast, European ancestry has been predominantly in Argentina (0.65 – 0.67), Brazil (0.82), Colombia (0.60 - 0.64) and Uruguay (0.65 – 0.92). While in the Caribbean higher levels of African ancestry has been reported.

Within South America, Homburger et al found statistically significance differences among countries, for instance, Peru reported a higher proportion of Native American ancestry (0.683) compared to Argentina (0.277), Chile (0.387), Colombia (0.274) and Ecuador (0.501) ($p< 0.001$). While Argentina reported a higher proportion of European ancestry (0.673) than Peru (0.26), Chile (0.572) and Ecuador (0.408) ($p= 0.018$) (114).

The variation of ancestry has been also reported within regions in the same country. In Brazil, the highest levels of European ancestry were observed in the South, while African ancestry was highest in the East and Native American in the North West (Amazonia) (167). In Colombia, the highest levels of Native American ancestry are in the South West of the country, European ancestry on the central areas and African ancestry in the coastal regions (167). The results in Colombia are consistent with those reported by *Wang et al.*, where higher Native American ancestry was observed in areas such as Pasto and Peque located in the South, While in Medellin higher European ancestry was observed (166).

On the contrary, Chile, Peru and Mexico have reported the least regional variation, the lowest levels of African ancestry and an uniform distribution between Native American ancestry and European ancestry (167,168).

In Argentina and Uruguay, European ancestry predominates, however studies have shown difference on these proportions. In Argentina, *Wang et al.* reported that there

was a higher proportion of Native American ancestry in the region of Salta which had a higher Pre-Columbian density compared to Tucuman and Catamarca (166).

Avena et al. showed variations on the European ancestry among four geographical regions in Argentina, highest European ancestry was observed for Buenos Aires (76%) compared to North West Argentina (33%) and North East Argentina (54%) (169). As shown in table 5, the proportion of European ancestry varied between the two cities in Uruguay (170).

We have summarized in table 5 different genome wide studies of Latin American populations. We consider important to clarify that the populations included in these studies, have been collected from known genomic datasets such as POPRES (168,171), HapMap (168), or as a part from larger studies GWAS (114). Which may not be representative for each country population. However, Genome studies are limited as they represent many difficulties such as elevated cost, long periods of time, and ethical concerns.

Table 5. Genetic ancestry among Latin American countries

Subcontinent	Country	Author	Average proportion of ancestry			
			European	Native American	African	East Asian
North America	Mexico	Bryc et al, 2010		0.5	0.056	
		Ruiz-Linares et al, 2014	0.37	0.56	0.05	
		Norris et al, 2018	0.46	0.51	0.03	
The Caribbean	Dominican Republic	Bryc et al, 2010			0.42	
	Puerto Rico	Bryc et al, 2010			0.24	
		Norris et al, 2018	0.72	0.16	0.12	
South America	Argentina	Avena et al, 2012	0.65	0.31	0.04	
		Homburger et al, 2015	0.67	0.28	0.04	0.01
	Brazil	Ruiz-Linares et al, 2014	0.82	0.09	0.09	
	Chile	Ruiz-Linares et al, 2014	0.49	0.48	0.05	
		Homburger et al, 2015	0.57	0.39	0.03	0.02
	Colombia	Ruiz-Linares et al, 2014	0.60	0.11	0.29	
		Homburger et al, 2015	0.63	0.27	0.09	0.01
		Norris et al, 2018	0.64	0.23	0.07	
	Ecuador	Bryc et al, 2010		0.39	0.07	
		Homburger et al, 2015	0.41	0.50	0.07	0.02
	Peru	Ruiz-Linares et al, 2014	0.29	0.64	0	
		Homburger et al, 2015	0.26	0.68	0.03	0.03
		Norris et al, 2018	0.18	0.8	0.02	
	Uruguay (Montevideo)	Sans et al,1997	0.92	0.01	0.07	
	Uruguay (Tacuarembo)		0.65	0.20	0.15	

Individual estimation of genetic ancestry was performed through the ADMIXTURE program for Ruiz-Linares et al (167), Norris et al (171), Homburger et al (114) and Avena et al (169).
LAMP program was used by Bryc et al (168)

III.5. Article 2: ALS mortality in Latin America: a meta-analysis

Heterogeneity of ALS have been also observed among mortality studies around the world. Higher rates have continue to been reported in Europe and North America and furthermore among Caucasian non-Hispanic populations compare to Black, Hispanic and Admixed populations.

Lower incidence and mortality rates have been observed in Latin American countries compared to Europe and North America as previously described in chapter 2. ALS epidemiological studies in Latin America, have also reported heterogeneity of ALS occurrence with higher rates in certain countries such as Uruguay (127) and Argentina (128) and lower rates in Mexico (118) and Ecuador (5,172). Nevertheless, the methodological differences explained in chapter 2, have make it difficult to draw firm conclusions in the region.

ALS research is limited in Latin America, and is underrepresented in International ALS studies. Population-based registries in Europe have provided reliable epidemiological data but these are geographically limited. Latin American countries faced different difficulties, which made the implementation of these registries complicated. There are no institutions that collects medical data at regional or national level, access to medical files and other administrative data is challenging. There is an important problem in access to health, with a low number of specialized physicians with respect to the population and tertiary level centers, as most of them are only located in the capital cities. There is a double burden of disease, which make it difficult to the government to provide funding to more rare diseases. Because of this difficulties death certificates and national mortality registers can helped provided reliable epidemiological data in this region. In most of Latin American countries this information is collected, is of public access and is available in different formats (electronic files). Mortality databases provide different information as age and sex, place of death and cause of death. All this characteristics make it feasible to performed mortality studies in the region.

To provide further original evidence and a better understanding of ALS heterogeneity and the associated factors: ancestral origin and socio-economic status. We conducted a meta-analysis using general population-based data to describe ALS mortality following homogenous methodology among 10 Latin American countries, sources of heterogeneity were also explored.

In the following sections we present the complete methodology for this study, the principal results and some additional figures that were not presented in the publication, and we discussed supplementary points of this work. A copy of the published article is presented at the end of the chapter.

III.5.1. Methodology

An online search for the national annual mortality registers for each Latin American country according to the United Nation classification, was performed to identify ALS deaths in the region from 1990 to 2019.

National annual mortality registries collect causes of death from standard death certificates which are filled by health professionals. These certificates gathers the causes of deaths, which are all those diseases, morbid conditions, or injuries, which either resulted in or contributed to death. Mortality registries in Latin American countries follow the guidelines for mortality coding according to the recommendations provided by the World Health Organization (143). Which provides the procedures to an accurate selection of the underlying cause of death and the antecedents originating the cause of death (143).

The International Classification of diseases (ICD) codes are used for tabulation and coding among mortality registries. The ICD purpose is to permit the systematic recording analysis, interpretation and comparison of mortality and morbidity data collected in different countries or areas and at different times (143).

National mortality registers established by the National Institutes of Statistic for each country were available online for eight countries:

- Argentina Direction of Statistics and Health Information (DEIS) (173).
- National Institute of Statistics (INE) of Chile (174).
- Colombia National Administrative Department of Statistics (DANE) (175).
- National Institute of Statistics (INE) of Costa Rica (176).
- National Institute of Statistics (INE) of Ecuador(177).
- National Institute of Statistics (INE) of, Guatemala (178).
- National Institute of Statistics and Geography Informatics of Mexico (INEGI) (179).

- National Institute of Statistics (INE) of Uruguay (180).

From a previous systematic review of ALS studies in Latin America (181), we identified mortality studies using data from national registries in Brazil, Cuba, Chile and Ecuador (4–6,165). For the countries where mortality data were not online available (Brazil (6) and Cuba (4)). The authors were contacted to obtain data (underlying cause of death, sex, age group and ethnic classification if available).

All death records in the mortality registries were searched. In order to keep uniformity among all the countries, to identify ALS cases we used only the underlying cause of death as in some mortality database only this information was given. The underlying cause of death has been designated as the cause of death for primary tabulation and is defined as the disease or injury that initiated the train of morbid events leading directly to death. Cases younger than 15 years were excluded to reduce likely misclassified cases.

The ICD-9 code 335.5 from 1990 to 1996 and ICD-10 code G12.2 from 1997 to 2019 were used to identify ALS deaths as a recommended approach for ALS/MND (140) . The 9th revision ICD code includes ALS, progressive muscle atrophy (PMA), progressive bulbar palsy (PBP), pseudobulbar palsy, primary lateral sclerosis (PLS) and other motor neuron diseases. The 10th revision of the ICD code mentions ALS, motor neuron disease, unspecified, familial motor neuron disease, PBP, PLS, progressive spinal muscle atrophy, and other motor neuron diseases (143).

We collected the demographic information including sex and age or age group at the time of death.

We obtained from the Annual Demographic Yearbook published by the United Nations Statistics Division the population at risk for each country and the mid-year population per year was considered to calculate the mortality rates (182). Subcontinent classification was performed according to the United Nations Statistics Division. Country classification by income was obtained from the World Bank's classification by income level (183). As we include different periods, we took into consideration the middle year of the period for each country as the reference for the income classification

A description of ALS cases and population at risk by age and sex for each country is available in appendix 2.

Ethnic group information was available in only three databases. To assure homogeneity, we collected the proportion of each ethnic population from a nonprofit private corporation “Latino Barómetro”, which carries out an annual public opinion survey using a standardized methodology among Latin American countries. This information was available from 2007 to 2018. Ethnic group information in the “Latino Barometro” databased is gathered as the participant self-reported identification among the different categories. This information is asked as follows: *What ethnicity or race you identify best with?* Each participant can chose among, Caucasian (White), Admixed, Black, Asians, Indigenous, Mulatto, other race, or no answer.

To obtain the proportion for Caucasian population for each country, we collected the crude data for each year and the calculation for the overall period was calculated.

The Latino Barometro study is performed in 18 Latin American countries with the objective to study the economy, democracy and society as a whole. The results of the study are normally used by socio-political actors regional and international, as well of governmental and media actors. Data was collected by a standard survey used among all countries. Probabilistic sampling is used to assure representativeness of the population. The Latino Barometro database and methodology used for each year is available on the Latino Barometro website (184). The proportion for each ethnic group and country is available in table 6.

We followed the guidelines for Meta-analyses and Systematic Reviews of Observational Studies (MOOSE) (185).

Specific epidemiological criteria for ALS mortality studies were followed (140). Such as the description of the population at risk, mortality information was available for all ages and sex and standardization by age and sex was performed.

R statistical software version 3.6.1 (The R project for statistical computing) and Stata version 11.1 (Stata Corporation, College Station, TX, USA) were used to conduct analyses. Qualitative variables were described as frequencies and percentages. Frequency counts of ALS deaths were categorized in 5-year age increments. Crude mortality rates per 100,000 person-years of follow-up (PYFU) were calculated along with 95% confidence intervals (95%CI) based on the Poisson distribution. Direct age and sex standardization was performed using the US 2010 population(186).

Male to female sex ratio was calculated. . The crude mortality sex ratio was the ratio of the crude mortality in males divided by the crude mortality in females. The standardized mortality sex ratio was the ratio of the standardized mortality in males by the standardized mortality in females.

To assess the relationship between crude mortality rates and proportion of Caucasian population we performed a simple linear regression.

Meta-analysis was conducted and forest plots were generated. To asses statistical heterogeneity the Cochran's Q-test ($p < 0.1$) and I^2 statistics were used. I^2 percentage allows to classify heterogeneity as follows: 0% no heterogeneity, 25-50% low, 50-75% moderate and 75-100% as high. Because the heterogeneity was statistically significant, a random-effect meta-analysis was performed..

In order to investigate heterogeneity with key covariates we performed stratified sub-group analysis: i) Proportion of Caucasian population, ii) Income level and iii) Geographic localization (Subcontinent). The proportion of Caucasian population was categorized in three groups (<25%, 25-50%, 50-75%). This categorization was performed as the distribution was divided in quartiles, and the higher proportion of Caucasian population was 74%. Geographic localization was classified into two subcontinents: a) Central America and The Caribbean, and b) South America. Mortality data from nine countries were used for the proportion of Caucasian population subgroup analysis, as this information was not available for Cuba in Latino Barómetro.

III.5.2. Results

Overall, 28,548 ALS deaths were identified considering a population of 819 million PYFU covering 10 Latin American countries. Fifty-five percent of ALS cases were males (15,717 ALS cases) and 45% were female (12,831 ALS cases).

Crude and Standardized ALS mortality

Crude ALS mortality ranged from 0.07 to 1.24 per 100,000 PYFU among Latin American countries. Mortality remained variable after standardization, the highest standardized mortality rates per 100,000 PYFU were in Uruguay (1.30, 95%CI: 1.22–1.38), Costa Rica (1.16, 95%CI: 1.08–1.25) and Chile (0.98, 95%CI: 0.95 –1.02), while the lowest rates were observed in Guatemala (0.19, 95%CI: 0.15-0.23), Ecuador (0.35, 95%CI: 0.33–0.38) and Mexico (0.44, 95%CI: 0.43–0.45).

ALS mortality in Latin America by age and sex

Overall ALS mortality exhibit and age-related pattern, with a peak age of crude mortality among the 75 to 79 age group, and at 60 to 69 years of standardized mortality. Followed by a sudden decrease in older ages. Male ALS crude and standardized mortality was higher among all age groups, except for the >80 years standardized mortality.

Similar patterns where observed in each country. Figure 4 shows ALS standardized mortality by age and sex for South American countries. The age peak varied among countries, age peak in Argentina and Chile was among the 60 to 64 years age group, and on 65 to 69 years age group for Brazil, Colombia and Uruguay. While in Ecuador ALS mortality was stable from 55 to 69 years. Male and female standardized mortality followed a similar pattern, with a higher standardized mortality of males among all ages, except on the > 80 years age group.

For the Caribbean and Central American countries (Figure 5), Mexico and Costa Rica followed a similar pattern as South American countries. While in Cuba male standardized mortality age peak was among the 60 to 64 years age groups, but this was not the case for the female standardized mortality which was higher in the >80 years age group. An irregular pattern was observed in Guatemala.

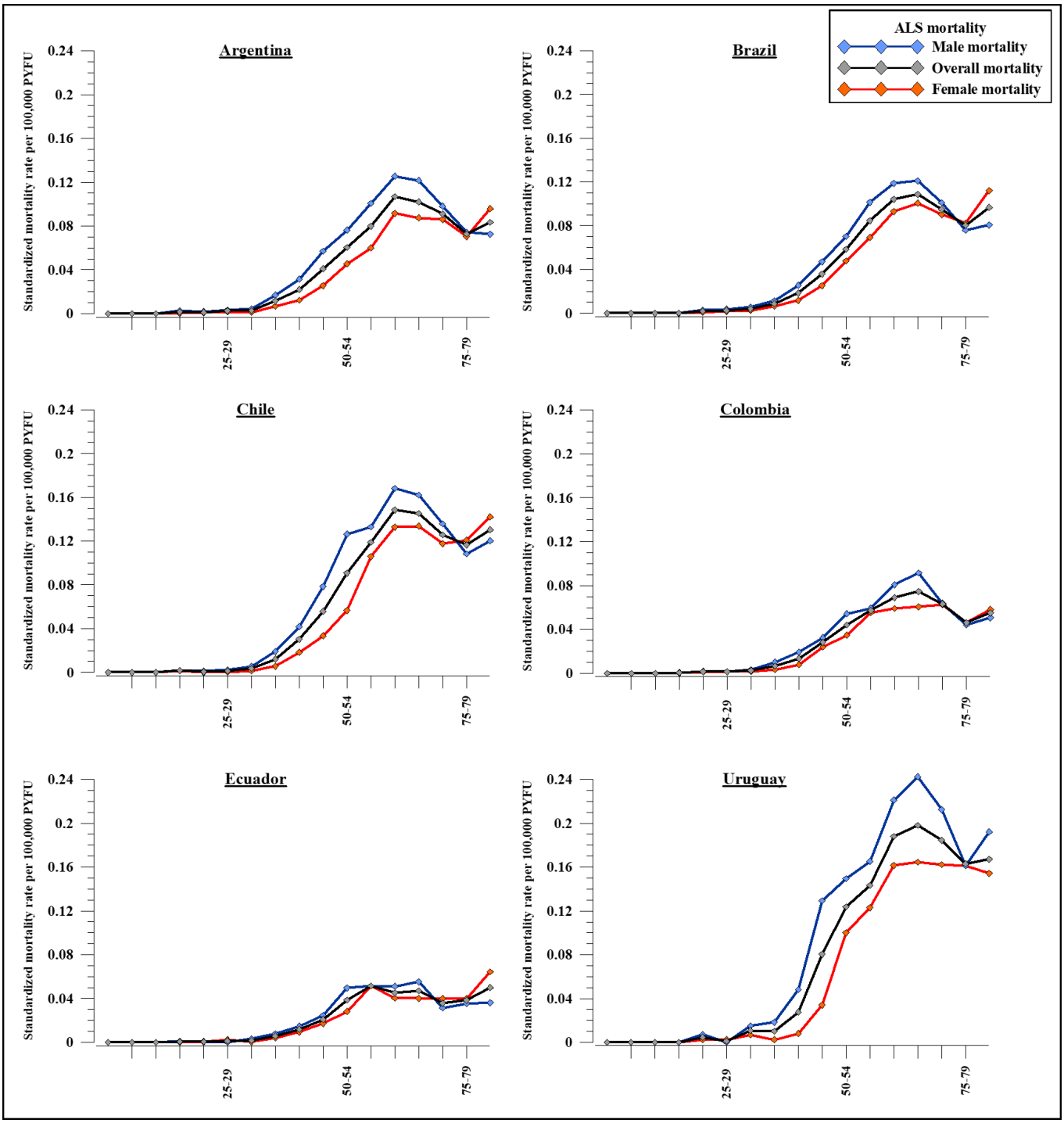

Figure 4. South American countries, ALS standardized mortality by age group and sex.

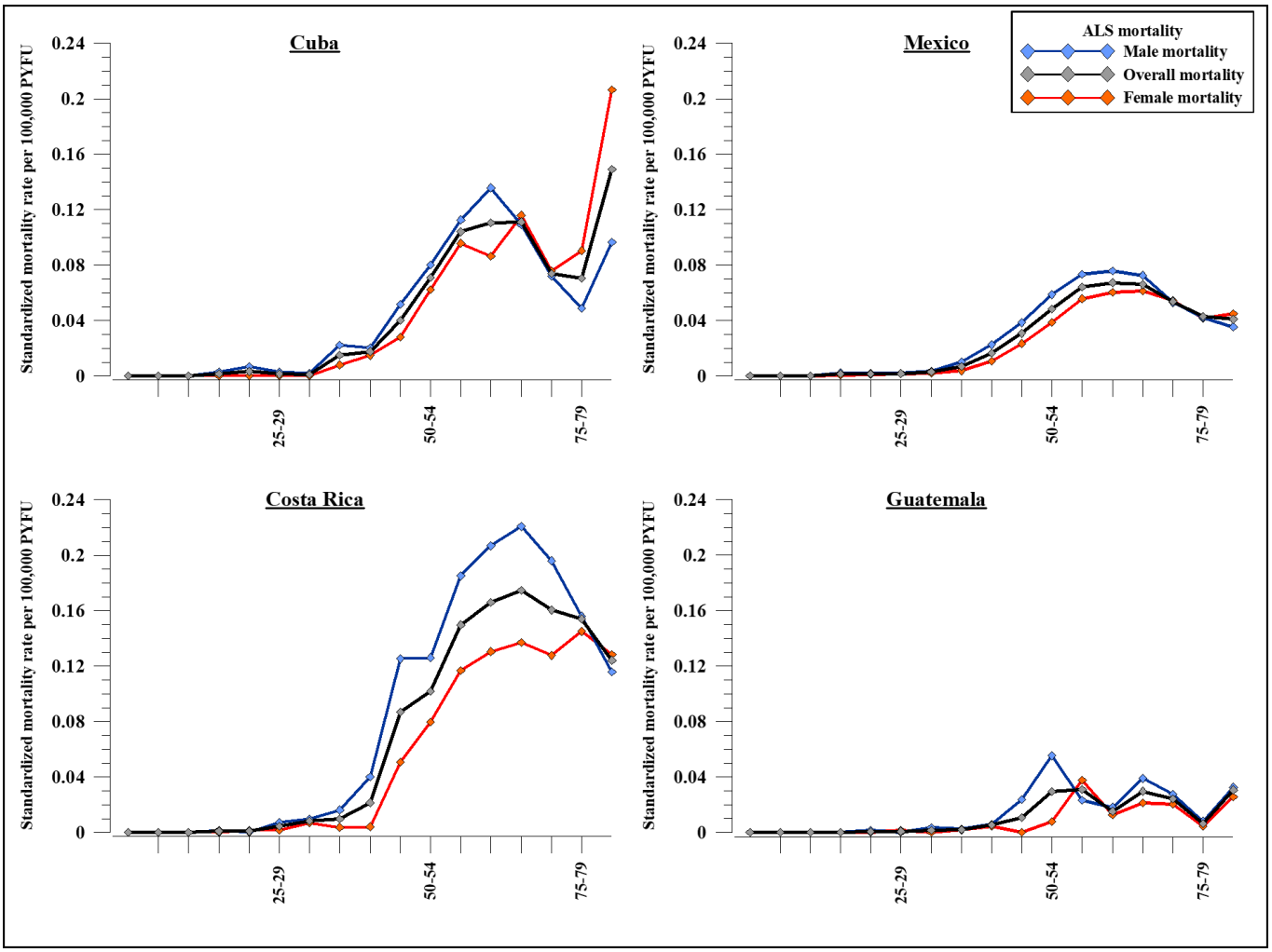

Figure 5. The Caribbean and Central America countries, ALS standardized mortality by age group and sex.

Meta-analysis

The overall pooled crude mortality of ALS per 100,000 PYFU was 0.38 (95%CI: 0.28–0.53). The pooled standardized mortality per 100,000 PYFU was 0.62 (95%CI: 0.49–0.77). A high level of heterogeneity was observed in both rates (Cochran's Q p<0.001; I2=99.7%).

Subgroup-analysis: ALS mortality variability in Latin America

A higher mortality rate was observed among countries with a higher proportion of Caucasian population. Standardized rates among countries with a proportion of Caucasian population less than 25% were remarkably low (0.32, 95%CI: 0.24–0.42), while the standardized mortality rate was higher in countries that had 50-75% Caucasian population (0.95, 95%CI: 0.67-1.35).

Upper-middle-income countries displayed higher mortality compared to lower-middle-income countries. When comparing standardized estimates, upper middle-income countries showed a higher rate (0.82, 95%CI: 0.62–1.09) compared to lower middle-income countries (0.40, 95%CI: 0.28–0.56) per 100,000 PYFU.

Caucasian population and ALS mortality in Latin America

Simple linear regression was carried out to further investigate the relationship between ALS crude mortality and the proportion of Caucasian population for each country. The scatterplot showed that there was a strong positive linear relationship between the two confirmed by a Pearson's correlation of 0.83 (Supplementary figure 1). Simple linear regression showed a significant relationship between the two (p=0.005). The slope coefficient for proportion of Caucasian population was 0.012 so the crude mortality increase by 0.012 for each 10% increase of Caucasian population. R2 value was 0.70 (Figure 6).

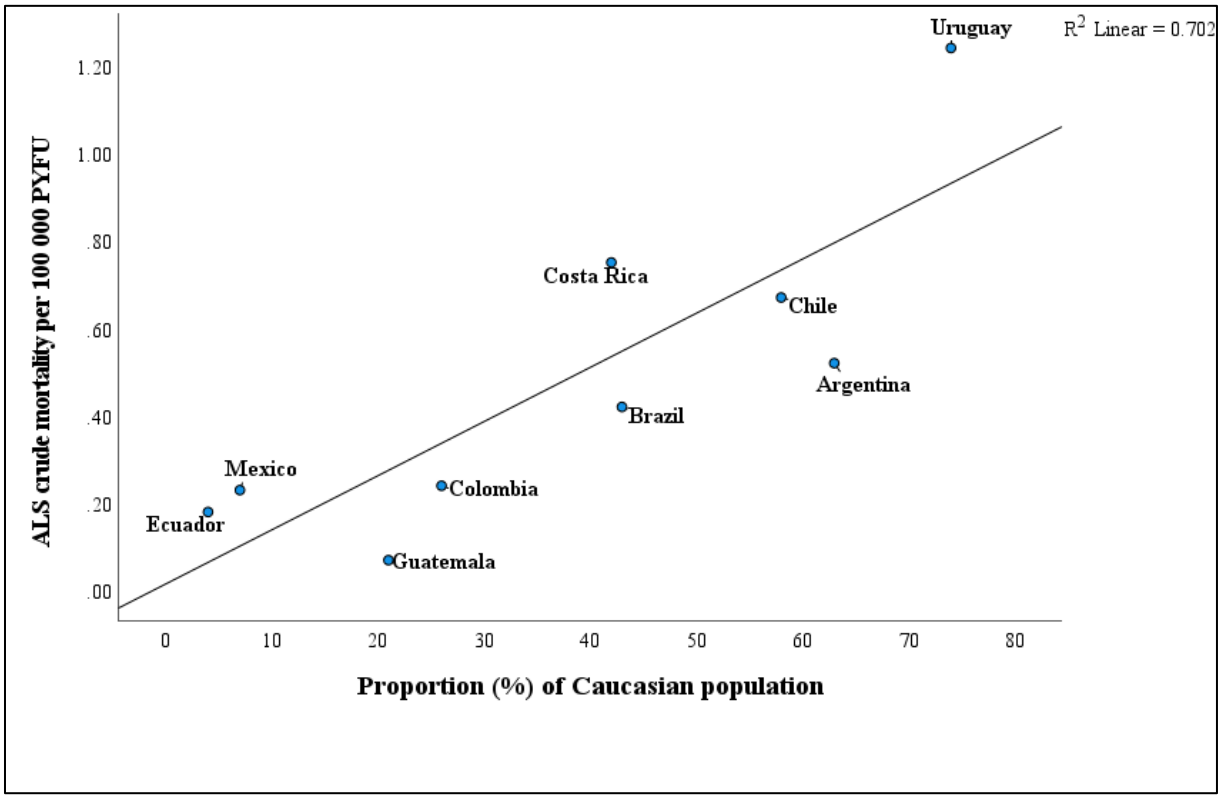

Figure 6. Linear regression: ALS mortality rates relationship with proportion of Caucasians in Latin American countries

III.5.3. Discussion

This meta-analysis confirms that there is a lower ALS occurrence in Latin American countries compare to Europe and North America.

Heterogeneity of ALS mortality was observed among the different Latin American countries. Stratified analysis showed a higher mortality among the countries with a higher proportion of Caucasian population. Differences among income were also observed with a higher mortality among countries with a higher income level.

In the following section we present our article publication, discussing the possible explications of heterogeneity. Here we provide a complementary discussion of: the age-related pattern of ALS, the differences of ethnic classification and Latin American ancestry and the limitations of death certificates.

ALS age-related pattern

ALS mortality in Latin American countries exhibited an age-related pattern that consisted of a progressive increase leading to a peak (around 60 to 69 years of standardized mortality) followed by a sudden decrease. Which is consistent to reports in Europe (13).

A younger age is suggested in Latin America compared to Europe and North America. A dose-response meta-analysis of ALS incidence reported an age peak in Europe around 70 years. Some differences were observed among Latin American countries also. This differences could be explained by differences in life expectancy and access to health leading to an underestimation of cases in the elderly population. This underestimation could be explained by different reasons: i) difficulties in access to health, such as, less access to specialized care due to the limited number of physicians, the lack of transport and less autonomy, could leave this population without a ALS diagnosis. ii) Due to the array of comorbidities in elderly population, ALS diagnosis can be more difficult leading to a delay in ALS diagnosis, in addition due to the different comorbidities elderly patients could die from other causes before ALS diagnosis (70). iii) A higher age at onset is associated to a shorter survival, which could lead to elderly patients dying without establishing a definite ALS diagnosis. iv) Because of different comorbidities, it can be challenging for identifying the underlying cause of death when filling death certificates (187)

Latin American ancestry and ethnic self-identification

As previously discussed in the beginning of this chapter, Latin America is composed of a predominantly Admixed population, from European, African and Native American populations. Genome-wide ancestry studies have showed that there is a variation of ancestry among countries and individuals from the same country. This genome studies are limited in the region due to the high cost they represent.

ALS studies evaluating the epidemiological differences among ethnic groups have used ethnic self-identification as a proxy of ancestral origin. However, the main limitation is that there is a lack of standard classification. In Latin America definition of ethnicities varies from country to country, according to the census 2010 in Ecuador, ethnic classification was done by self-identification based on cultural and traditional aspects (188). While the Census in Cuba this classification is performed by the skin color (189).

To assure a homogenous ethnic classification among countries, the proportion of Caucasian population was obtain from the Latino Barometro studies for all countries. Even though ethnic self-identification is not an objective assessment of ancestral origin, we can observe that the results from Latino Barometro (table 6) are consistent from those reported in genome wide studies in the region (table 5).

Countries that reported a higher level of Native American ancestry such as Mexico and Ecuador (table 5), had a higher proportion of Admixed population (table 6). While countries with a higher level of European ancestry, where the countries with a higher proportion of White population (Argentina, Brazil, Chile and Uruguay).

This results are also consistent with those reported in national census, the 2010 census in Ecuador reported that 71.9% of the population identified as Admixed, 6.1% as White, 7.2% as Black and 7% as Indigenous (177).

The 2011 census in Uruguay reported that 87.7% of the population classified as White, 4.6% as Black, 0.22% as Asian, 2.35% as Indigenous and 0.14% as other race (180).

The total number of individuals and the proportion for each ethnic group according to the Latino Barometro studies from 2007 to 2018 are described in table 6.

Some limitations on the classification of ethnic groups of the Latino Barometro study needs to be acknowledge. The proportion among the categories: “Other”, “Do not

know" and "No answer" is higher in some countries compared to others for instance, the proportion of the "Do not know" category is higher than 8% in Colombia and Guatemala and almost 20% in Mexico, while in other countries is lower than 6%. Which could in partly explained some differences. The higher proportion of participants in these categories (other, do not know and no answer) could be explained by the lack of a standard definition and differences among countries. In Mexico the national population census do not performed an ethnic or race classification. In the national 2018 census of Guatemala, ethnic classification is performed as "village of belonging" and is categorize in: "Maya", "Garifuna", "Xinka", "Afro descendant", "Ladino" synonymous of Mestizo but mostly used in Guatemala, and "Foreigner" (190). In Colombia, the 2018 national census recognizes four ethnic groups which are: i) the Indigenous populations, ii) the Black or Afro-Columbian or Afro descendant, iii) the "Raizales" communities of el Archipielago de San Andres, Providencia and Santa Catalina population and iv) the "Rrom" or gipsy population (191). Contrary to these countries, the Caucasian, Admixed, Black and Asian ethnic groups are of more common use (Uruguay, Ecuador, and Brazil). These differences can make it difficult for participants to self-identify in the categories of Latino Barometro.

Limitations of mortality data on ALS epidemiology

This study is limited due to the accuracy of death certifications to identify ALS cases. As some physicians filling a death certificate may not have full knowledge of the individual medical history. Also there is a high potential for misdiagnosis. Studies in Japan, United States and Scotland, estimated a positive predictive value of 72.0% to 90.4% when assessing hospital data and death certificates (140). There are no studies evaluating the accuracy of death certificates in Latin America, but due that ALS is well recognized in advance stages we could expect a lower rate of misclassification. In addition our results are consistent with studies reporting mortality rates among Hispanic populations in the United States, which have showed a good accuracy with a true positive rate of 0.865; 95%CI: 0.859 – 0.870 (192).

Another limitation is the differences of time periods among the studies. Higher death rates have been observed after the implementation of the ICD-10 revision, which could be a reflection of the higher sensitivity and lower specificity (158). In addition, the evolution of health systems and the improvements of ALS diagnosis in recent years could lead to identifying a higher number of cases in studies performed in recent years

(140). Nevertheless, in our study we can observe that in countries reporting death on the same time period (1990 -2017/2019) such as Chile, Ecuador and Mexico, notable differences were showed. Also, in countries where only the ICD-10 revision was used such as Brazil, Uruguay, Cuba and Guatemala differences on ALS mortality were observed.

We are aware of the limitations of comparing ALS mortality data in Latin America, to incidence studies in Europe. The differences in access to health could showed higher rates in countries with a better access. Thus, this study is the first to provide a pooled rate of ten different countries from an under represented region.

Conclusion

This meta-analysis using population-based data and a homogenous methodology among Latin American countries confirmed a lower ALS occurrence. Subgroup analysis provided important clues that can explain ALS heterogeneity, a higher mortality among the countries with a higher proportion of Caucasian population supports the hypothesis of a higher risk among this population. Socio-economic status should be taken in consideration in further studies assessing epidemiological variations. New research assessing gene association and ancestral origin are needed in the region.

Table 6. Ethnic classification among Latin American countries according the Latino Barometro studies 2007-2018.

Country	White N= 39,339	Admixed N= 35,519	Black N= 4,135	Asian N=436	Indigenous N= 8,759	Mulato N=4,920	Other N= 2,188	Do not know N= 7,583	No answer N= 1,203
Argentina	7514	2627	110	33	204	86	323	876	227
N = 12000 (%)	(62.60)	(21.90)	(0.92)	(0.28)	(1.70)	(0.72)	(2.69)	(7.30)	(1.89)
Brazi	5206	2015	2043	44	230	1599	633	259	53
N= 12082l	(43.10)	(16.70)	(16.90)	(0.40)	(1.90)	(13.20)	(5.30)	(2.10)	(0.40)
Chile	6937	3216	36	32	745	94	144	643	153
N= 12000	(57.80)	(26.80)	(0.30)	(0.27)	(6.21)	(0.78)	(1.20)	(5.36)	(1.28)
Colombia	3135	5455	855	49	703	535	186	977	105
N= 12000	(26.10)	(45.50)	(7.10)	(0.41)	(5.90)	(4.46)	(1.55)	(8.10)	(0.88)
Costa Rica	4188	2858	243	72	444	1454	72	550	119
N=10000	(41.90)	(28.60)	(2.43)	(0.72)	(4.44)	(14.50)	(0.72)	(5.50)	(1.19)
Ecuador	514	9767	361	33	653	419	34	164	55
N=12000	(4.28)	(81.40)	(3.00)	(0.28)	(5.44)	(3.49)	(0.28)	(1.37)	(0.46)
Guatemala	2066	2507	83	65	3786	152	165	1077	99
N= 10,000	(20.66)	(25.07)	(0.83)	(0.60)	(37.90)	(1.50)	(1.65)	(10.80)	(0.99)
Mexico	903	6029	74	67	1777	235	317	2343	255
N=12000	(7.53)	(50.24)	(0.60)	(0.56)	(14.81)	(1.96)	(2.64)	(19.53)	(2.13)
Uruguay	8876	1045	330	41	217	346	314	694	137
N=12000	(74.00)	(8.71)	(2.75)	(0.34)	(1.80)	(2.88)	(2.60)	(5.78)	(1.14)

III.5.4. Article presentation

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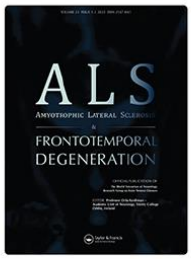

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RESEARCH ARTICLE

Amyotrophic lateral sclerosis mortality rates in Latin America and the Caribbean: a meta-analysis

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Abstract

Background: Recent studies have described a low occurrence of Amyotrophic Lateral Sclerosis (ALS) in Latin America. Significant differences in ALS risk have been reported among ethnic populations in the region. We conducted a meta-analysis using population-based data to describe ALS mortality rates in Latin America. We explored sources of heterogeneity among key covariates.

Methods: National mortality registries from Latin American countries were searched to identify ALS deaths according to the International Classification of Diseases (ICD-9: code 335.2 and ICD-10: code G12.2). Crude and standardized mortality rates were calculated. A random-effect meta-analysis was conducted to estimate pooled mortality rates. Subgroup analysis was performed as a means of investigating heterogeneity.

Results: Overall, 28,548 ALS deaths and 819 million person-years of follow-up (PYFU) from ten Latin American countries were considered. Standardized mortality varied among countries. The highest mortality rates were observed in Uruguay and Costa Rica at 1.3 and 1.2 per 100,000 PYFU, respectively. The pooled crude mortality rate was 0.38 (95%CI: 0.28–0.53) and the pooled standardized mortality was 0.62 (95%CI: 0.49–0.77) per 100,000 PYFU. Heterogeneity was high (I2: 99.9%, Cochran's Q $p < 0.001$). Subgroup analysis showed a higher mortality rate among countries with a higher proportion of Caucasian populations and higher income levels.

Conclusion: There is a lower ALS occurrence in Latin America compared to Europe and North America. This meta-analysis supports the hypothesis of a higher ALS risk among the Caucasian population. Further studies are needed to investigate the role of ancestral origins in ALS, taking socioeconomic status into consideration.

Keywords: *Amyotrophic lateral sclerosis, epidemiology, mortality, Latin America, heterogeneity*

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disease with a poor prognosis due to respiratory insufficiency, with a median survival time from diagnosis of around 15–20 months (1). Recent studies have suggested heterogeneity of ALS epidemiology among geographical areas and populations (2–5). Lower incidence and mortality rates of ALS have been described in Latin America compared to Europe and North America (6).

A lower ALS occurrence has been observed in Hispanic populations compared to Non-Hispanic populations in studies performed in the United States (5,7). In Latin America, studies from Cuba and Ecuador have shown significant differences among ethnic groups (3,4). Furthermore, the results described in Latin American countries were consistent with those observed in Hispanic populations in the United States.

This could imply that ancestral origin could play an important role in ALS occurrence, as

Supplemental data for this article can be accessed here.

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higher risks of developing ALS have been observed between ethnic groups (3–5). Variations of ALS occurrence could also be explained, by methodological heterogeneity and differences of socioeconomic status.

There is a major lack of information in some regions of the world, including Latin America. Population-based registries have played a key role in understanding descriptive ALS epidemiology (8). In countries where ALS registries are not available, mortality data has been a valuable source of information as it can be expected to identify all ALS cases due to the fatal outcome of the disease (9). Hence, mortality data could be considered as a proxy of ALS incidence if high-quality methodology is followed (10).

Latin America is an interesting region for ALS studies because of the diversity among ethnic groups. To improve our understanding of the role of ancestral origins in ALS occurrence, there is a need for high-quality studies using standardized methodology. In this context, we conducted a meta-analysis using general population data to describe ALS mortality rates in Latin America. Sources of heterogeneity were also explored.

Methods

We followed the guidelines for Meta-analyses and Systematic Reviews of Observational Studies (MOOSE) (11). We followed specific epidemiological criteria for ALS mortality studies (10). The Moose checklist is shown in Supplementary etable 1.

Source of information

We performed an online search of registries of annual mortality causes from all Latin American countries. Available information for each country was collected from 1990 to 2019. Mortality registries from the National Institutes of Statistics of eight countries were available online: Argentina (12), Chile (13), Colombia (14), Costa Rica (15), Ecuador (16), Guatemala (17), Mexico (18), and Uruguay (19).

We identified mortality studies using data from national registries in Brazil and Cuba, through a previous systematic review of ALS in Latin America (6). The authors were contacted to obtain the mortality data of their countries (Brazil (20) and Cuba (4)).

Case ascertainment

All death records in the mortality registries were searched. National registries collect causes of death from standard death certificates. Health professionals fill in these certificates. Registries in Latin American countries follow guidelines for mortality coding according to the recommendations provided by the World Health Organization (21).

The International Classification of Diseases (ICD) was used to identify ALS deaths: ICD-9 code 335.5 from 1990 to 1996 and ICD-10 code G12.2 from 1997 to 2019. The underlying cause of death was used to identify ALS cases. Cases younger than 15 years of age were excluded to reduce the risk of false positives.

Data collection

Demographic information was collected from each mortality registry including sex and age group at the time of death. The population at risk in each country was obtained from the Annual Demographic Yearbook published by the United Nations Statistics Division (22). The mid-year population per year was considered to calculate the mortality rates.

Subcontinent classification was performed according to the United Nations Statistics Division (23). Country classification by income was obtained from the World Bank's classification by income level. As we include large periods among countries, we took into consideration the middle year of the period for each country as the reference for the income classification (24). The proportion of ethnic groups was obtained from a nonprofit private corporation "Latino Barómetro," which carries out an annual public opinion survey using a standardized methodology among Latin American countries (25). Self-reported ethnicity is categorized into Caucasian, Admixed, Black, Asians, Indigenous, Mulatto, other race, or no answer. Information for ethnic groups was available from 2007 to 2018. To obtain the proportion of each ethnic group from each country, we collected the crude data for each year and then we calculated the proportion for the overall period. The Latino Barómetro database and methodology are published elsewhere (25).

Statistical analyses

Qualitative variables were described as frequencies and percentages. The frequency counts of ALS deaths were categorized in 5-year age increments. Crude mortality rates per 100,000 person-years of follow-up (PYFU) were calculated along with 95% confidence intervals (95%CI) based on the Poisson distribution. Direct age and sex standardization was performed using the US 2010 population.

A meta-analysis was performed using a random-effect model and Forest plots were generated. Pooled mortality rates were calculated. The Cochran's Q-test ($p < 0.1$) and I^2 statistics were used to assess statistical

heterogeneity.Heterogeneity was defined as high if greater than 75% (I^2 statistics).

We performed stratified analyses as a means of investigating heterogeneity with respect to a number of key covariates: (i) Proportion of Caucasian population, (ii) Income level and (iii) Geographic localization (Subcontinent). We categorized geographic localization into two subcontinent groups: (a) Central America and The Caribbean, and (b) South America. The proportion of Caucasian population was categorized (<25%, 25–50%, 50–75%, >75%). Mortality data from nine countries were used for the proportion of Caucasian population subgroup analysis, as this information was not available for Cuba in Latino Barómetro.

Analyses were conducted using R statistical software version 3.6.1 (The R project for statistical computing) and Stata version 11.1 (Stata Corporation, College Station, TX).

Results

Overall, 28,548 ALS deaths were identified considering a population of 819 million PYFU covering 10 Latin American countries. Fifty-five percent of ALS cases were males (15,717 cases) and 45% were female (12,831 cases). The total male/female sex ratio was 1.22. The characteristics of ALS mortality data are described in Table 1.

Crude and standardized ALS mortality among Latin American countries

Crude ALS mortality ranged from 0.07 to 1.24 per 100,000 PYFU. Mortality remained variable after standardization (Figure 1), showing the highest standardized mortality rates per 100,000 PYFU in Uruguay (1.30, 95%CI: 1.22–1.38), Costa Rica (1.16, 95%CI: 1.08–1.25) and Chile (0.98, 95%CI: 0.95 – 1.02). While the lowest rates were observed in Guatemala (0.19, 95%CI: 0.15-0.23), Ecuador (0.35, 95%CI: 0.33–0.38) and Mexico (0.44, 95%CI: 0.43–0.45).

Age-related profile and sex ratio of ALS mortality in Latin America

The peak age of crude mortality was between 75 and 79 years followed by a decrease after 80 years. A similar pattern was observed for standardized mortality (Figure 2). The crude mortality sex ratio was 1.30, while the standardized mortality sex ratio was 1.27. The crude and standardized mortalities by sex in each country are shown in Table 2.

Meta-analysis

Crude and standardized ALS mortality are reported in Figure 3. The overall pooled crude mortality of ALS per 100,000 PYFU was 0.38 (95%CI: 0.28–0.53), with high heterogeneity (Cochran's Q $p<0.001$; I^2=99.9%). The pooled standardized mortality per 100,000 PYFU was 0.62 (95%CI: 0.49–0.77). A high level of heterogeneity was also observed (Cochran's Q $p<0.001$; I^2=99.7%). Male and female pooled standardized mortality was 0.69 (95%CI: 0.55–0.88) and 0.54 (95%CI: 0.44–0.68), respectively.

Stratified analysis. A higher mortality rate was observed among countries with a higher proportion of Caucasian population. The crude mortality rate for countries with a proportion of Caucasian population less than 25% was 0.15 (95%CI: 0.10–0.21), 0.42 (95%CI: 0.26–0.70) for countries with 25–50%, and 0.76 (95%CI: 0.51–1.13) for countries with 50–75%. Heterogeneity was high

Table 1. Characteristics of ALS mortality data by countries.

Country	Period	ICD code	Duration of study	Number of ALS deaths			Sex ratio[a]	PYFU
				Total	Male	Female		
South America								
Argentina	1995–2018	G12.2	24	4936	2708	2228	1.21	942,326,443
Brazil	2004–2013	G12.2	10	8036	4348	3688	1.17	1,904,851,795
Chile	1990–1996	335.2	28	3003	1663	1340	1.24	443,327,868
	1997–2017	G12.2						
Colombia	1992–1996	335.2	24	2478	1370	1108	1.23	1,012,372,492
	1997–2015	G12.2						
Ecuador	1990–1996	335.2	30	722	388	334	1.16	404,321,939
	1997–2019	G12.2						
Uruguay	1997–2019	G12.2	22	962	533	429	1.24	77,536,023
Central America and the Caribbean								
Costa Rica	1999–2019	G12.2	21	711	430	281	1.53	93,679,955
Cuba	2001–2006	G12.2	6	427	222	205	1.08	67,403,216
Guatemala	2009–2016	G12.2	8	88	56	32	1.75	122,197,136
Mexico	1990–1997	335.2	30	7185	3999	3186	1.25	3,125,274,168
	1998–2019	G12.2						

ICD: international classification of diseases; PYFU: person years follow up.
[a]Sex ratio number: number of ALS male deaths over the number of ALS female deaths.

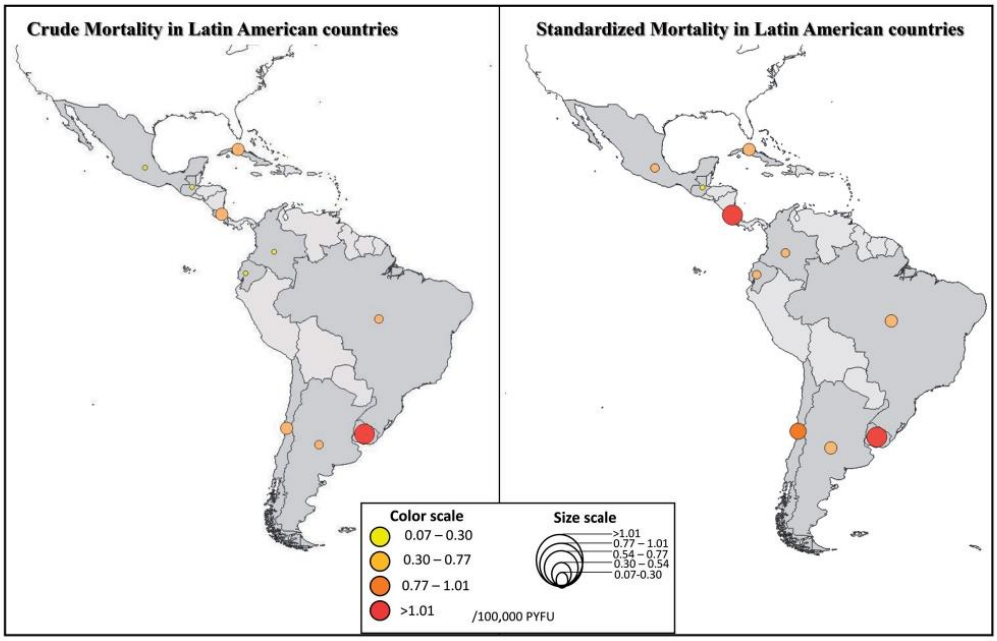

Figure 1. ALS mortality in Latin America: Crude and standardized mortality based on the 2010 US population.

(Cochran's Q $p < 0.001$; I^2 =99.9%). As shown in Figure 4, this finding remained consistent after standardization. Countries with a proportion of Caucasian population less than 25% showed a remarkably low estimate (0.32, 95%CI: 0.24–0.42), while the mortality rate was higher in countries that had 50–75% Caucasian population (0.95, 95%CI: 0.67–1.35).

Upper-middle-income countries displayed higher mortality compared to lower-middle-income countries. The crude mortality was 0.56 (95%CI: 0.37–0.84) for upper middle-income countries and 0.21 (95%CI: 0.12–0.37) for lower-middle-income countries. When comparing standardized estimates, upper-middle-income countries showed a higher rate (0.82, 95%CI: 0.62–1.09) compared to lower-middle-income countries (0.40, 95%CI: 0.28–0.56) per 100,000 PYFU (Figure 5).

Regarding geographic localization, crude and standardized mortality in South America was 0.45 (95%CI: 0.31–0.65) and 0.68 (95%CI: 0.53–0.88), respectively. In Central America and the Caribbean countries, the crude and standardized mortality was 0.30 (95%CI: 0.14–0.65) and 0.53 (95%CI: 0.29–0.95) per 100,000 PYFU (Supplementary eFigure 1).

Discussion

The present meta-analysis reports ALS crude and standardized mortality rates using population-based data from Latin America. Our findings support the evidence of a lower occurrence of ALS in this geographic region compared to Europe and North America. A higher mortality rate was observed among countries describing a higher proportion of Caucasian population and higher income level.

Age pattern and sex ratio of ALS mortality in Latin America

ALS mortality in Latin America exhibits a specific age-related pattern, characterized by low mortality rates in younger ages (before 40 years of age), and a sudden decrease in older ages (70 years of age), similar to reports from Europe, North America and East Asia (26). Recent studies have suggested a younger age at onset in Latin America compared to Europe and New Zealand (6). Age peaks for ALS incidence in European populations ranged between 71.6 and 77.4 years and around 75 years in East Asia (26). In Latin America, the highest peak of ALS standardized mortality was in the 60–69 year age group. This differences could be related to life expectancy, under ascertainment of cases and difficulties in access to healthcare (27).

A male predominance was observed in Latin America, similar to reports in Europe, North America and New Zealand (28). A recent dose–response meta-analysis of population-based studies reported a pooled male to female ratio of 1.28, a crude incidence sex ratio of 1.33 and a sex ratio of

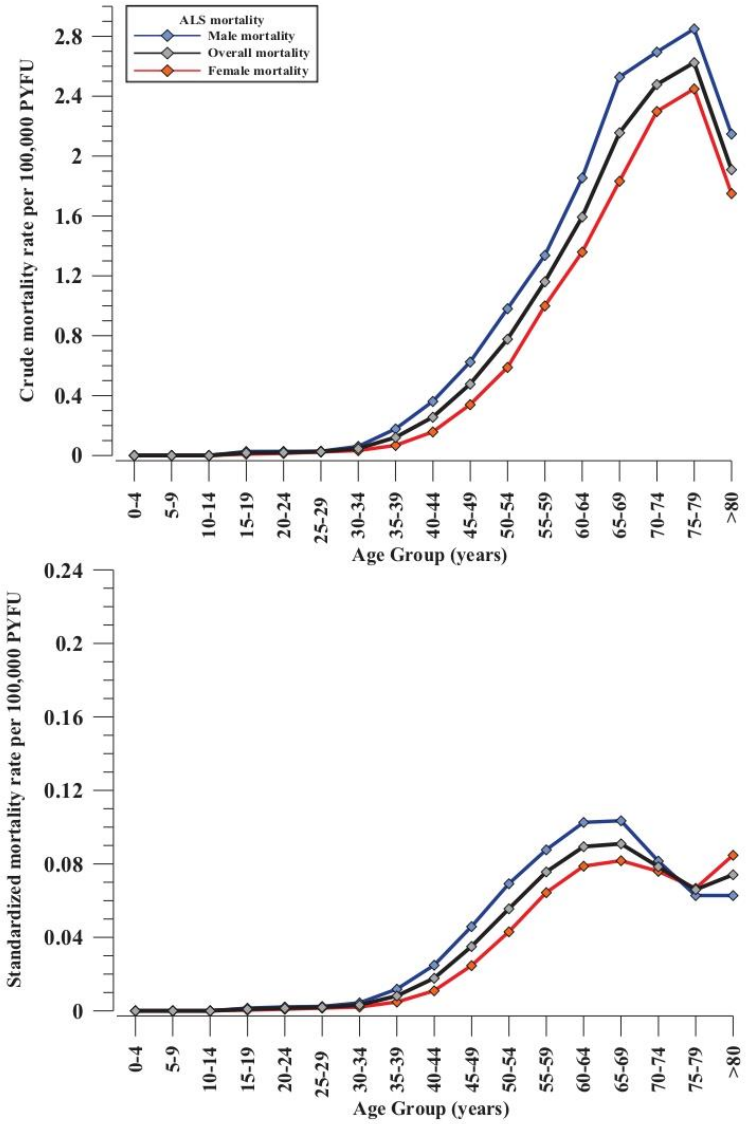

Figure 2. ALS crude and standardized mortality by age group and sex.

standardized incidence of 1.35, which is consistent with our findings (29).

ALS variability in Latin American countries

Recent evidence supports a low ALS occurrence in Latin America. A recent systematic review, found that methodological issues, make it difficult to draw firm conclusions of ALS epidemiology in this region (6). In this meta-analysis, we confirm a low occurrence of ALS in Latin America. This approach provides reliable epidemiological data to gain important insights into ALS heterogeneity among geographical areas.

ALS mortality rates were heterogeneous among Latin American countries. Geographic regions with a similar ancestral origin population (Europe, North America and New Zealand) have shown homogenous incidence rates, while significant differences were found between Europe and Asia (2). A recent study in South Africa described a significant difference in ALS occurrence among populations, with a lower incidence rate among the population of African ancestry compared to those of European ancestry (30). Epidemiological studies performed in the United States showed that incidence rates were lower in Hispanic populations compared to Non-Hispanic White populations (5,7). Differences among ethnic population groups

Table 2. ALS crude and standardized mortality by sex in Latin American countries.

	Crude mortality (95% CI) per 100,000 PYFU				US 2010 standardized mortality (95% CI) per 100,000 PYFU			
Country	Male	Female	Overall	Sex ratio[a]	Male	Female	Overall	Sex ratio[b]
South America								
Argentina	0.59 (0.57–0.61)	0.47 (0.45–0.48)	0.52 (0.51–0.53)	1.25	0.79 (0.76–0.82)	0.58 (0.56–0.61)	0.68 (0.66–0.70)	1.36
Brazil	0.46 (0.45–0.48)	0.38 (0.37–0,40)	0.42 (0.41 – 0.43)	1.21	0.76 (0.74–0.80)	0.64 (0.62–0.64)	0.70 (0.68–0.72)	1.18
Chile	0.75 (0.71–0.79)	0.60 (0.56–0.63)	0.67 (0.65–0.69)	1.25	1.10 (1.04–1.15)	0.87 (0.82–0.91)	0.98 (0.95–1.02)	1.26
Colombia	0.27 (0.25–0.28)	0.21 (0.20–0.22)	0.24 (0.23–0.25)	1.29	0.51 (0.48–0.54)	0.41 (0.39–0.42)	0.46 (0.44–0.48)	1.24
Ecuador	0.19 (0.17–0.21)	0.15 (0.14–0.18)	0.18 (0.17–0.19)	1.27	0.36 (0.32–0.39)	0.33 (0.29–0.37)	0.35 (0.33–0.38)	1.09
Uruguay	1.42 (1.30–1.54)	1.07 (0.97–1.17)	1.24 (1.16–1.32)	1.32	1.56 (1.42–1.69)	1.08 (0.97–1.18)	1.30 (1.22–1.38)	1.44
Central America and the Caribbean								
Costa Rica	0.93 (0.84–1.02)	0.59 (0.52–0.65)	0.76 (0.71–0.82)	1.57	1.40 (1.27–1.54)	0.93 (0.82–1.04)	1.16 (1.08–1.25)	1.50
Cuba	0.65 (0.57–0.74)	0.60 (0.52–0.69)	0.63 (0.57–0.69)	1.08	0.76 (0.66–0.86)	0.78 (0.67–0.89)	0.77 (0.70- 0.85)	0.97
Guatemala	0.09 (0.06–0.11)	0.05 (0.03–0.06)	0.07 (0.06–0.09)	1.80	0.24 (0.17–0.30)	0.13 (0.08–0.18)	0.19 (0.15- 0.23)	1.84
Mexico	0.26 (0.25–0.27)	0.20 (0.19–0.21)	0.23 (0.22–0.25)	1.30	0.49 (0.47–0.50)	0.40 (0.38–0.41)	0.44 (0.43–0.45)	1.22

[a]Sex ratio for crude mortality: male crude mortality by female crude mortality.
[b]Sex ratio for standardized mortality: male standardized mortality by female standardized mortality.
PYFU: person years follow up.

have been showed among Latin American countries (6). A study in Cuba showed that ALS mortality rate was considerably lower in Admixed populations (0.55 (95%CI: 0.40–0.72)) compared to White populations (0.93 (95%CI: 0.83–1.03)) per 100,000 PYFU (4). In Ecuador, a country with a predominant admixed population, showed a low ALS occurrence (adjusted mortality 0.33 (95%CI: 0.30–0.36)) per 100,000 PYFU and a statistical difference was found between comparisons of admixed and other ethnicities (3). A study in Brazil showed that the Caucasian population has a higher risk for ALS death compared to the general population (20). Mortality rates observed in previous studies in Latin America were consistent with those observed in Hispanic populations in the United States (5,7).

We performed a linear regression to explore the correlation between ALS mortality rates and the proportion of Caucasian population. The analysis showed that there was a strong positive linear correlation (Pearson's correlation = 0.83, $p = 0.005$). Crude mortality increases by 0.012 for each 10% increase in the Caucasian population. R^2 value was 0.70 (Supplementary efigure 2).

Researchers have proposed that ALS risk variability could be associated with ancestral origin, as studies have shown a higher ALS occurrence among European populations which could share common "at risk" alleles, increasing ALS susceptibility (4). In contrast, admixed populations could show a lower risk for ALS because of the combinations of this alleles (4). Latin American populations reflect a continuous admixture of Native American, European and African ancestries shaped by the interaction of migrants and Native American indigenous peoples, due to historical events such as colonization and the slave trade (31,32). Ancestral origin is heterogeneous in Latin American and the Caribbean countries. A genome-wide pattern investigation of population structures showed that individuals from Mexico and Ecuador have the highest levels of Native American ancestry (31). Colombia and Brazil have shown widespread genetic patterns, which vary between geographical regions within the country. In Colombia, for instance, the highest levels of African ancestry have been shown to be in the coastal regions, with a higher level of European ancestry in central areas (33). In Brazil, a higher level of European ancestry has been evidence in the south, conversely a higher level of African ancestry has been described in the East (33). A higher proportion of European ancestry has been exhibited in Chile, Argentina and Uruguay (32,34,35). Ethnic identification has been used as a proxy of ancestral origin. However, this is prone to several limitations including the lack of a standardized definition. For instance, ethnicity is self-reported based on cultural and traditional aspects in Ecuador (36), while ethnic classification is performed using skin color in Cuba (37). To address this issue, we used ethnic data collected

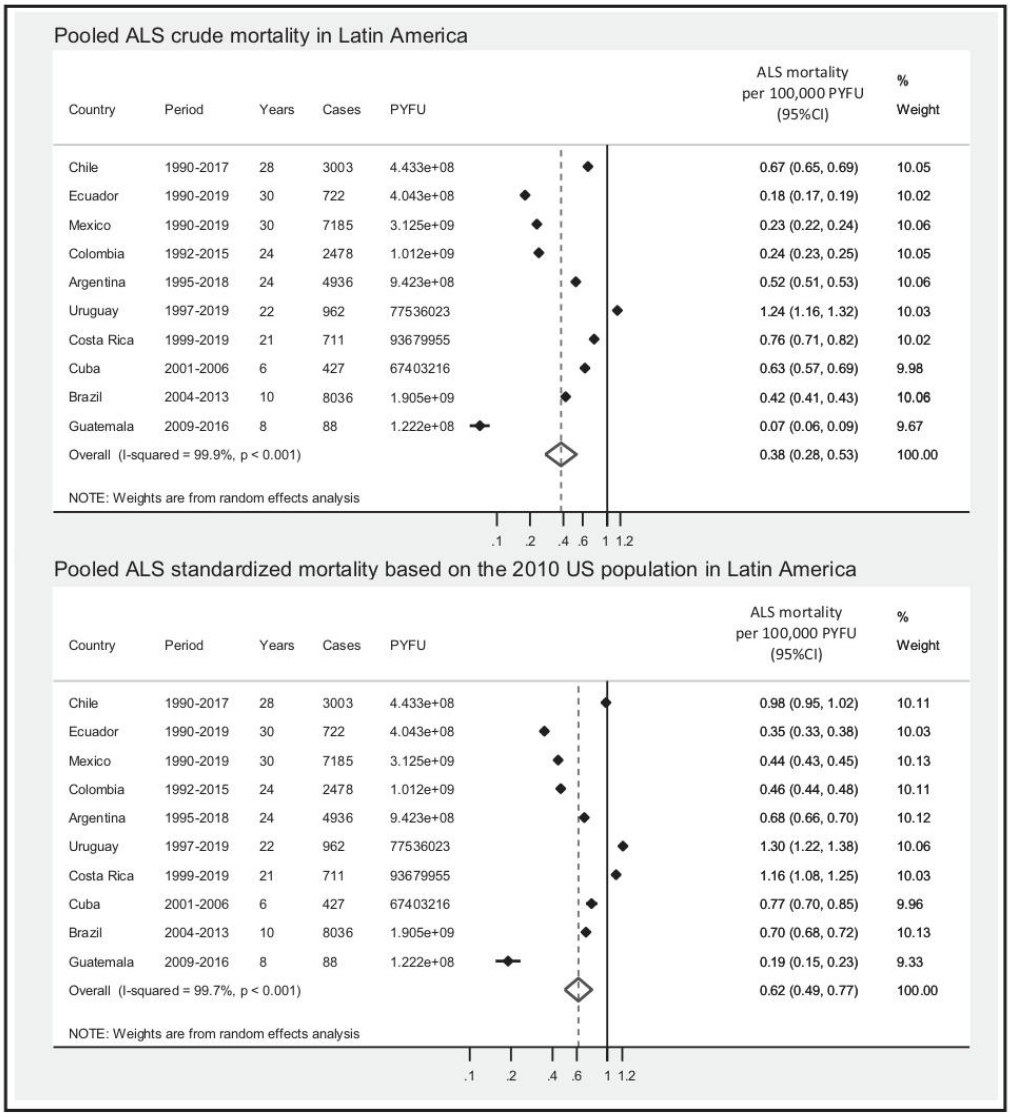

Figure 3. Meta-analysis: forests plots and pooled estimates of ALS mortality in Latin America. Crude and age- and sex-standardized based on the 2010US population.

using a homogenous methodological framework among countries (Latino Barometro). Further studies using objective assessments of ancestral origin are needed in ALS research.

Socioeconomic factors have been considered an important determinant to take into consideration for ALS variations. The Global Burden of Disease Study of motor neuron diseases reported a higher age-standardized prevalence and incidence in countries with a higher socio-demographic index (SDI) compared to low and middle SDIs. Age-standardized prevalence, however, was lower in certain geographic regions with high SDIs (38). A population-based study suggests that ALS incidence could be associated with socioeconomic status (SES) and race. After using adjustment models for age, sex and race they showed that the participants in the highest-income quartile had a higher relative risk for ALS compared to the lowest-income quartile. The relative risk of having ALS was significantly lower among Blacks and Asians than among Whites (39). On the contrary, another study in the United States, after using adjusted models to control socioeconomic

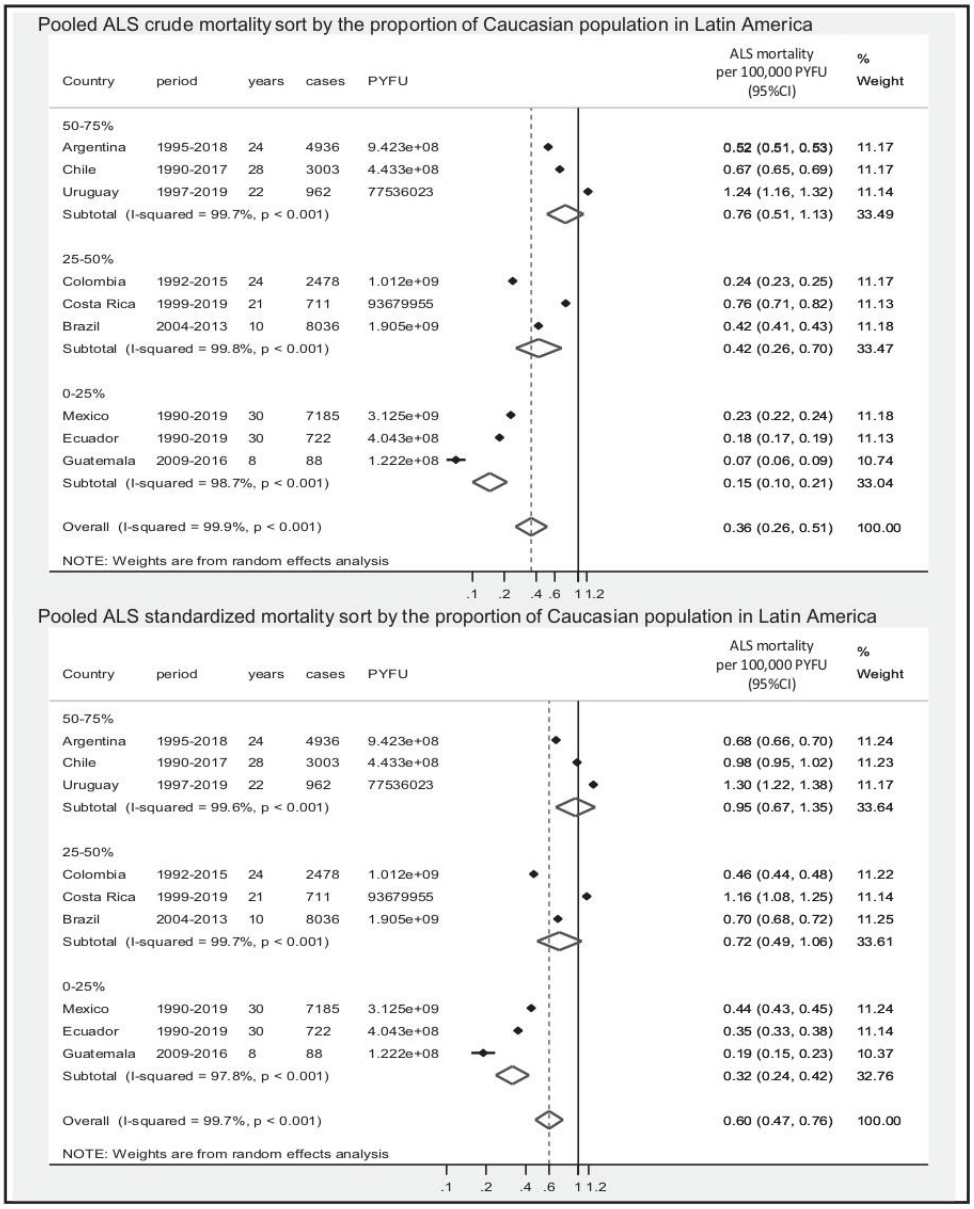

Figure 4. Meta-analysis: forests plots and pooled estimates of ALS mortality in Latin America. Crude and age- and sex-standardized based on the 2010US population by proportion of Caucasian population.

factors, type of health insurance and birthplace, a lower risk for ALS was observed in Non-Hispanics Blacks and Hispanics versus Non-Hispanic White populations (40).

A lower mortality in lower-middle income countries could be explained by difficulties in health care access, social inequalities, inadequate case ascertainment and scarce medical resources (27). According to the World Health Organization, the median number of neurologists per 100,000 population for lower-middle-income countries was 0.13 and 1.09 for upper-middle-incomes (41). The Pan American Health Organization showed that the ratio of neurologists per 100,000 habitants was 0.92 in Central America, 0.48 in the Caribbean and 1.59 in South America (42).

Regardless of these factors, lifestyle and environmental factors cannot be dismissed as possible sources of epidemiological heterogeneity for ALS. Some authors have propose that ALS could be the

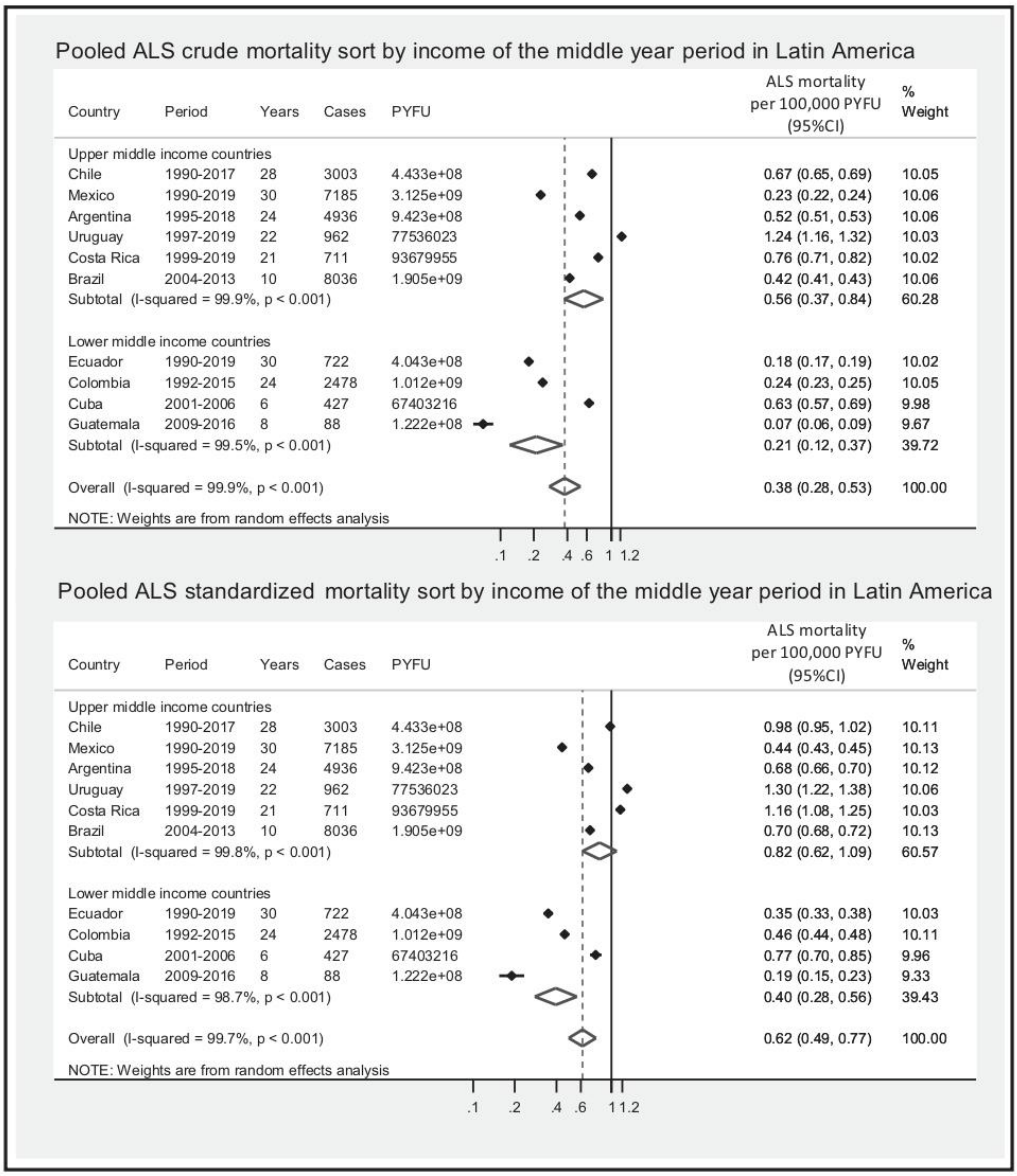

Figure 5. Meta-analysis: forests plots and pooled estimates of ALS mortality in Latin America. Crude and age- and sex-standardized based on the 2010 US population by income of the middle year period.

result of a complex interaction between environmental risks and genetic predisposition (43).

Mortality data

Population-based registries are the gold standard methodology for epidemiological studies in ALS. These registries were mostly developed in European countries. The key point for ALS registries is the capacity to identify a reference population in a well-define geographic area, ensuring case identification among all possible sources, which is possible because of the structured national health systems and specific funding (44). Latin American countries' health systems face different challenges including a double burden of diseases that makes rare diseases have less or inexistent government funding. In countries where no ALS registries exist and incidence studies are challenging, the use of death certificates can be a key tool in estimating ALS occurrence since they allow a population-based approach and provide standard data collection instruments among countries.

The use of death certificates as a source for descriptive epidemiology has raised different

concerns among researchers as mortality studies present limitations that could lead to an underestimation of cases. Various studies have shown, however, that death certificates have good sensitivity for ALS case identification (45). Mortality studies conducted in Hong Kong and England exhibited mortality rates consistent with incidence rates for similar time intervals (46,47). Mortality data can be used as a proxy of ALS incidence; because of the fatal outcome of the disease; we could assume all ALS cases will be identified (10).

Limitations and strengths

Our study had certain intrinsic strengths. First, there was a population-based approach and a homogenous methodology following high standard criteria for reporting mortality studies. Second, we considered the sex and age structure of the population per year in each country to estimate mortality rates. Third, a long period was investigated to include a sufficient number of events. Lastly, we explored ALS heterogeneity considering key covariates through subgroup analysis.

Some limitations need to be acknowledged. Self-reported ethnicity was considered as a proxy of ancestral origin which could lead to bias, as this is not an objective assessment of the ancestral origin of individuals and is normally based on traditional cultural aspects and physical appearance (48). Nevertheless, the results of previous studies of the genomic patterns in Latin America are consistent with the reports of the self-reported Caucasian proportion from the "Latino Barómetro". Another limitation was that some registries only provided the underlying basic cause of death and not the secondary causes, to assure a homogenous methodology we considered only the basic cause of death, which could lead to an underestimation of cases.

Conclusion

This meta-analysis using population-based data confirmed a lower ALS occurrence in Latin America, supporting the hypothesis of a higher risk in developing ALS for populations of Caucasian origin. Furthermore, subgroup analysis showed ALS heterogeneity, with higher mortality among countries with upper-middle income levels. Further studies are needed to investigate the role of ancestral origins in ALS, taking into consideration socioeconomic factors, gene association and environmental interactions.

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Ethical approval

No ethical approval was required, as the information is available in open access and anonymized.

Disclosure statement

The authors report no conflicts of interest. The authors are responsible for the content and writing of this article.

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Chapter IV. : Clinical practices for diagnosis and management of ALS among neurologist in Latin America

IV.1. Challenges and importance of Amyotrophic lateral sclerosis diagnosis

As describe in chapter one, ALS poses a challenging diagnosis based on clinical criteria according to the involvement of upper and lower motor neuron in different regions, and complementary neurophysiologic examination, followed by an exclusion of other diseases with the use of neuroimaging and laboratory exams.

Due to the difficulties of ALS diagnosis, different diagnostic criteria has been implemented to assure appropriate patient inclusion for scientific studies and to allow early entry of patients to clinical trials. Since the introduction in 1994 of El Escorial Diagnostic Criteria (EEDC), different revisions have been performed as explain in chapter one. However, these different criteria have conducted to potential differences of ALS worldwide.

The use of a standardized criteria is fundamental for comparisons among geographical areas. For instance, the implementation of a standard diagnostic criteria among European population-based ALS registries have helped provided homogenous ALS rates in European countries (10). A study of six population-based registries in three European countries reported a crude annual ALS incidence rate of 2.16 per 100,000 person-years, similar rates were reported among the 3 countries (90). Lower incidence rates have been reported in Asian countries and heterogeneity within Asian countries has been observed. In Korea crude ALS incidence rate was 1.20 per 100,000 person-years, in this study the Korean Classification of diseases was used for case identification (193). In contrast, other studies the used the Airlie house criteria, crude incidence rates varied from 0.60 per 100,000 person-years in Honk Kong (194), to 0.88 per 100,000 PYFU in Beijng (195).

Variability of ALS diagnostic delay has been observed among different countries. A meta-analysis found that mean diagnostic delay in European studies was around 12 months and 10 months in New Zealand (9). While in Asian countries mean diagnostic delay has varied from 14.8 months in Beijing (195), 12.0 months in Turkey (196) and 11.7 months in Korea (193).

Diagnostic delay has been associated to different factors including: i) delays related to the site of onset and age of onset, ii) progression rate, iii) delays from referral to specialist, iv) and misdiagnosis of ALS.

Studies evaluating factors for diagnosis delay have observed that patients with spinal onset and older age at onset have presented longer diagnostic delays (197,198). The rate of progression has been another associated factor, patients with a more aggressive progression of disease will seek more rapidly medical assistance, and the well-established signs and symptoms can make more easy ALS diagnosis for clinicians.

Multiple specialist referrals have resulted in barriers to an early diagnosis in ALS (198). Significant differences has been observed in studies that compared diagnostic delay when the patients were first seen by a neurologist compared to other specialist (for ex, otorhinolaryngology, rheumatology, physiotherapy) or non-neurologist (197,199–201). A study by *Household et al.* showed that patients who were referred to a neurologist in a first instance, had a shorter diagnostic delay of 10 months compared to other patients that underwent multiple referrals before being evaluated by a neurologist (mean diagnostic delay of 12 months) (199). Similar Results were found by *Palese et al.* diagnosis delay longer than 12 months was 3.15 (95%CI: 1.36 -7.29) times more likely in patients which first referral was a non-neurologist (197).

Diagnosis can be difficult especially in early stages of the disease with a slow disease progression, as initial symptoms of ALS are often subtle. The probability of misdiagnosis on early stages of the disease are high especially for young clinicians because of the differential diagnosis of other motor neuron diseases including ALS-mimicking syndromes leading to a long diagnostic delay (202).

Misdiagnosis by either the primary care physician or specialist has been reported in 13 to 68.4% of cases among different studies (198). In the study by *Palese et al.* In 30.6% of patients a MND was considered or suspected as differential diagnosis, in 24.6% another diagnosis was posed and in 22.4% no diagnosis was hypothesized and further exams were requested at the first neurologist visit (197). An international study on the diagnostic process among 6 countries (Argentina, Brazil, Germany, Italy, Spain and USA), they evaluated the diagnosis delay among 201 patients. They found that the mean time needed for a neurologist to reach diagnosis of ALS was 7 months. In This

study misdiagnosis was relatively frequent in around 45% of patients, from these 28% of misdiagnoses were made by neurologists (203).

All these factors make ALS diagnosis challenging for neurologist and even more for non-neurologist. The fatal unraveling of ALS can also present a difficulty for neurologist to pose this diagnosis. In a study in Portugal, some of the neurologist seem to be more inclined to pose a more benign diagnosis or treatable conditions(200).

The introduction of electro diagnostic exams into ALS diagnostic criteria (Airlie House and Awaji criteria) have increase the sensitivity of ALS diagnosis. However, there is a need of well-trained and experienced electrophysiologist to performed and interpreted the data (198).

The difficulties of ALS diagnosis could lead to heterogeneity among epidemiological indicators (incidence, prevalence and mortality) as previously described. Differences of clinical characteristics could also be a result of differences in diagnosis. For instance a long diagnostic delay in a certain area could imply a less aggressive form of the disease or a higher proportion of spinal form onset compare to another area with a shorter diagnostic delay. However, these differences could also be a result of a higher misdiagnosis among neurologist or longer referral time.

Early diagnosis has become of major importance and an increasing pressure for physicians, as clinical studies have shown improvement on the disease progression if neuroprotective drugs are used in early stages of ALS (204). Delayed diagnosis often results in high cost for the patients due to different procedures and investigations to reached diagnosis. An earlier diagnosis also helps patients to an effective symptomatic treatment and therapy interventions to improve quality of life. As well, an early diagnosis helps patients to plan their futures in a financial, social, psychological and spiritual aspects (198).

IV.2. Management in amyotrophic lateral sclerosis

The management of amyotrophic lateral sclerosis involves, symptomatic and disease modifying treatment accompanied of a multidisciplinary care.

The use of Riluzole, non-invasive ventilation (NIV) and a multidisciplinary care follow-up have been showed to improve survival, it is unclear if the use of percutaneous

endoscopic gastrostomy improves survival, however according to international guidelines it is effective in stabilizing body weight in ALS patients.

According to European and American guidelines symptomatic treatment involves sialorrhea, muscle spasms, pseudobulbar affect, depression, anxiety insomnia and fatigue. Multidisciplinary care involves a team composed of neurologist, pneumologist, nutritionist, gastroenterologist, rehabilitation medicine physician, speech therapist, occupational therapist, dietitian, specialized nurse, dentist, psychologist, social counsellor and palliative care physician (57,79).

Recommendations on respiratory management include counseling about potential treatments, pulmonary tests on follow-up visits to assess respiratory insufficiency and the use of non-invasive ventilation and invasive ventilation (57,79). The timing and criteria for initiating NIV is not clear, a study showed that an early intervention when the forced vital capacity (FVC) >65% of predicted showed a longer median survival since diagnosis of 2.7 years compare to 1.8 years in subjects with a FVC below 65% p=0.045 (205). Invasive ventilation can also prolong survival for many years, but this represents a high economic, emotional and social burden for patients and caregivers (57).

ALS patients present nutritional insufficiencies due to the grade of dysphagia, nutritional management consist of dietary consistency, modification of food consistency, prescription of high-caloric and high-protein supplements (57,79). Weight loss has been found to be an important independent factor for worse prognosis in ALS (206). Follow up of patients should include body weight revision at each visit. When important weight loss is present enteral nutrition by percutaneous endoscopy gastrostomy (PEG) should be advised to stabilize body weight. For optimal safety, PEG should be performed before vital capacity falls below 50% of predicted (57,79).

There is limited information on palliative care but increasing evidence has showed that palliative care can improve patients quality of life (207). The aim of palliative care is to address emotional, psychological and spiritual support and maximize quality of life, leading to a peaceful death. Both European and American guidelines consider that palliative care should be offer as a multidisciplinary approach accompanied by discussions for end of life (57,79).

The progression of the disease leads ALS patients to severe impairment and loss of autonomy, the increased need for this multidisciplinary care leads to a considerable burden for the patient, caregivers and health systems. ALS patients need a support for assistance of daily living activities and special equipment which leads to significant costs such as direct medical and non-medical costs and loss of household income. According to a 2014 estimate of ALS economic costs in United States cost per year and per patient were estimated at 63,693 dollars, annual prescription medication cost were at 2473 dollars (208). A cross-sectional survey in Germany estimated a mean annual cost of illness per patient at 78,256 euros, they also showed that increase clinical severity stage rise medical costs and decreased quality of life (209).

Management of ALS requires organized health systems with specialized medical resources and specific funding, for instance in France, management of ALS patients was modified in 2003, the French Ministry of health recognized ALS referral centers and resource allocation (210). Which allows that patients to receive adequate management and free of cost, thus improving quality of life.

Studies have found that patients treated in ALS tertiary centers are more likely to use percutaneous endoscopic gastrostomy and non-invasive ventilation having therefore a longer median survival time, in addition they found that patients were admitted less frequently to hospitals conversely to patients followed by general neurological clinics (211). However, referral bias has been reported in ALS tertiary centers as more younger patients attend ALS tertiary centers which could partly explain the longer survival (70,211).

A study that evaluated the application of the European guidelines in six ALS centers, found that ALS centers provided appropriate care of patients from the diagnosis until the end of life according to the guidelines, but there was a need for further improvement for the palliative care and assessment of cognitive and behavioral symptoms (210). A study in United States that evaluated the care of patients three years prior the publication of the American guidelines of 1999, found that there were some deficiencies particularly in gastrostomy use and non-invasive ventilation (212). These studies showed that even though in specialized ALS centers, management of ALS is challenging.

Median ALS survival time has been heterogeneous around the world. Clinical characteristics as a younger age at onset and type of onset (spinal) are known to have

a longer survival. Variability of ALS survival around the world could also be explained by differences of ALS management and health systems (9,213). For instance, longer survival has been observed in Japan compare to Europe and United States, regarding respiratory management, tracheostomy is performed in a higher proportion (30%) in Japanese patients compare to Europe and United States (0-10%), while non-invasive ventilation appears to be higher in United States compared to Japan and Europe (214,215). Mean survival in South Korea has reported to be around 50 months, longer than European countries and United States, which could be partly explained because in South Korea ALS is classified as a rare intractable disease, meaning that patients are financially supported by the government RID registry program and have co-payment reduction benefits (193).

IV.3. ALS diagnosis and management in Latin America

IV.3.1. Diagnosis

Lower ALS occurrence has been reported in Latin America compare to Europe and North America, this lower occurrence could be explained by different factors including under ascertainment of cases. It is known that data from Europe is reported from population-based registries that used a uniform ALS criteria (Airlie House criteria). But what do we known of ALS diagnosis in Latin America?

According to our systematic review of ALS in Latin America, the EEDC and Airlie House criteria were the most common diagnostic criteria used among the studies. In studies evaluating ALS incidence, most of the studies used the EEDC criteria, in studies published before 2005 clinical judgment was use, while in the study of Ecuador the ICD codes were used to identify cases. The EEDC criteria has been showed to have a low sensitivity compare to Airlie House and Awaji. In addition, the clinical probable-laboratory supported category in Airlie House criteria implies a higher identification of ALS patients compared to the EEDC criteria.

The EEDC and the following revisions were created for research purposes for inclusion of patients into clinical trials and not for clinical practice. ALS is a rare disease, even more in areas where ALS research is limited, at this point we don't know if these criteria are of common use among neurologists in Latin America. According to our systematic review most of ALS studies in the region were hospital-based, the most common pathway to identify cases was using ICD codes and a confirmation of diagnosis

regarding the clinical history on the medical file. ICD-codes were also the source for case ascertainment among mortality studies. The non use of ALS diagnostic criteria among neurologists could lead to a lower identification of cases, as suspected or possible ALS cases could go unnoticed.

The differences on ALS diagnosis had also showed differences among survival. For instance a study that compared survival in ALS patients from Uruguay and Limoges (referral center) found that ALS patients from the Limoges centers presented a longer median survival (28 months) compared to those in Uruguay (19 months), this variation could be explained as 82% of ALS cases in Uruguay were classified as definite according to the Escorial criteria classification and 0% of cases were suspected or possible category, this results could suggest under diagnosis of these categories or delayed referral to neurological expertise. On the contrary, patients from the Limoges referral center showed a distribution according to the criteria as expected for other European centers (125).

Electro diagnostic studies have played a key role in identifying early neurodegeneration signs before clinical presentation allowing an early ALS diagnosis and have also helped in differential diagnosis. The structure of Latin American health systems could lead to longer diagnostic delay, as patients on the public system could have long waiting list for this examination. As shown in table 7 from studies performed in Latin America only five studies reported electromyography for ALS diagnosis, also all the studies reporting EMG were either from social security or ALS referral centers which is not representative from the general population and there is unknown information on the practices among general neurologist clinics on the diagnosis of ALS.

IV.3.2. Management

ALS poses a complex management due to the need of a multidisciplinary approach, the constant need of specialized resources (physicians, medical equipment and pharmacological treatment) which represents a major challenge for health systems where medical resources are limited. A multicenter study of nine hospitals among eight African countries, showed that there was a low degree of availability of multidisciplinary care and disease modifying drugs.

As described in chapter one, Latin America health systems faces different inequalities including a low number of specialized physicians, low medical expenditure, low

medical resources (hospitals, neuro-imaging machines) among others. This difficulties could make ALS management even more challenging compare to other regions with better access to health as European and North American countries.

Worldwide variations on ALS survival has been observed which could be partly explained by differences in management. In Latin America, mean survival time has varied among countries from 19 months to 68.6 months

ALS studies in Latin American countries have reported mean survival time ranging from 19 months to 68.6 months (181). This wide range could be explained by differences in management among countries. But what do we know of ALS management in Latin America. In table 7 we have summarize information from different articles from our systematic review that provide information of ALS management. We focused in three main characteristics of ALS management: use of Riluzole, NIV and PEG.

Riluzole has been shown to slow the course of ALS (216,217). Riluzole is a highly costly medication, in countries where no free medical care is available and ALS treatment is not covered by insurance or the government only wealthier patients could have access to it. Riluzole was reported in studies from Argentina, Brazil, Costa Rica and Uruguay, however, the proportion of patients taking the medication were less than 60% (table 7). This could be related to the health regulations and accessibility in each country for instance, in Brazil according to the ministry of health protocol only patients with definite or probable diagnosis are allowed to have free access to Riluzole (218). In Costa Rica, Riluzole is given to all patients according to the specialist criteria (219). While, in Uruguay Riluzole is not available and is not free of charge (125).

The use of non-invasive ventilation was reported on studies from Mexico, Argentina and Brazil (table 7). We can observe that the proportion of patients using NIV varied among the studies, for instance in the study in Argentina only 30% of patients use NIV, in this study median survival time since diagnosis was of 15.41 months among the group the use NIV and 10.88 months among the group that not used NIV. A higher proportion of patients that use NIV was observed in Brazil, median survival since diagnosis in this study was 19 months (220,221). Studies from Mexico have reported longer survival times (64.7 and 68.6 months), in the study by *Sanchez et al.* we can observed in table 7 that a large proportion of patients were under invasive ventilation which could explain the long survival (mean survival since diagnosis of 42.51 months)

(222). In the study by *Martinez et al.* the proportion of patients under NIV was not reported, a long survival (median survival since diagnosis 47 months) was showed in this study , however this study was performed in a private specialized center, were most of the Mexican patients came from the highest socio-economic status and there was no representation from rural areas(223). Because of the huge disparities in access to health in Mexico, patients with a higher socio-economic status and from urban areas can have more rapidly access to NIV, PEG and Riluzole. Percutaneous endoscopic gastrostomy was reported among three studies (Mexico and Costa Rica).

Another important aspect of ALS management is multidisciplinary care. Interdisciplinary treatment has been reported in studies from Argentina (220), Brazil (221) and Costa Rica (219). In the study in Argentina all patients were studied by a neurologist and a pneumologist (220). In Brazil, patients were followed by a neurologist, occupational therapist, motor and respiratory physical therapist, psychologist, nutritionist and social assistant (221). In Costa Rica, evaluation by rehabilitation physician and respiratory therapist was reported (219).

Studies evaluating ALS management among health systems in Europe and Africa have helped to identify important gaps. There is limited information of ALS management in Latin America, according to the information found we can observed that there are some differences among countries which could be a result of the organization of health systems. But this can also be a result in difference of management among neurologist. ALS guidelines have helped established uniform management among physicians, for instance a study in France show the implementation of European ALS guidelines in six ALS referral centers (210). A uniform management can helped improve quality of life of all patients and help authorities to decide in the approval of drugs to reduce health disparities.

Table 7. Diagnostic and management characteristics of ALS studies in Latin America

Country	Author	Study period	Type of center	Diagnostic criteria	EMG	Riluzole	NIV	PEG
Mexico, Mexico city	Sanchez et al., 2019 (222)	2000-2015	Social security (public)	AH	Yes	No	Mechanical ventilation (71.11%)	Yes
Mexico, Monterrey	Martinez et al., 2011 (223)	2005-2010	Specialized centre (private)	AH	NM	NM	Yes	Yes
Argentina, Buenos Aires	Sivori et al., 2007 (220)	1999-2004	ALS referral center (public)	AH	NM	Yes (45% of patients)	NIV (30% of patients)	NM
Brazil, Federal district	Moura et al., 2015 (218)	2005-2014	ALS referral center (public)	Awaji	Yes	Yes	NM	NM
Costa Rica, San José	Abadia-Cubillo et al 2015 (219)	2009-2014	National center of pain and palliative care (social security)	NM	Yes	Yes (60% of patients)	NM	Yes
Brazil, Sao Paulo	Favero et al., 2017 (221)	1999-2011	Clinical investigation on neuromuscular disease (public)	EEDC	Yes	Yes (59% of patients)	Yes (86%)	NM
Uruguay, Montevideo	Gil et al., 2009 (125)	2002-2004	Multiple sources (neurologist, other specialist, hospital medical records and death certificates)	EEDC	NM	Yes (11% of patients)	NM	NM

EMG: electromyography; NIV: non-invasive ventilation; PEG: percutaneous endoscopic gastrostomy.

AH: Airlie house criteria; EEDC: El Escorial Diagnostic criteria; NM: not mentioned

IV.4. Article 3: Clinical practices on the diagnosis and management of ALS among the neurologist in Latin America

A lower occurrence of ALS in Latin America could be explained by ancestral origin, socio-economic status, genetic and environmental factors, nevertheless under ascertainment of cases due to under diagnosis or misdiagnosis of ALS should be taken in consideration.

Variations on worldwide clinical characteristics more particularly survival could be partly explained by differences in ALS management. ALS is a complex disease that affects patients and care givers in a physical, psychological and socio-economical way. Improving quality of life should be a priority.

ALS poses a difficult diagnosis. Challenges in the diagnosis of ALS in Latin America have been reported, *Bucheli et al.* evaluated the clinical and electromyogram examinations in a cohort of 20 ALS patients in Ecuador. Misdiagnosis was found in three patients and they found that many EMG diagnoses presented different errors, and that the utility of EMG in the support of ALS diagnosis is low, leading to longer diagnostic delays.

Information of ALS in Latin America is limited, most of the research is made from hospital data and from certain ALS referral centers, information from other general neurologist clinics remains unknown. In addition ALS represents a high economic burden for patients, caregivers and health systems. Latin America health systems presents different challenges more importantly in access to health.

In developed countries, management of ALS has been in accordance of international guidelines and have shown to improved survival. For instance, in the study by *Gil et al.*, longer survival was observed for patients from the Limousine France referral center compared to patients followed in different clinics in Uruguay. The authors discussed that in Uruguay, nutritional and respiratory evaluations are not systematic and the proportion of patients with gastrostomy or non-invasive ventilation are significant different in the referral center in Montevideo compared to other towns in the country, as well, Riluzole is not free of charge (125).

A description of the clinical practices on the diagnosis and management of ALS among the neurologist in Latin America could provide information of the differences on ALS management as well to identify areas for further improvement. In addition, an

evaluation to assess the compliance of ALS guidelines could help promote the use of guidelines among neurologist. In this context we have performed a survey to describe the clinical practices on the diagnosis and management of ALS among neurologist in Latin America and to identify associated factors to a higher compliance to ALS international guidelines.

IV.4.1. Methodology

IV.4.1.1. Study design

We performed an observational cross-sectional study among neurologist of Latin America countries. First a pilot study was carry out in Ecuador from January to March 2020, and secondly an online survey was performed among Latin American countries from September 2020 to January 2021. Neurologist were identified by different sources: neurology associations, online yearbooks and key neurologist in each country.

Pilot study

In the pilot study, three main sources were used to identify neurologist; first we made a collaboration with neurologist in the biggest cities in Ecuador (Quito, Guayaquil and Cuenca) who provide us the contact information from different colleagues. Second, we performed an online search from the yearbook of the Ecuadorian Neurological Society (SEN) associates, as well, among online medical directories. The workplace and email address were collected from each neurologist. Third, we participated in the SEN annual congress in Guayaquil on October 2019, where we contacted different neurologists that had attended.

An online invitation was send to all the neurologists in Ecuador, in addition a visit was performed to the neurologist whose workplace address was available (In Quito and Cuenca).

A brief description of the study and an inform consent was provided to all participating neurologist.

Latin America online survey

For the online survey two main sources were used, we performed a collaboration with the Pan American Federation of Neurological Societies (PAFNS) to contact the different neurological societies in the region and we also contacted different key partners in Latin America that had worked with the Institute of Epidemiology and Tropical Neurology (IENT network).

The PAFNS is the World Federation of Neurology (WFN) regional organization for Latin America with a representation over nineteen associations of Neurology from Latin America. With our collaboration with the PAFNS, an online invitation was send by the PAFNS to all the neurological societies (associated to the PAFNS). , Two modalities were employed if a positive response was obtained from the neurological society: i) the online survey was send directly by the neurological society to their members, or ii) the neurological society provided the list of their associates and the online survey was send by our team.

The IENT network, is composed of different researchers and neurologist that have worked on neurological diseases in Latin America and have performed important collaborations with our research team. We provided to the IENT network an online invitation. This invitation was then share by each member of the IENT network to different colleagues who then also share the invitation to other colleagues, creating at the end a snowball effect.

Each online invitation included: a cover letter describing the study, a Kobo collect link to access the online survey, and an inform consent.

IV.4.1.2. Data collection

Data collection was carry out through a standard questionnaire using the Kobotoolbox software. To secure and save the data, we used a private and safe server of the University of Limoges.

A questionnaire was performed, based on the European Federation of Neurological Sciences (EFNS) task force and the American Academy of Neurology (AAN) guidelines of diagnosis and management of ALS.

The questionnaire was composed of 34 questions organized in 6 sections collecting the following information:

i) Socio-demographic data: Sex and age

ii) General information: Time of neurological practice, type of workplace, sub-specialty in neurology, diagnosis of ALS cases.

iii) Diagnosis: criteria for diagnosis, complementary exams, differential diagnosis.

iv) Care: medicine prescription, multidisciplinary care, nutritional and respiratory management.

v) Follow up: patient follow up visits, muscular testing, ALSFRS-R.

vi) End of life: palliative care and place of death

The complete questionnaire is available in appendix 3.

The questionnaire was available in two different languages (Spanish and English). The initial questionnaire was pilot tested in a sample of 20 researchers and neurologist from different countries (Latin America: Honduras and Ecuador; Europe: France and Italy), to assess clarity and comprehension, the time needed to complete the questionnaire was evaluated. All participants provided written or oral feedback.

IV.4.1.3. Evaluation of the compliance of ALS guidelines

To assess the compliance of ALS guidelines among the neurologists in Latin America, we performed a score of a total of 40 points divided in diagnosis practices and management practices. The score was designed by the chief of the neurology department and the ALS expert center in Limoges, France and the principal investigator of this study. The score was composed of 20 points for the practices in diagnosis and 20 points for the management practices.

Diagnosis was evaluated among the following aspects:

- Use of any diagnosis criteria (3 points)
- Use of clinical examination diagnosis (5 points)
- Use of electromyography to support diagnosis (7 points)
- Use of neuro-imaging to support diagnosis (3 points)
- Use of Laboratory exams to support diagnosis (2 points)

Management was evaluated among the following aspects:

- Communication of diagnosis face to face with the patient (2 points)
- Use of Riluzole (1 point)
- Provides symptomatic treatment (1 point)
- Provides a multidisciplinary care (3 points)
- Use of clinical guidelines (2 points)
- Follow up of patients every 3 months (2 points)
- Use of ALSFRS-R (2 points)
- Use of spirometry or nocturnal oximetry for evaluation of respiratory insufficiency signs (3 points)
- Follow up of weight loss (3 points)
- Use of palliative care at end of life (1 point)

We classified the compliance of ALS guidelines into two categories: low-middle compliance and high compliance. In order to obtain the two categories, we divided the distribution in tertiles (low, medium and high), the higher tertile was considered as participants with a high compliance of ALS guidelines and low and medium tertiles were considered as low-middle compliance.

IV.4.1.4. Ethics

A protocol for the pilot study was accepted by the Ethics committee of the Central University of Ecuador on December, 2019. A written inform consent was provided to each participant. Anonymization of participants was performed.

IV.4.1.5. Statistical Analysis

All findings were reported using the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (224).

Descriptive statistics were reported on frequencies and percentages for qualitative variables, medians with their IQRs were used to describe quantitative variables. The Shapiro-Wilk test was used to explore the normal distributions of continuous variables.

Percentages were compared using Pearsons X^2 and fisher exact test when effectives were less than five. Means were compared with the Mann-Whitney test.

A multivariate regression model was conducted to identify the factors associated to a higher compliance with ALS guidelines. Variables with a missing data higher than 20% were not included. Sociodemographic, professional information and ALS experience information were used associated factors. Information about subspecialty in neurology were coded into dummy variables for the regression analysis.

In the univariate analysis, variables with a p value <0.25 were selected in the full multivariate model. Multivariate logistic regression with backward elimination was followed. Odds ratio (OR) and 95% confidence intervals (95%CI) were calculated. A p value <0.05 was considered statistically significant.

Descriptive and analytical analysis were conducted using IBM SPSS statistics version 22 software. All missing data was reported.

IV.4.2. Results

Overall, 160 participants from 15 Latin American and the Caribbean countries responded to our survey. As describe in the flowchart in Figure 7, we included 151 neurologist from 12 Latin American countries after exclusions. The countries with the highest participation rate were Ecuador (n= 45) Colombia (n=33) and Argentina (n=24) as shown in figure 8. Countries that had only one participant were excluded for the analysis. Neuro-pediatrics and neuro-physiatrist were also excluded (n=4).

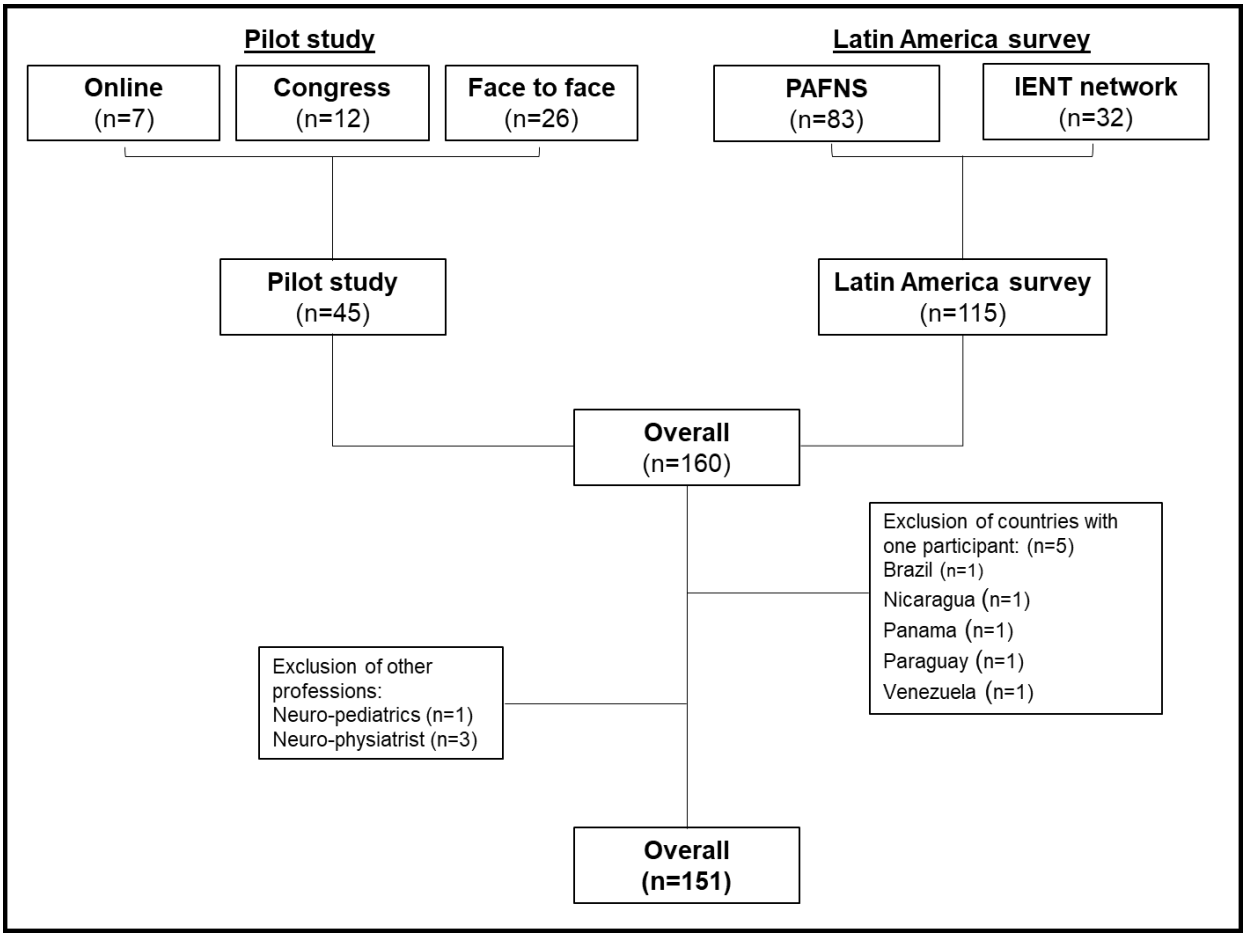

Figure 7. Flowchart, number of participants

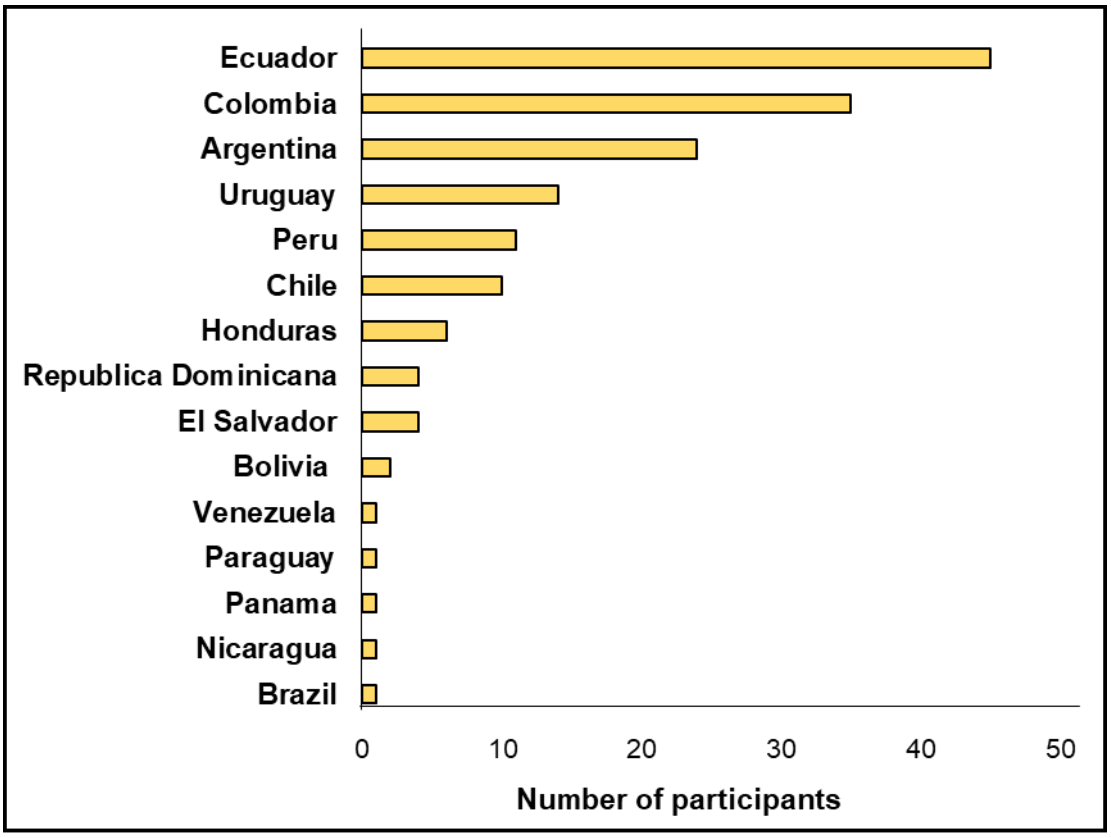

Figure 8. Number of participants by Latin American country.

Compliance of ALS guidelines score

The median of the total score was 28.0 (IQR: 24.0 – 31.0) points. The median for the diagnostic part score was 15.0 (IQR: 10.0 – 15.0), and for the treatment part median score was of 14.0 (IQR: 12.0 – 16.0).

According to the classification, 92 neurologists had a low-middle compliance to ALS guidelines and 59 neurologist were categorized as having a high compliance to ALS guidelines.

IV.4.2.1. Characteristics of neurologists in Latin America

The participant neurologist had a median age of 43 years and 53% were male. Most of the physicians worked on the private sector (48.0%), or in both sectors (public and private) (46.7%). More than 50% of neurologists had a subspecialty, having neuro-muscular subspecialty was the most frequent (45.0%) of the participants that had a subspecialty. The majority had received a training or workshop on ALS (72.1%). Almost of them (94.7%) have diagnosed at least one ALS case in the last 5 years. The median number of ALS cases diagnosed in the last 5 years was of 5.0.

General practitioners (30.4%) was the most frequent source who normally refers ALS patients, followed by other neurologists (29.7%).

Table 8 summarizes the socio-demographic and professional characteristic of the respondents. Missing data is reported on table 8.

Regarding differences between the low-middle and high compliance group. Statistical differences were observed among different variables. According to the institution of work, the proportion for the high compliance group was low for the public sector and high in the private sector compare to the low-middle compliance group (p=0.039). The proportion of neurologists with a neuro-muscular subspecialty was higher among the high compliance group (62.2%) compared to the low-middle compliance (30.2%) (p=0.022). The median number of diagnosed ALS cases in the last five years was higher in the high compliance group compared to the low-middle compliance group (p<0.001).

Table 8. Socio-demographic, professional and ALS experience data of Latin America neurologist.

	Overall (n=151)	Low-middle compliance (n=92)	High compliance (n=59)	p value
(a) Socio-demographic characteristics				
Sex n (%)[¶]				
Female	47 (47.0)	23 (45.1)	24 (49.0)	0.697[†]
Male	53 (53.0)	28 (54.9)	25 (51.0)	
Age (years)[¶] Median (IQR)	43.0 (38.0 - 53.0)	46.0 (38.0 - 58.0)	40.0 (37.5 - 49.0)	0.177[≠]
(b) Professional characteristics				
How long have you been practicing neurology? n(%)[¶]				
< 5 years	29 (19.5)	19 (21.1)	10 (16.9)	
5-10 years	28 (18.8)	14 (15.6)	14 (23.7)	0.430[†]
> 10 years	92 (61.7)	57 (63.3)	35 (59.3)	
Type of institution where you work? n(%)[¶]				
Public	8 (5.3)	8 (8.8)	0 (0.0)	0.039[‡]
Private	72 (48.0)	40 (44.0)	32 (54.2)	
Both	70 (46.7)	43 (47.3)	27 (45.8)	
Do you have a sub-specialty in neurology? n(%)[¶]				
No	69 (46.3)	47 (52.2)	22 (37.3)	0.074[†]
Yes	80 (53.7)	43 (47.8)	37 (62.7)	
If yes, what is your specialty? n=79(%)				
Neuro-muscular	36 (45.0)	13 (30.2)	23 (62.2)	0.022[‡]
Other	16 (20.0)	11 (25.6)	5 (13.5)	
Epileptology	9 (11.3)	7 (16.3)	2 (5.4)	
Abnormal movements and extra pyramidal	9 (11.3)	5 (11.6)	4 (10.8)	
Cognitive	5 (6.3)	5 (11.6)	0 (0.0)	
Sleep medicine	2 (2.5)	1 (2.3)	1 (2.7)	
Neuro-vascular	3 (3.8)	1 (2.3)	5 (5.4)	
(c) ALS experience information				
Have you received a training or workshop on ALS? n(%)[¶]				
No	36 (27.9)	25 (34.2)	11 (19.6)	0.067[†]
Yes	93 (72.1)	48 (65.8)	45 (80.4)	
Have you diagnosed ALS in the last 5 years? n(%)[¶]				
No	5 (3.4)	5 (5.6)	0 (0.0)	0.15[‡]
Yes	143 (94.7)	84 (94.4)	59 (100.0)	
If yes, how many cases have you diagnosed? Median (IQR)	5.0 (3.0 - 15.0)	5.0 (3.0 - 10.0)	10.0 (5.0 - 22.5)	<0.001[≠]

[†] Chi^2

[‡] Fisher exact test

[≠] Mann-Whitney test

[¶] Missing data: sex and age (n=51); time of practice (n=2); institution of work (n=1); sub-specialty (n=2); training in ALS (n=22); diagnosis of ALS in the last five years (n=3); number of diagnosed ALS cases (n=7).

IV.4.2.2. Clinical practices on the diagnosis of ALS

Diagnostic criteria

Overall, Airlie house was the most frequent criteria (46.2%) followed by El Escorial (27.6%) and Awaji (21.4%).

A significant difference was observed among neurologists with a low-middle and high compliance groups (p=0.011). Airlie house was the most frequent among both groups. Awaji criteria was used by 30.5% of the neurologist in the high compliance group compare to 15.1% in the low-middle compliance. Other criteria was only used by the low-middle compliance group (8.1%). (Figure 9a).

Differential of diagnosis

Regarding the test that physicians requested to rule out other causes, clinical examination (85.8%), electromyography (98.6%) and neuro-imaging (81.1%) were frequently used among the neurologists for differential of diagnosis.

According to the differences among the compliance to guidelines groups, 96.6% of the neurologists in the high compliance group used clinical examination compare to 78.7% in the low-middle compliance (p=0.002). Electromyography was equally used in both groups. Biomarkers were the least requested among both groups (figure 9b).

In overall, motor multifocal neuropathy (87.0%) was the disease most considered by the neurologists, followed by radiculopathy (61.6) and autoimmune syndromes (58.9) as the differential diagnosis in ALS suspected cases. No significant differences were observed among the two groups (figure 9d).

Diagnosis confirmation

For confirmation of diagnosis we asked to the participants which exams were considered the most important for confirmation of diagnosis. In overall, electromyography was the most frequent test used (90.5%), followed by clinical examination (78.4%). Neuro-imaging (23.0%), laboratory exams (6.1%) and biomarkers (1.4%) were the least frequent.

Concerning the compliance groups, statistically significant differences were observed among the use of clinical examination (p<0.001), electromyography (p<0.001), neuroimaging (p<0.001), and laboratory exams (p=0.03). As a higher percentage of neurologist in the high compliance group used these exams 98.3%, 100%, 44.1% and

11.9% respectively, compared to 65.2%, 84.3%, 9.0% and 2.2% in the low-middle compliance respectively (figure 9c).

Communication of diagnosis

The support of family was considered important for communication of diagnosis, as 87.2% of the participating neurologists preferred communicate diagnosis face to face with the patient and a member of the family. No statistical difference was found among the compliance groups (figure 9e).

The information normally provided at diagnosis was: name of the disease (90.0%) the absence of a drug to cure the disease (86.7%) complications (78.7%) and prognosis (72.7%) of ALS. The possible genetic role was the information least provided (33.3%) (figure 9f).

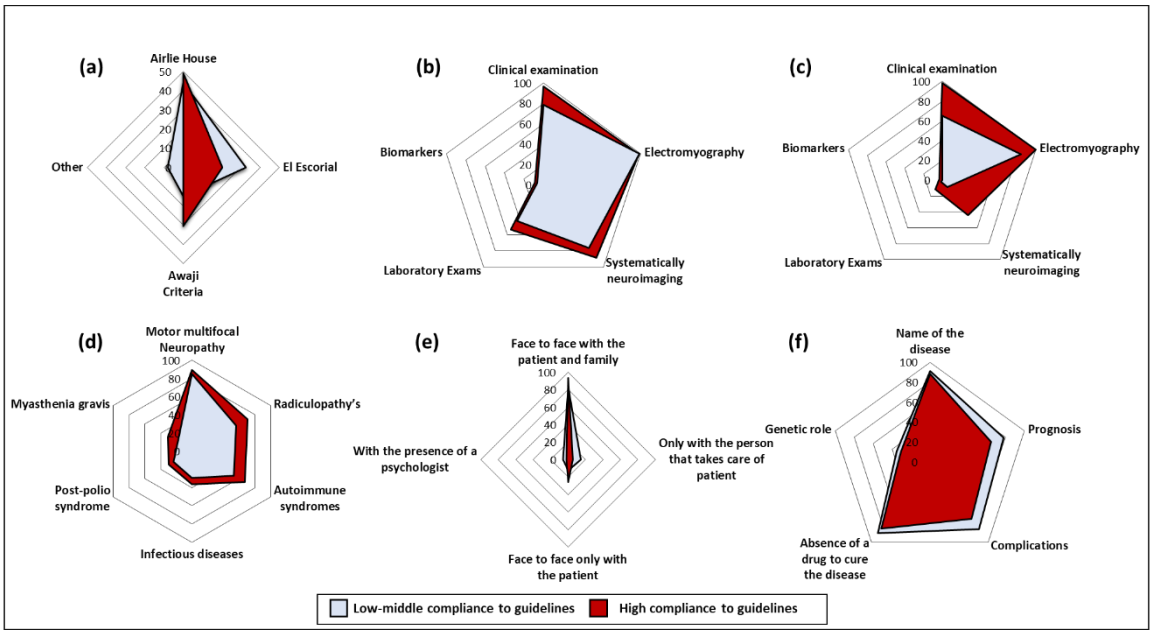

Figure 9. Radar charts, clinical practices of ALS diagnosis according to the compliance to guidelines groups.
(a) Diagnostic criteria (b) exams for differential of diagnosis (c) test for confirmation of diagnosis (d) diseases consider as differential diagnosis (e) diagnosis communication (f) information provided at diagnosis.

IV.4.2.3. Management of ALS

Disease modifying therapies

Overall, 77.6% of neurologist use Riluzole. In the high compliance group 86.2% of neurologist prescribed Riluzole and 71.9% in the low-middle compliance group, this difference was statistically significant (p=0.042).

Multidisciplinary care in the management of ALS

The multidisciplinary care was mostly composed by: rehabilitation therapist (72.5%), psychologist (69.7%), pneumologist (67.6%), nutritionist (64.8%) speech therapists (53.5%), gastroenterologist (45.8%) and palliative care (28.9%). Social counselor, specialized nurse and dentist were the least common disciplines chosen for ALS multidisciplinary team management.

As shown in figure 10, a higher proportion of neurologists of the high compliance group was observed among all disciplines compare to the neurologists in the low-middle compliance. Statistical significant differences were observed among the following disciplines: psychologist (p=0.015), pneumologist (p=0.004), nutritionist (p<0.001), speech therapist (p=0.006) and gastroenterologist (p=0.027).

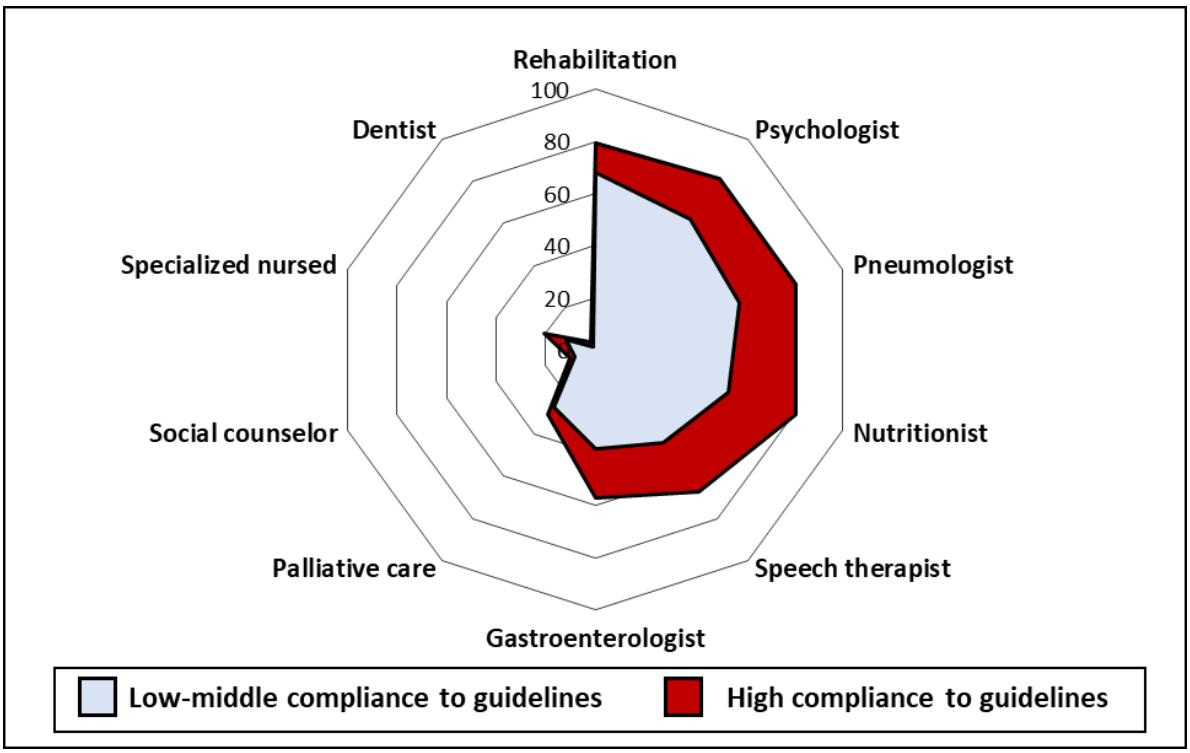

Figure 10. Radar chart (proportion of neurologist) of multidisciplinary team in the management of ALS in Latin American, according to compliance of guidelines groups.

Nutritional and respiratory management

Concerning how the neurologists handles nutritional aspects in ALS patients, Nutritionist referral (90.5%) was the preferred option by the neurologists. Indication of gastrostomy when severe swallowing problems are presented was a common practice as, 83.2% of neurologists indicated a gastrostomy.

Management of respiratory failure was as follows: 55.1% of neurologist preferred the referral to a pneumologist followed by the use of non-invasive ventilation (36.1%). No statistical differences were found between compliance groups. (Table 9)

Palliative care and end of life

Only 42.1% of neurologist worked with a palliative care team, and 51.7% affirm that patients had defined their final wishes.

A higher proportion of neurologist in the high compliance group affirm that patients had defined their final wishes 63.8%, while in the low-middle compliance only 43.7% affirm this (p=0.018)

Table 9. Nutritional, respiratory and palliative care in the management of ALS. (a) Nutritional aspects (b) respiratory aspects (c) palliative care and end of life

Management of ALS	Overall (n=151)	Low-middle compliance (n=92)	High compliance (n=59)	p value
(a) Nutritional aspects				
How do you handle the nutritional aspects of ALS patients?				
Refers to a nutritionist, n (%)¶				
No	14 (9.5)	10 (11.4)	4 (6.8)	0.353†
Yes	133 (90.5)	78 (88.6)	55 (93.2)	
Nasogastric tube, n (%)¶				
No	81 (55.1)	46 (52.3)	35 (59.3)	0.400†
Yes	66 (44.9)	42 (47.7)	24 (40.7)	
Supplementary nutritional support, n (%)¶				
No	101 (68.7)	61 (69.3)	40 (67.8)	0.845†
Yes	46 (31.3)	27 (30.7)	19 (32.2)	
Do you indicate a gastrostomy if the patient has severe swallowing problems? n (%)¶				
No	25 (16.8)	19 (21.1)	6 (10.2)	0.080†
Yes	124 (83.2)	71 (78.9)	53 (89.8)	
(b) Respiratory aspects				
How do you handle a patient who starts with signs or symptoms of respiratory failure? n (%)¶				
Refers patient to pneumologist	81 (55.1)	52 (58.4)	29 (50.0)	0.807‡
Noninvasive ventilation	53 (36.1)	29 (32.6)	24 (41.4)	
Oxygen only	9 (6.1)	6 (6.7)	3 (5.2)	
Tracheostomy	4 (2.7)	2 (2.2)	2 (3.4)	
(c) Palliative care and end of life				
Do patients have a follow-up by a palliative team? n (%)¶				
No	84 (57.9)	53 (60.9)	31 (53.4)	0.372†
Yes	61 (42.1)	34 (39.1)	27 (46.6)	
Have patients previously defined their end-of-life wishes? (Consents to non-resuscitation, no tracheostomy) n (%)¶				
No	70 (48.3)	49 (56.3)	21 (36.2)	0.018†
Yes	75 (51.7)	38 (43.7)	37 (63.8)	

† Chi^2

‡Fisher exact test

¶Missing data: refers to a nutritionist (n=4); nasogastric tube (n=4); supplementary nutritional support (n=4); gastrostomy (n=2); respiratory aspects (n=4); follow-up palliative care (n=6); end of life wishes (n=6).

IV.4.2.4. Factors associated with guidelines compliance

We performed a multivariate logistic regression model to identify factors associated to a high compliance of guidelines. Neurology professional information and ALS experience characteristics were considered in the univariate model. Having a sub-specialty in neurology, having received a training or workshop of ALS, and the number of ALS cases diagnosed in the last five years were included in the full multivariate model.

The final model was obtained after backward elimination. The analysis showed that having a subspecialty in neurology was independently associated to a high compliance of ALS guidelines (p=0.015). Neuro-muscular subspecialty was 3.34 (95%CI: 1.37-8.12) times more likely to have a high compliance to guidelines compared to not having a subspecialty at all.

Table 10 presents the multivariate model including univariate analysis, the full multivariate model and the final multivariate model.

Table 10. Professional and ALS experience characteristics associated to a higher compliance of ALS guidelines. Univariate and multivariate analyses.

	Univariate model (n=151)		**Full multivariate model (n=125)**		**Final multivariate model (n=125)**	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Time of exercise						
< 5 years	1.00					
5-10 years	1.90 (0.65 - 5.51)	0.437				
> 10 years	1.16 (0.48 - 2.79)					
Subspecialty in neurology						
No	1.00		1.00		1.00	
Neuro-muscular	3.78 (1.61 - 8.82)	0.004	4.01 (1.33 - 12.11)	0.033	3.34 (1.37- 8.12)	0.015
Other sub specialty	0.99 (0.44 - 2.24)		1.02 (0.42 - 2.48)		1.02 (0.42 - 2.47)	
Training or workshop in ALS						
No	1.00	0.070	1.00	0.672		
Yes	2.13 (0.94 - 4.82)		1.21 (0.49 - 3.00)			
How many cases have you diagnosed?	1.00 (0.99 - 1.02)	0.226	0.99 (0.97 - 1.01)	0.367		

OR: Odds ratio; CI: Confidence interval

¶Missing data: time of exercise (n=2); subspecialty (n=2); training (n=22); ALS cases (n=7).

IV.4.3. Discussion

This study is the first description of clinical practices, and the use of guidelines on diagnosis and management of ALS among neurologists in Latin American countries. According to the use of guidelines a median score of 28 points of 40 was reported among the participating neurologist. We identified practices in accordance to guidelines and areas for further improvement. As well the associated factors for a higher compliance of guidelines were identified.

Regarding diagnosis of ALS, the most common diagnostic criteria was Airlie House and the El Escorial Diagnostic criteria (EEDC), which is consisted to our findings in a systematic review of ALS literature in Latin America (181), as well is the criteria used among population-based registries in Europe (10). The use of clinical evaluation and electromyography were listed as the most important exams for ALS diagnostic confirmation. Communication of diagnosis to the patient and a family member was prioritize.

Regarding management, Riluzole was a common practice among neurologists. On working with a multidisciplinary team we found that working with a rehabilitation therapist was a frequent practice followed by working with a pneumologist and nutritionist. According to the compliance groups, the high compliance group worked in a higher proportion with different disciplines. The use of gastrostomy when severe swallowing difficulties appear were a frequent practice. However, we found need for further improvement in specific areas such as, the integration of multiple disciplines in the care of ALS patients, and the implementation of palliative care and a discussion of wishes at the end of life.

Multivariate analysis showed that a higher compliance to ALS guidelines was associated to having a neuro-muscular sub-specialty compare to neurologists without a sub-specialty, which could be explained due to their specialized formation. Also, having received a training or workshop on ALS could improve compliance to guidelines.

Diagnosis

Diagnostic criteria for ALS was developed by international consensus to standardize diagnosis and patient recruitment in clinical trials, initially the aim of these criteria were for research projects and not for clinical practice criteria, however, due to the lack of a

formal diagnostic criteria EEDC, Airlie house and Awaji criteria have been widely used on clinical practice (225). Nevertheless these criteria have high complexity due to the different diagnostic categories. A study that evaluated the inter-rater agreement of the Airlie House criteria and Awaji, by eleven experienced physicians from ten different countries, found that the inter-rater agreement was poor for the “possible” (kappa coefficients of 0.14 for Airlie House and 0.33 for Awaji) and “probable laboratory-supported” (kappa coefficient of 0.25 for Airlie House), but it was high for the “Not ALS” (kappa coefficients of 0.59 for Airlie House and 0.65 for Awaji), “Definite” (kappa coefficients of 0.50 for Airlie House and 0.45 for Awaji) and “Probable” (kappa coefficients of 0.49 for Airlie House and 0.35 for Awaji) categories from the Awaji and Airlie house criteria (225).

A systematic review of ALS literature in Latin America, reported that for some studies only the ALS cases classified as “Definite” or “Probable” are considered which could explain the lower incidence rates in the region compared to Europe and North America (181). Also, the difficulties in access to health and diagnostic delay could lead to identifying ALS cases in an advanced form leading to potential differences on ALS clinical characteristics. This was showed in the study by *Gil et al.* in Uruguay, most of cases were classified as Definite, while none of the cases were classified in the possible and suspected categories and when comparing survival rate to patients in Limoges France (with a distribution among all categories), longer survival was reported in France (125).

In our study we observed that, neurologist that had a high compliance for guidelines have a higher used of Awaji criteria and electromyography, this may be because of the electro diagnostic interpretation in this criteria, as we found that neurologist with a neuro-muscular sub-specialty had a higher compliance to guidelines they could have a greater experienced in electro diagnostic studies.

Studies have found that because of the complexity of the different categories in Airlie house and Awaji criteria, misunderstanding is common among physicians and patients in having or not the disease, and it is not clear that patients will evolve through all the categories, leading to patients initially identified as possible died from ALS without being classified as definite (53). As diagnostic certainty increased with disease progression (226). A systematic review of ALS in the region found that most of the studies were in a retrospective design and from hospital discharge data or death

certificates (181), the results of these studies could be impact as maybe suspected or possible categories to not be coded as ALS, therefore reporting lower incidence or mortality rates in the region.

Because of the different limitations in the already known diagnostic criteria, a new diagnostic criteria has been proposed known as the Gold Coast criteria, which is reduced to two simple categories “ALS” or “not ALS” which could help to provide more uniform diagnosis (53).

Management

Riluzole

Riluzole is widely used in European countries as well in United States and Japan (227). The used of Riluzole has been documented in other countries such as China (228) and in Africa, but the availability of Riluzole varies among regions in Africa (93,213). Riluzole is an expensive medication the used of this drug depends on the availability of the medicine among the countries.

A study that evaluated six ALS referral centers in France showed that Riluzole was offered and monitored among all patients and normally prescribed within 2 months after confirming diagnosis. This may be because Riluzole is free of charge in France due to a resource allocation from the French health ministry (210). In a study that evaluated the effects of Riluzole on survival from different countries, the proportion of patients in China using Riluzole was low compare to other European countries, which can be due to the effect that ALS treatment is not covered by insurance in China, and the costs of Riluzole are expensive (229). This lower proportion of patients using Riluzole in China was also observed in a study comparing prognostic factors between China and Germany (91). The proportion of patients using Riluzole in Africa was low (26.3%), and even lower in South Africa compared to North Africa, the authors found that the cost of Riluzole were about the same as the average monthly household income in Southern Africa and it is not funded by the health or private insurances (93). In a further study of nine hospital centers form eight African countries, Riluzole was only available in centers from South Africa, Senegal, Tunisia and Togo. When available this medication was unaffordable and infrequently used probably due as this treatment is either partially or fully funded by the patients (213).

In our study the prescription of Riluzole was different among countries. Nearly all, of the neurologist in Argentina (100%), Colombia (97.0%), Dominican Republic (100%), Bolivia (100%) and Uruguay (83.3%) prescribed Riluzole. On the contrary, in Chile 100% (n=9) of neurologist did not use Riluzole in the treatment of ALS patients.

Riluzole is not available in all Latin American countries. For instance, in Ecuador, Riluzole is not considered as an essential medicine accepted by the basic list of medicines of the ministry of health in Ecuador (230) and this was also reported by local neurologist. An Argentinian foundation called the “Esteban Bullrich Foundation” carried out a first report to analyze the current situation of ALS in 18 Latin American countries. Regarding the availability of Riluzole, this was not available in countries such as Bolivia, Ecuador and Honduras (231).

Private local laboratories Tuteur Laboratory in Argentina and Sanofi in Uruguay produced Riluzole. In Argentina patients can have access through ALS associations.

On the contrary, in Brazil, the ministry of health order that patients can have access to Riluzole free of charge (231). In Costa Rica, Riluzole is available on the social security list of essential medicines, patients that are adhered to this program can have access to it (232) .

Multidisciplinary care

Management of ALS requires a multidisciplinary approach, guidelines from Japan, United States and Europe have found that the attendance or availability of multidisciplinary care can increase survival, improve quality of life and decreased complications (227).

A study in United Kingdom that compared survival between patients that were followed in multidisciplinary clinics and patient’s that were followed by general neurologist clinics. Multidisciplinary clinic provided a specialist care composed by a team of neurologist, respiratory physiologist, dietician, specialist nurses, physiotherapists, occupational therapist, speech and language therapist and social workers. Patients in multidisciplinary clinics are evaluated every 8-10 weeks, in each evaluation baseline weight, pulmonary function and ALSFRS-R are measured, when necessary neurologist in the clinic referred patients to respiratory physicians and gastroenterology physicians. On the contrary, patients followed by general clinics are evaluated less frequently and an early introduction to NIV or PEG is more uncommon. In this study

longer survival was observed in patients followed in multidisciplinary clinics (median survival since onset 36.8 months (IQR: 23.1 – 95.1)) compared to patients followed in general clinics (median survival since onset 28.0 months (IQR: 18.7 – 42.5)). This longer survival in multidisciplinary clinics could be associated to a higher used of Riluzole, NIV and PEG compared to patients in general clinics or a higher proportion of bulbar onset among patients in general clinics. However, an independent positive effect on survival has been associated to multidisciplinary clinics (233).

Similar results were found in a study in Italy, a longer median survival since onset of 10 months and less admission to hospitals were observed among patients attending a tertiary center compared to patients followed by general neurological clinics. Tertiary centers in Piemonte and Veruno, were composed by an interdisciplinary team, evaluation of patients were every 8 weeks, follow up of nutritional and respiratory aspects were was performed, PEG and NIV were proposed and Riluzole was available free of charge. Patients attending general neurology clinics were seen every 6 months and they did not undergo regular nutritional and respiratory evaluations leading to a lesser attention towards early introduction to PEG and NIV. (211).

A recent study in United Kingdom reported that integrating a more equipped multidisciplinary input improve survival in ALS (73). In this study, to assess whether survival and care provision has changed over time, they evaluated the same center at different time-periods, they reported a higher median survival since diagnosis of 21.6 months (95%CI: 19.2-24.0) for the most recent period (2008-2011) compared to the previous period (1995-1998) median survival since diagnosis of 19.2 months (95%CI: 15.6-21.6) (73). In this center integration of a full multidisciplinary team was achieved around 2006, this team was composed by specialist nursing, diet planning, physiotherapy, speech and language therapy, respiratory, psychological and palliative care services. The implementation of Non-invasive ventilation and gastrostomy that has increased over time could be associated as good predictors of survival, nevertheless prescription and treatment strategies with NIV and gastrostomy could be related to the specialized team knowledge and practice (73).

A younger age at onset and less proportion of bulbar onset have been associated to ALS multidisciplinary clinics, which make it unclear whether this multidisciplinary approach increases survival (70). However, ALS multidisciplinary clinics have been identified as independent factors for a better survival (73,233). This shows that an

integrated multidisciplinary team of experts can improve survival due to a better recognition of symptoms leading to an early introduction of NIV and PEG. The more frequent evaluation of patients can result in a more promptly treatment of symptoms and reducing complications of these (73,233).

Multidisciplinary care have also improved quality of life in ALS patients. In a study in Netherlands, quality of life was compared between patients evaluated by general ALS care and a multidisciplinary team consisting in: rehabilitation medicine and at least a physical or occupational therapist, speech pathologist, dietician and social worker. The proportion of patients with communication, mobility or speech problems that received adequate aids and appliances was higher in the multidisciplinary care compare to general care (93.1% vs 81.3%, p=0.008. Quality of life assessed by the 36-item Short Form Health Survey (SF-36) on the mental summary scale was better in patients evaluated by multidisciplinary care (beta coefficient of 4.28; 95%CI: 1.2 -7.4, p=0.01) and it was even better in social functioning (beta coefficient of 15.0; 95%CI: 6.8 – 23.3, p<0.001) and mental health (beta coefficient of 4.5; 95%CI: -0.2 - 9.2., p=0.06) (72).

In our study, multidisciplinary care team is mainly composed by rehabilitation therapist and in a lesser proportion by pneumologists, nutritionists and psychologists and even lower by speech therapists, palliative care, social counselor and specialized nurses. Which are similar to the results of an evaluation of nine hospital centers in Africa (TROPALS), all hospital centers systematically offered neurologists and physical therapist expertise while respiratory specialist were only available in 5 hospitals and other disciplines such as gastroenterologist, occupational therapist, dentist, palliative care, dietician and specialized nurse were less provided (213).

On the contrary, an evaluation of six ALS centers in France according to the European guidelines, neurological, pulmonary, gastroenterologist, psychologist, dietician, specialized nurse, speech therapist, occupational therapist and social worker expertise are highly available, while rehabilitation and physiotherapy are less common (210).

In this survey, significant differences were observed among groups, neurologists in the high compliance group, worked in a higher proportion among all disciplines. Which shows that the promotion of ALS guidelines could help improve survival and quality of life by the implementation of a multidisciplinary care of ALS patients.

Non-invasive ventilation and gastrostomy

The use of gastrostomy and non-invasive ventilation seems to varied among countries. Regarding the use of PEG, studies in Japan have reported a proportion of patients ranging from 29-58%, in United States from 8-43% and in European countries was from 6-45%. On the other hand, the use of non-invasive ventilation seems higher in United States (19-87%) compared to Europe (3-44%) and Japan (7-46%), while the use of tracheostomy was higher in Japan than in United States and Europe, probably due to the less flexibility to terminate mechanical support in Japan (227).

In our survey we assessed the practices on patients with early signs or symptoms of respiratory insufficiency, the most common options was referral to a pneumologists followed by the use of non-invasive ventilation, no differences were observed among the compliance to guidelines groups. Referring to a pneumologists and or indicating NIV are considered good practices according to guidelines. Nevertheless, we are limited in this question to known the criteria which neurologists in Latin America used to consider early signs or symptoms of respiratory insufficiency and whether NIV was recommended by the pneumologists. In a survey conducted among all consultant neurologists in the United Kingdom to assess the clinical application of NIV (234). Only 20% of neurologists requested a respiratory function test at every clinic visit while 46% requested this only if patients were symptomatic, regarding the criteria for NIV referral 32% of the neurologists relied on symptoms only and 43% used a combination of symptoms and physiological impairment (Orthopnea, breathlessness, morning headache, daytime sleepiness, and nocturnal hypoxemia) (234). Reliance of symptoms alone is not a sensitive way in recognizing significant respiratory muscle weakness even more when mobility is limited which leads to an underestimation of severe respiratory insufficiency. Consequently, in some cases survival can be shorter following the onset of respiratory symptoms such as orthopnea (234).

The use of spirometry was more frequently used to monitor respiratory function according to the neurologists in this survey. Which was also a frequent practice among the neurologists in the UK survey (234). Spirometry alone does not accurately predict the onset of respiratory failure, compared to maximum respiratory pressure measurements (234).

Use of NIV have increased through the years, in the study in United Kingdom among consultant neurologists, they observed that there has been an increased in the number

of patients referred for NIV (from 234 patients to 612 patients) and the total number currently being treated with NIV (126 patients to 431 patients) has also increased from 2000 to 2009 respectively (234). They compared the practice of the seven highest referring neurologists to that of the others, and showed that the practice of the referrals (mean new patients/year of 50.6) was higher compare to others (mean new patients/year of 8.4) and they also found that the highest referring neurologist monitored respiratory function more often and were more likely to consider early intervention with NIV (234).

We also, assessed the use of gastrostomy in patients with severe dysphagia, which was a common practice among neurologist. Referral to a nutritionist was also a common practice in almost all neurologists in Latin America. Limitations in whether which criterion does neurologists used for gastrostomy indication are also present in this question. This results are consistent with the results in the study by *Marin et al.* in France, 82.4% of cases were evaluated by a dietitian (210).

Reports of the use of NIV and PEG in Latin America literature is limited, some have reported the use of both interventions, the proportion of patients using NIV have been reported between 30% and 86%, while the proportion of patients that underwent PEG have not been reported. The promotion of guidelines among the neurologists in Latin America, could help implement standardized criterion and promote early intervention to improve survival (218–220,223).

Palliative care

Half of the neurologist responders in our survey affirm that patients discussed their wishes at the end of life, a Knowledge Aptitudes and Practices (KAP) survey regarding care at the end of life showed that neurologist support a patient's right to refuse life sustaining treatment but this is not an easy option for neurologist as they believe that they are killing their patients. They showed that there was a gap regarding medical, legal and ethical guidelines for patients in terminally diseases and further education should be provided (235). In the study in France by *Marin et al.* a lower proportion of patients received an early input from a palliative care team and discussion on end of life.

Palliative care includes a complete assessment of the patient and family considering physical, psychological, social and spiritual aspects (207).

IV.4.3.1. Challenges in Latin America health systems

ALS progressive course requires a multidisciplinary management and an intensive use of medical resources. The loss of autonomy of patient's results in a high burden for health care systems and caregivers. A study from a large cohort of ALS patients in Germany estimated the cost of illness taking in account direct medical costs (drugs, doctors consultations, supportive medical devices, hospital treatments, surgery, rehabilitations and further therapies such as speech therapy) and non-medical costs (travel expenses, investments in constructional changes, legal fees and care by non-professional caregivers) mean annual total cost of illness was estimated at 78,256 euros per patient, which was constituted of 35.9% of direct medical cost and 49.1% of direct non-medical costs and 15% of indirect cost (209). A case study in United States reported cost for total disease duration were $1,433,992 from which 85% were paid by insurance, 9% by family and 6% by charities (236). As shown in this studies ALS treatment cost are high, there is a need for specific funding's from health care systems.

Latin American health system faces different challenges, there is an important double burden of diseases, non-communicable diseases such as cancer, diabetes mellitus and cardiovascular diseases are the leading health problems, and represent a high burden for countries, as well the proportion of maternal, prenatal and nutrition problems are a major concern (237). This double burden of disease could make that governmental and charity aid is prioritize for most common diseases.

Public health sectors in Latin America, are coordinated by the ministry of health, this sector is normally finance by public resources and government. There is a variation among Latin American countries health care spending which ranged from 83 dollars PPP in Haiti to 2484 dollars PPP in Cuba. According to the organization for Economic Co-operation and development (OECD) in 2017, Latin American countries have a health spending per capita four times lower than the average of OECD countries (109).

Another challenge is that medical and structural health resources are limited in the region. According to the OECD, there is a major gap of physicians per 1000 population in Latin America, which is lower than the average health works needed to achieve high coverage for essential health interventions. Furthermore, the gaps among specialist physicians is even greater, according to the WHO Atlas country resources for neurological disorders, the median neurological workforce per 100,000 population was of 2.3 for the region of the Americas and 1.4 for lower-middle-income countries, from

these the median number of neurologist was of 0.70 in the Americas and 0.13 for lower-middle-income (238).

Access to health is a persistent problem in Latin America. Health facilities are predominantly located in the capital cities or the largest ones, and there is a gap of specialist among urban and rural areas. The WHO in 2017 reported that for the region of the Americas, 78% of the neurologist were located in urban area compared to only 17% in the rural area (238).

Access to medicines is a core element and one of the main priorities of public health policy. In Latin America, treatment gap is a major concern which has been showed for other neurological diseases such as epilepsy (239). As previously describe Riluzole access is limited in Latin American countries.

Computed tomography (CT) scanners and magnetic resonance imaging (MRI) units are essential for differential diagnosis in ALS. Significant differences has been observed in the availability of these technologies in the regions, with usually being the high-income countries with a higher number. The OECD reported that the highest number of CT scanners and MRI units was reported in Chile with 24 scanners and 12 units per million population, which is below than the average of the other OECD countries (109). This difference in resources could prolong diagnostic delay in countries where this resources are limited.

New ALS research evidence of ALS estimates, clinical characteristics and the impact of ALS in quality of life could help inform policies and to create new interventions and programs. However research in mental and neurological problems have been neglected more specifically in lower-middle-income countries. Increased training in research and health interventions among human resources, academic recognition, financing programs could help increased research production and highlight the related health problems within countries (240) .

IV.4.3.2. Recommendations on ALS clinical practices

A high proportion of neurologist followed good practices according to guidelines. However, some improvements should be recommended, international guidelines on ALS diagnosis and management should be distributed among neurologist and other sub-specialties of neurology with the aim to unified criteria’s and provided high standard management to prolong survival and improve quality of life of ALS patients.

Neurologists with a neuro-muscular subspecialty showed to have a higher compliance, however specialized physicians are limited in the region, and only patients living in capital cities or with a high-income status could have access to this type of physician.

Some aspects of multidisciplinary care shuold be strengthen, Pneumologist and Nutritionist should be the pillar disciplines of the multidisciplinary team on the management of ALS patients. Inclusion of this disciplines should be implemented since the beginning of management and not only when difficulties start. As nutritional and respiratory complications are associated to a poor survival on ALS patients. Inclusion of other disciplines should be also recommended, speech therapist, palliative care, specialized nursed. Palliative care follow up at the end of life should be implemented and decisions of patients for the end of life should be discussed with time.

Further improvement are needed in Latin America, new guidelines adequate to the Latin America context could be performed. This guidelines should promote multidisciplinary care on ALS patients, frequent monitoring of respiratory and nutritional function at each clinical visit, uniform criteria for referral of cases for early intervention of NIV and PEG. Implementation of palliative care and early discussion of end of life should be also implemented.

Nevertheless, management of ALS patients represents high cost, in order to neurologist can adhere completely to ALS guidelines, health systems should be able to provide all the medical facilities, human resources and access to medicines needed on the management of ALS patients. Governmental financing is crucial to improve access and quality of health among Latin American countries. In addition, joint research and training programs on ALS diagnosis and management could be implemented among neurology societies as ALS patients may benefit of clinical trials and International collaborations. Training of ALS should also be implemented among other disciplines as general medicine physicians, pneumologists, nutritionist, palliative care, gastroenterologist, specialized nurses, occupational and speech therapists.

IV.4.3.3. Limits and strengths

The main strength of this work relies on the international collaborations established with the PAFNS and the IENT network. This collaboration allowed us to have a representation on Latin American countries but mostly from neurologist associated to a neurological society which could represent a selection bias. The PAFNS encourage regional collaboration and work as a platform for ALS research and education.

Second, our survey was developed according to the European and American guidelines on ALS diagnosis and management. In addition, the score that evaluated the compliance of ALS guidelines was developed by an ALS expert neurologist and epidemiologist in Limoges, France.

Some limitations need to be acknowledge, there was a small number of neurologist respondents for some countries, response rate was not calculated given the questionnaire was openly distributed by different sources (invitations to participate were sent by the neurology societies, PAFNS, neurologists and researchers). However, data collection was performed during the COVID-19 pandemic, which was a huge impact in Latin American countries, in some countries neurologist needed to double the work to help fight the pandemic. Another reason could be that only the neurologist that had diagnosed ALS cases were more interested in participating, representing a selection bias. Another limitation, is that we have a large number of neuro-muscular specialists, which is a selection bias, it can be assumed that neuro-muscular specialist were more motivated and better informed about the latest ALS standards than other neurologist. Some variables such as sex and age had a large proportion of missing data as this variables were not available in the pilot study.

IV.4.4. Perspectives

Given the collaboration with the PAFNS-EpiMACT could be an approach to implement ALS research among Latin American countries, this could also help to develop a consortium among key neurologist to create guidelines for the management of ALS patients adapted to the health context of Latin American countries. The PAFNS could serve as a platform for neurologist to share case series and discussed among international partners. Further education of ALS management and standard diagnostic criteria to neurologist through webinars, seminars and congress from international ALS experts could enhance training and unified criteria.

IV.4.5. Conclusion

This survey describes the clinical practices of ALS diagnosis and management on different Latin American countries. Good practices were found on the diagnosis and care of ALS patients.

Regarding diagnosis, the practices of neurologists in Latin America are consistent with diagnostic practices in Europe and North America, we could assume that a common diagnostic criteria should provide precise occurrence data. However, further studies are needed to evaluate the inter-agreement of this criteria among neurologists.

Further improvement is needed in the care for ALS patients most especially in the integration of a multidisciplinary care. Specific training and constant educational programs among large samples of general neurologist and other sub-specialty in neurology should be implemented. The inclusion of a palliative care team and discussion about end of life decisions should be strengthen as Latin America health systems faces different challenges which could make it difficult to adhere to international guidelines, regional guidelines adhere to the health systems context should be encouraged. This survey was performed among neurologist further studies should be performed among ALS patients to evaluate management and identify further treatment gaps.

Chapter V. ALS in Ecuador

V.1. Framework of ALS research in Ecuador

ALS research in Ecuador has been limited as in other Latin American countries. To the best of our knowledge two epidemiological studies have been conducted in Ecuador. These studies have provided information of ALS epidemiology (incidence and mortality) and clinical characteristics of ALS patients in the country.

V.1.1. ALS epidemiology in Ecuador

ALS incidence in Ecuador

ALS epidemiology was studied for the first time in Ecuador in 2014 by *Bucheli et al.* This study aimed to estimate the incidence of ALS. Data from two major hospitals in Quito, the capital city of Ecuador was investigated, i) “Hospital Eugenio Espejo” from the public health network (2000-2012) and ii) “Carlos Andrade Marin Hospital” from the social security network (2006-2012). Both hospitals are tertiary centers and the largest referral centers in Quito and at national level.

Electronic medical records were identified by the ICD-10 code G12 and G12.2, medical records were evaluated to confirm ALS diagnosis using the EEDC (172).

ALS crude incidence rate was 0.2 and 0.6 per 100,000 PYFU for each hospital. The combine standardized incidence rate was 0.26 (95%CI: 0.21-0.30) per 100,000 population based on Ecuador 2010 population, 0.29 (95%CI: 0.24 –0.35) per 100,000 population on the US 1990 population (172).

This study reported a lower incidence rate compared to European and North American countries. Nevertheless some methodological issues in this study should be highlighted. First, this is a hospital-based data which represents a selection bias and an underestimation of cases. Second, the population at risk is not described in this study, supplementary data indicates that the population at risk in this study was the outpatient and inpatient population for each hospital during the different study periods. However, the crude rates reported on the study are based on the Pichincha 2010 population. Third, ALS crude rates were reported for each hospital, but standardized rates to the Ecuador 2010 and US 1990 population were combined even though

different time periods were studied for each hospital. Finally, according to the supplementary data, patients from other cities outside Quito were included.

These different factors could explain this low incidence in Ecuador.

ALS mortality in Ecuador

A population-based study was performed in 2018 by *Luna et al*. aiming to estimate ALS mortality in Ecuador Data from the annual national mortality registry (INEC) was used to determine ALS deaths from 1990 to 2016, . Death caused was based on the underlying and contributory causes using the ICD-9th and 10th revision, code 335.2 was used for the 1990-1996 period and code G12.2 was used from 1997 through 2016. Population at risk was obtained from the annual demographic yearbook by the United Nations Statistics Division.

In addition, a comparison of ALS mortality rates among ethnic groups was performed. Ethnic data in Ecuador was collected using the INEC definition and classification, ethnic groups were classified as “Mestizos”, “Indigenous”, “Afro-descendants”, “Whites” and “other groups”. To estimate the population at risk according to ethnic groups, projections from the 2010 Ecuador census were performed (5).

ALS crude mortality rate in Ecuador was 0.16 (95%CI: 0.15 – 0.18) per 100,000 PYFU and standardized mortality based on the 2010 US population was 0.18 (95%CI: 0.17 – 0.19) per 100,000 PYFU (5).

Mortality rates differed among ethnic groups, age-sex standardized mortality rate was 0.37 (95%CI: 0.20 -0.53) in White populations, 0.49 (95%CI: 0.43 -0.55) in Admixed populations, 0.26 (95%CI: 0.05- 0.47) in Black population, and 0.19 (95%CI: 0.05 - 0.34) in other ethnics per 100,000 PYFU respectively. Significant differences were reached between Admixed populations and other ethnics group (p=0.015) (5).

A low ALS mortality was reported in this study. Furthermore, Ecuador has a predominantly Admixed population, which supports the evidence of a lower occurrence among Admixed populations.

Some concerns have been raised regarding mortality data. However this study allow a population-based approach and considered a large period of study (27 years) in Ecuador where this had not been previously achieved.

V.1.2. Clinical Characteristics in Ecuador

ALS clinical characteristics have been reported in only one study in Ecuador in the study by *Bucheli et al.* (172). ALS was predominantly in males with a sex ratio of 1.35:1, mean age at onset for sporadic ALS cases was 54.29 ±15.06(SD), males showed a younger age at onset (51.48 ± 14.7 SD) compared to females (58.12 ±14.76 SD). Bulbar onset was higher among females (23%) compared to males (16%). Mean diagnostic delay was 15.9±12.3 SD months (172). No statistical test were performed to evaluate differences.

This study reported some insights of ALS clinical characteristics, the design used in this study make it difficult to provided firm conclusions, as hospital-based studies have shown to present younger ALS cases and less likely to have a bulbar onset (70).

V.2. Justification of a research project in Ecuador

The previous studies reported a low ALS incidence and mortality compared to other countries in Europe and North America. Clinical characteristics reported in Ecuador, appear to be different to those reported in European and North American ALS patients, indicating a younger age at onset and a longer diagnostic delay in Ecuadorian ALS patients.

ALS occurrence in Europe and North America are normally reported from population-based studies using different sources of case ascertainment to assure case exhaustiveness. The methodological design in the studies in Ecuador make it difficult to provide reliable comparisons. Furthermore, there is no information of ALS clinical management, survival and prognostic factor of ALS patients in the Ecuadorian population.

Differences of ALS occurrence has been observed among ethnic groups, even more a lower risk of ALS among Admixed populations compared to Caucasian populations have been suggested (2,4,6). The diversity of ethnics and the predominance of Admixed population make Ecuador an interesting country to study the association of ancestral origin and ALS. Nevertheless, at this point there is a need to provide reliable epidemiological indicators (incidence), a clear description of clinical characteristics and survival in the general population of Ecuador.

V.3. Ecuador

Ecuador is located in South America, with a total population of 14,483,499 inhabitants according to the 2010 population and housing census conducted by the National Institute of Statistics and Census of Ecuador. Sixty-three percent of the population lives in urban areas while 37% lives in rural areas. Quito and Guayaquil, considered as the metropolitan cities, concentrate the largest percentage of the national urban population, 41% of the population lives in these two cities (177).

Quito, the capital of the country has a total of 2,239,191 inhabitants, with a predominant female population, the average age of the population is 29.5 years, only 46.1% of the employed population had general insurance, and at the general level only 19.1% had private health insurance, so most of the population attends public health centers by the ministry (177).

Guayaquil, the second most populated city in Ecuador has 2,350,915 inhabitants with a predominance of women, with an average age of 29.1 years, only 36% of the employed population has general insurance, and of the total population only 11.4% has private health insurance (177).

Cuenca, capital of the province of Azuay, is the third most populated city after Quito and Guayaquil. According to the 2010 housing and population census, it had 505,585 inhabitants, the majority of whom are women (266,088), with an average age of 28.9 years and only 37.3% of the working population has general health insurance (177).

Ecuador is a multiethnic country, with a predominantly Admixed population, according to the 2010 Ecuador census, 79.3% of the population self-identifies as "Mestizo" (mixed origin between European and Native American ancestry), while the other part of the population is categorized as 6.1% Caucasians or Whites, 7.2% Afro-Ecuadorian or Africans and 7.0% as Indigenous populations (177).

V.3.1. Ecuador health system

Health system in Ecuador is a fragmented systems in two sectors, the public and private. The public sector is composed by the Public Health Ministry (MSP) and the social security institutions: the Ecuadorian Social Security Institute (IESS), The Armed Forces Social Security Institute (ISSFA), and the National Police Social Security Institute (ISSPOL). The private sector is formed by private lucrative hospitals, clinics

and consulting rooms and other non-profit organizations (241). The MSP provides the most extensive services and covers around 51% of the population. Workers of the formal sector have the right to the IESS, which covers around 20% of the population. While ISSFA and ISSPOL is accessible to the military and police workers and covers around 5% of the population (241).

An observational study of ALS in Cuenca, Ecuador was performed. Before presenting this study, there is a need to explain that an initial project was planned in Ecuador but different challenges were presented that did not allow to finish this project.

V.4. A research project in Ecuador

With the aim to contribute to the scientific literature and describe ALS incidence, clinical characteristics and survival in the general population in Ecuador, a retrospective study among different sources of case ascertainment (Hospitals and neurologist private consulting rooms) was planned.

V.4.1. Methods

In order to achieve our objective an observational descriptive study with a retrospective design was planned in the three biggest cities of Ecuador; Quito, Guayaquil and Cuenca.

Different sources would be used for case ascertainment in each city. ALS cases would be identified in: i) Hospitals and clinics from the public sector (including the different administrations MSP, IESS, ISSFA and ISSPOL) and from the private sector. ii) Neurologist from each city would be invited to participate and iii) private insurance companies and iv) ALS associations.

The list of hospitals and clinics from the public sector for each city were searched on the Ministry of Health webpage. Private hospitals were search online, in addition we confirmed this list with collaborating neurologists in each city.

Neurologists were identified during the same time we were performing another study (clinical practices of the diagnosis and management of ALS a pilot study in Ecuador) the strategy of neurologists identification is described in chapter 4.

All patients diagnosed with ALS according to Airlie House criteria during 2009 to 2019 living at the moment of diagnosis in Quito, Guayaquil and Cuenca would be included.

To identify ALS cases we used two strategies according to the source:

Hospitals: ALS cases would be identified using the ICD-10 codes G12 and G12.2 in each hospital. Each medical file was requested to confirm ALS diagnosis. Diagnosis confirmation was considered if this diagnosis was established by a neurologist in the medical file.

Neurologists: we requested to each neurologists the list of patients they had diagnosed in the study period, access to medical file was requested, if this access was not granted we provided a list of variables that we were searching.

Private insurance companies and ALS association: the list of patients under the diagnosis of ALS would

To categorize each ALS case into the Airlie House criteria, we would collected the following information: i) signs and symptoms of lower and upper motor degeneration since onset until diagnosis, ii) If electro diagnostic studies were performed information of neurodegeneration would be collected. ALS cases would be classified by a neurologist from the expert center of ALS in Limoges, France.

Data would be collected in an Ad-hoc form. We collected sociodemographic data: date of birth, sex, residence address. Pathological antecedents: comorbidities, familiar history of neurological disease, smoking habits. Clinical information: signs and symptoms of upper and lower neurodegeneration, age at onset, age at diagnosis, type of onset, presence of dyspnea and dysphagia, status at latest medical visit (live or dead), date of death, date of latest medical visit. Exams: electro diagnostic studies (EMG) and neuro imaging. Management: use of NIV, tracheostomy, gastrostomy, use of Riluzole, and multidisciplinary management.

A study protocol was approved by the ethics committee of Universidad Central del Ecuador on December 10th, 20190, code 00013-UL-E-2019.

Information of ALS patients was respected in a dignified, accurate and appropriate manner at the individual and group level. We ensured these principles by anonymizing the data, to which only the principal investigator had access, confidentiality in the data collection and storage was ensured.

V.4.2. Challenges in Ecuador

This project was started on October 2019, nevertheless different problems related to the field work were found that did not allow to finish it.

A first mission was carried out on September 29, 2019, with a planned duration of three months. Unfortunately, on October 3, 2019 protests against the government began throughout the country; the demonstrations were violent, which is why the Ecuadorian government declared a state of exception, and thus the project was stopped two weeks after arrival in Ecuador.

A second mission started on January 29, 2020, with a planned duration of 5 months in Ecuador. In March 2020, the health crisis related to Covid-19 started. On March 14, the President of Ecuador declared strict quarantine and on March 17, the closure of the borders. The project was stopped a second time.

During the month and a half of the mission in 2020, we encountered several logistical problems related to authorizations to access medical records. Despite an ethical authorization by the ethics committee of the Central University of Ecuador, each hospital requested additional approval from their specific ethics committee. This process was time consuming and affected the completion of the work. Secondly, we found a large refusal to participation from the neurologists, as they needed approval from each patient in order to share the information. Third, there was a lack of electronic records and classification of medical records in different private hospitals and neurologists, for this reason access was not granted.

Initially our objective was to estimate ALS incidence rate using different sources, this was not possible due to different reasons: we only had access to hospital data and only few neurologists accepted to participate, between the different sources there was not a common time period and it was not possible to assure the place of residence of the ALS cases at the moment of diagnosis.

Survival analysis were also planned, however information of status (live or dead) or if tracheostomy was performed was not available on the medical files.

A third mission to Ecuador needed to be planned, however due to the Covid-19 pandemic this was not possible. Because of these different challenges the project was stopped. During the second mission, data collection was achieved in Cuenca as this project was started in this city.

In the following section we present the information collected in Cuenca and further challenges that were presented during this study.

V.5. ALS in Cuenca, Ecuador

Objective

To describe the clinical characteristics of ALS patients in Cuenca, Ecuador.

V.5.1. Methods

This study was performed in Cuenca, the third most populated city of Ecuador. This is the capital city of the Azuay province, it covers an area of 8,639km^2 and is located about 2560 meters above sea level. with a total population of 505,585 inhabitants from which 52.6% are females according to the 2010 national census (177). Since 2010 to 2017 there has been a population growth of 15% (242). Cuenca is a multiethnic city, with a predominantly Admixed population, 89.7% identifies as Mestizo. There is a predominance of young population 57% of the total population is younger than 30 years of age and only 7% belongs to the >65 age group. (177).

V.5.1.1. Study design

We performed an observational cross-sectional study, retrospective case collection of ALS incident and prevalent cases from 2009 to 2019 was carried out.

V.5.1.2. Case ascertainment

ALS cases were identified in public and private hospitals and clinics, ALS cases were also identified among neurologists consulting rooms in the region.

In the public and private hospitals we requested to the statistics department the list of medical files coded G12.0 and G12.2 according to the ICD-10 classification. A revision of each medical file was followed to confirm ALS diagnosis. ALS cases were then classified into the El Escorial Diagnostic Criteria and Airlie House criteria by a neurologists from the ALS expert center in Limoges. In order to perform this classification we collected the signs and symptoms of upper and lower motor degeneration since onset to diagnosis, results from electromyography and magnetic resonance images were also collected when this were available.

All incident and prevalent cases were including independent from their place of residence.

V.5.1.3. Data management

Data was collected in an access Ad-hoc form. The information collected is detailed in the previous section. We provided some definitions of certain variables.

Age at onset was considered as the age when the first sign or symptom of upper or lower motor degeneration was reported on the medical file.

Age at diagnosis was considered as the age the patient had when the diagnosis of ALS was posed by a neurologist on the medical file.

Type of onset was classified into spinal or bulbar by a neurologist of our team, to perform this classification we collected the signs and symptoms of upper and lower motor degeneration and the region where this was presented at the moment of onset.

Multidisciplinary management was considered if other disciplines rather than neurology had evaluated the patient.

Use of Non-invasive ventilation and gastrostomy was considered if this was reported on the medical file.

Other variables collected were the ALSFRS-R at diagnosis and at the latest visit (if reported on the medical file), weight before the onset of ALS and the weigh at the latest medical visit.

V.5.1.4. Ethics

Besides the protocol approval from the Universidad Central del Ecuador ethics committee, an authorization from each hospital direction office was obtained. Anonymization of patients was performed.

V.5.1.5. Statistical analysis

All findings were reported using the guidelines of Stregthning the Reporting of Observational Studies in Epidemiology (STROBE).

Descriptive and analytical analysis were conducted using IBM SPSS Statistics V. 28.0.1. Quantitative variables were expressed as medians and interquartile ranges (IQR) The Shapiro-Wilk test was used to explore the normal distribution of continuous

variables. Qualitative variables were described using frequencies and percentages. For comparative analysis, X^2 test was used for nominal variables, and fisher exact test. Students test was used for comparison of dichotomous variables with a normal distribution and Mann-Whitney test for those with a non-normal distribution.

All missing data was reported.

V.5.2. Results

In overall 72 ALS cases were identified during 2009-2019 using two sources of case ascertainment in Cuenca, Ecuador. More than the half were male cases (55.9%) with a male/female sex ratio of 1.26.

Sources of case ascertainment

Hospitals

We identified 11 hospitals in Cuenca. Three hospital belong to the public sector from different administrations IESS, MSP and ISSFA, all hospitals from the public sector accepted to participate. In these hospitals outpatient and inpatient data was available. A total of 68 ALS cases were identified in the public sector hospitals.

From the private sector eight hospitals were identified, from these only four hospitals accepted to participate. In private hospitals only inpatient data was available. No cases of ALS were found among private hospitals as shown in table 11.

A description of the participating hospitals and the years were data was available is shown in table 11.

Table 11. Hospitals identified in Cuenca, Ecuador

Hospital	Administration	Participated	Years available	ALS cases
Hospital Jose Carrasco Arteaga	Public (IESS administration)	Yes	2009-2019	36
Hospital Vicente Corral Moscoso	Public (MSP administration)	Yes	2009-2019	31
Hospital General Tarqui	Public (ISSFA administration)	Yes	2009-2019	1
Hospital Catolico	Private	No		
Hospital Latino	Private	Yes	2013-2019	0
Hospital Bolivar	Private	Yes	2013-2019	0
Hospital del Rio	Private	Yes	2009-2019	0
Hospital Santa Ana	Private	No		0
Hospital Santa Ines	Private	No	2009-2019	
Hospital Monte Sinai	Private	No		
Hospital San Juan de Dios	Private	Yes	2016-2019	0

As shown in table 11, for some private hospitals ALS cases were only searched in different time periods 2013-2019 or 2016-2019. Due to the fact that electronic information was not available from previous years.

Neurologists

A total of 17 neurologists were identified in Cuenca, all neurologists were invited to participate but only six neurologists accepted to participate. A total of 24 ALS cases were found as follows:

- Neurologist 1: a total of 10 cases were reported from 2009-2013.
- Neurologist 2: a total of 8 cases were reported from 2015-2019.
- Neurologist 3: a total of 6 cases were reported from 2015- 2019.
- Neurologists 4, 5 and 6: no cases were reported from 2017-2019.

A total of 72 ALS cases were identified. ALS cases were identified simultaneously between the sources from the public sector, seven cases were simultaneously found between the hospitals from the social security administrations (IESS, ISSFA) and the ministry of health (MSP) administration. Among the neurologists and hospitals, two

cases were found simultaneously between the MSP and Neurologists and 11 cases with the IESS and ISSFA, as shown in figure 11.

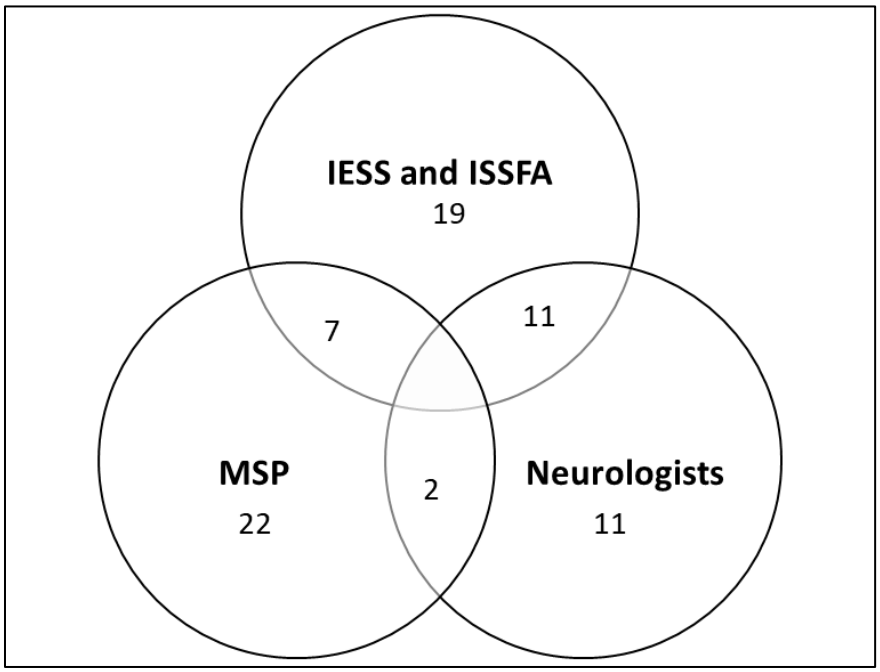

Figure 11. Number of ALS cases among different sources

Pathological antecedents

Comorbidities such as diabetes or hypertension were reported in 27.8% of cases. Familiar antecedents of neurological disease were reported in 5.8% of patients and these were: Alzheimer (n=1), Dementia (n=1), Parkinson's disease (n=1) and Stroke (n=1). History of smoking was reported in 13.9% of cases.

Familiar ALS was reported for 2.8% of cases.

V.5.2.1. ALS diagnosis

Electromyography (EMG) was reported on 69.4% of cases and a confirmation of ALS was reported in 84.0% of EMG reports.

In agreement to the classification performed by the neurologists expert according to clinical signs and symptoms reported on the medical files, 30.6% of cases were classified as clinically definite and 37.5% as clinically probable of the Airlie House criteria and 5.6% were classified as suspected according to the EEDC.

Neuro-imaging studies were only reported in 30 ALS cases Magnetic Resonance Imaging (MRI) was the most frequent exam (table 12).

Table 12. ALS diagnosis characteristics in Cuenca, Ecuador

ALS diagnosis	**Overall** (n= 72)
Airlie House criteria n (%)	
Clinically definite	22 (30.6)
Clinically Probable	27 (37.5)
Clinically Probable- Laboratory supported	7 (9.7)
Clinically Possible	12 (16.7)
Suspected (EEDC criteria)	4 (5.6)
EMG performed, n (%)	
Yes	50 (69.4)
No	22 (30.6)
Nerve conduction velocity, n (%)	
Yes	38 (52.8)
No	34 (47.2)
Neuro-imaging studies, n (%) ¶	
Brain MRI	9 (30.0)
Brain MRI; CT Scan	2 (6.7)
Brain MRI; Lumbar MRI	11 (36.7)
CT Scan	3 (10.0)
Lumbar MRI	5 (16.7)

EMG: Electromyography; MRI: Magnetic Resonance Imaging;
CT scan: Computerized Tomography scan
¶ Missing data: neuro-imaging studies (n=42)

V.5.2.2. Clinical characteristics

Median age at onset was 60.0 (IQR: 47.7 – 68.0) years with a median diagnostic delay of 10.0 (IQR: 6.5 – 16.0) months. More than a half of cases presented a spinal onset (64.2%) while bulbar onset was present in 35.8% of cases.

When comparing characteristics according to sex, no statistical difference was observed according to Airlie House criteria (p=0.582) (table 13).

Males showed a higher proportion of spinal onset (68.6%) while females showed a higher proportion of bulbar onset (32.1%) no statistical difference was observed (p=0.952) (table 13).

Median age at onset and at diagnosis was older for males (60 years of age) compare to females (58.5 and 59.5 years) (table 13).

Median diagnostic delay was longer among males (11.0 months) than females (9.0 months) but no statistical differences were observed p=0.842 (table 13).

Table 13. ALS clinical characteristics in Cuenca, Ecuador

Clinical Characteristics	Overall (n=72)	Male (n=38)	Female (n=30)	P value
Airlie House criteria, n(%)				
Clinically definite	22 (30.6)	13 (34.2)	8 (26.7)	
Clinically Probable	27 (37.5)	15 (39.5)	11 (36.7)	0.582[a]
Clinically Probable- Laboratory supported	7 (9.7)	4 (10.5)	3 (10.0)	
Clinically Possible	12 (16.7)	5 (13.2)	6 (20.0)	
Suspected (EEDC)	4 (5.6)	1 (2.6)	2 (6.7)	
Site of onset, n (%) [¶]				
Spinal	43 (64.2)	24 (68.6)	19 (67.9.)	0.952[b]
Bulbar	24 (35.8)	11(31.4)	9 (32.1)	
Age at onset[¶]				
Median (IQR)	60.0 (47.7-68.0)	60.5(47.7 - 68.2)	58.5 (46.7 – 64.0)	0.623[c]
Age at diagnosis[¶]				
Median (IQR)	60.0 (48.0-69.5)	60.0 (47.5 - 69.5)	59.5(47.7 – 68.0)	0.975 [c]
Diagnostic delay[¶]				
Median (IQR)	10.0 (6.5-16.0)	11.0 (6.0 - 16.0)	9.0 (6.5 - 16.0)	0.849[d]

[¶] Missing data: Site of onset (n=5); age at onset (n=15); age at diagnosis (n=16), diagnostic delay (n=16).
[a] Fisher exact test; [b] X^2; [c] Student test; [d] Mann Whitney

V.5.3. Management of ALS

Use of Riluzole was reported in 18 ALS cases (25.0%) (table 14).

Dysphagia was reported in 54.1% of patients, from which 16 cases have dietary consistency changes and 12 patients reported occasional chocking while a more severe dysphagia was reported in 11 cases (15.2%). However, in 41.7% of cases information of dysphagia was not reported in the medical files (table 14).

Gastrostomy was performed in only 7.0% and it was proposed in 15.3% of cases.

Regarding dyspnea, in 8.3% of cases no symptoms of dyspnea were observed, while low to middle efforts dyspnea was reported in 25% of cases and severe dyspnea in 6.9%. Missing data was reported 59.7% of cases (table 14).

Information on respiratory management was limited among the medical files, only 4.2% of patients were under non-invasive ventilation and tracheostomy was reported in one

case, oxygen was used more frequently (13.9%) but in 79.1% of cases no information of respiratory management was found (missing data) (table 14).

Multidisciplinary management was found in 43.1% of cases. Among the disciplines found, rehabilitation physician were the most frequent (36.1%), followed by psychiatry and pneumologist (13.9%), nutritionist was the less common (11.1%) (Table 14).

Table 14. ALS management in Cuenca, Ecuador

ALS management	**Overall** (n= 72)
Riluzole, n (%)	
Yes	18 (25.0)
No	54 (75.0)
Gastrostomy, n (%)	
Proposed	11 (15.3)
Performed	5 (7.0)
Missing	56 (77.7)
Respiratory, n (%)	
Oxygen	10 (13.9)
Non-invasive ventilation	3 (4.2)
Tracheostomy	1 (1.4)
Intubation	1 (1.4)
Missing	57 (79.1)
Multidisciplinary team, n (%)	
Yes	31 (43.1)
No	41 (56.9)
Nutritionist, n (%)	
Yes	8 (11.1)
No	64 (88.9)
Pneumologist, n (%)	
Yes	10 (13.9)
No	62 (86.1)
Rehabilitation, n (%)	
Yes	26 (36.1)
No	46 (63.9)
Psychiatry, n (%)	
Yes	10 (13.9)
No	62 86.1)

V.5.4. Discussion

This study reports clinical characteristics of ALS in a predominantly Admixed population in Cuenca, Ecuador. This study also, provide information of key aspects of the management of ALS among patients. This study highlighted the difficulties of ALS research in Latin American countries.

ALS diagnosis

According to a survey to describe the clinical practices on the diagnosis and management among neurologists in Latin America, ALS diagnosis criteria (EEDC, Airlie house) were known among neurologists. In this study we observed that in the clinical practice the categorization of this criteria was rarely used at least in Cuenca, as we only found 8 cases where this was reported. In addition when this was reported the evolution into other categories was not recorded.

According to our survey results (clinical practices) most of the neurologists considered electro diagnostic and neuroimaging studies as important complementary exams on the differential of diagnosis and confirmation. In this study, we observed that more than 30% of patients were lacking an electro diagnostic study and neuroimaging study. This could be a result to access to care, as these exams are normally made in the private practice or there are long waiting time in the public sector. However, this could be also due as this information was not recorded on the medical and we cannot be sure whether electro diagnostic studies were performed or not.

The limited access to electro diagnostic and neuroimaging studies could lead to longer diagnosis delay. In this study median diagnostic delay was around 10 months which is consistent with European countries (9), but shorter compared to another study in Ecuador by *Bucheli et al.* which reported a mean diagnostic delay of 15 months. Longer diagnostic delay has been observed in Latin American countries ranging from 12 months to 16 months (181).

This shorter diagnostic delay could be related to information bias, as we considered the date when the first sign or symptom of upper and lower motor degeneration was recorded on the medical file, and this could not represent the truth date of onset.

ALS clinical characteristics

Young age at onset and diagnosis has been reported in Latin American countries (124,127,134,218). Younger age at onset (median age at onset around 53 years) has been also reported in Africa (93). In contrast an older age at onset has been observed in ALS cases from European countries (around 60 and 65 years) (9). These differences of age at onset could be explained by different factors such as life expectancy, as Latin American and African countries have reported lower life expectancy compared to European countries. Differences of the age structure of the population should be also considered. However, this could be a result of selection bias due to the hospital-based approach of this study, as patients evaluated at referral centers have the tendency to be younger compared to the general population (70).

Bulbar onset was presented in 35% of ALS cases in Cuenca, this result is similar to other reports in Latin American countries such as Mexico (34.4% and 46.6%), Cuba (39.1%) and Uruguay (31.5% - 37%). This is also consistent with Western and Southern Europe countries (around 34%). However, this is a hospital-based study with a small sample size, and it is difficult to draw firm conclusions.

ALS management

Riluzole is highly used in European countries (210). On the contrary, a lower proportion of patients (29.4%) using Riluzole has been observed in Africa (93). Use of Riluzole was found in a low proportion of cases in this study. This results highlights the differences in access to Riluzole among countries, for instance in France Riluzole is free of charge (210), while in African countries this medication is extremely expensive and is not available among all African countries (93). According to the neurologist participating in this study, they explained that Riluzole is not systematically recommended to patients due to the high costs and as reported in chapter 4, this medication is not available in Ecuador and is not accepted in the list of necessary medicines from the ministry of health. Normally patients need to import this medicine from other countries which results in high costs for the patient. Which is similar to the challenges in access to care in Africa countries (213).

An evaluation of six ALS centers in France reported that a multidisciplinary team consisting in a neurologist, pulmonologist, speech therapist, gastroenterologist, dietician, social worker, psychologist, and occupational therapist was available among

almost all centers, in addition in 99.7% of cases appropriate communication was reached between the patient and this team (210). In contrast, an evaluation of nine center in Africa, multidisciplinary approach was mostly provided by a neurologist, physical therapist and in a lower proportion by respiratory physician and gastroenterologist, which is consistent with our findings (93). A multidisciplinary approach in Cuenca, Ecuador was found in a very low proportion of patients. There is a need to strengthen the approach from other physicians more specifically nutritionist and pneumologist as well palliative care, speech therapist among others. This results are in accordance to the results observed in our survey (clinical practices on the diagnosis and management of ALS chapter 4).

Respiratory and nutritional management is limited in Cuenca, the proportion of patients using non-invasive ventilation or with a gastrostomy is very low. This could be a result of the limitations of access to care and number of specialized physicians in the country, Cuenca is one of the three biggest cities in Ecuador, nevertheless most of this specialized medicine is located in Quito which shows the inequalities in access to care. ALS patients faced different difficulties, one of which is the reduced mobility and loss of autonomy. Travel time in bus from Cuenca to Quito is around 9 hours, and one hour flight which represents a major challenge for ALS patients leading to not receiving an appropriate management.

V.5.4.1. Limits and strengths

The strength of this work relies in the different sources used to identified ALS cases, diagnosis of ALS was based on the EEDC and Airlie house criteria performed by a neurologist ALS expert from our team.

Different limitations need to be acknowledge. First, a population-based study was not achieved, due to the large refusal of participation of neurologists, private insurance companies and private hospitals. Hospital-based studies have shown to present referral bias. In addition, hospitals from the MSP and IESS are the biggest referral hospitals, different persons from surrounding cities of Cuenca are referred to them, it is difficult to provide a well-definition of ALS cases, as the address of residence at the moment of diagnosis was not available. Information was available for different time periods, all these factors did not allow us to estimate ALS incidence rates in Cuenca.

Secondly, due to the retrospective data collection, information bias was present. There was an important number of missing data that do not allow us to provide reliable results of ALS clinical characteristics, survival, and management. The information provided on the medical files was limited, categorization according to a diagnostic criteria was not available, as well, age at onset, type of onset, familiar antecedent of ALS. Follow up information was also not available such as ALSFRS-R, weight and respiratory follow up. Most of this classification was performed according to the clinical history of signs and symptoms reported on medical files that does not provide a reliable source. For instance, for age at onset, we considered the age at the moment a sign or symptom was recorded in the medical file, however patients could have presented this symptom three or more months before requesting medical evaluation.

During this study we faced different challenges as already explained, an approbation from an ethics committee was obtained, however each hospital requested a second approbation by their own ethics committee which was time consuming. In some hospitals in order to have access to medical records a consent form by the patient was requested, in these hospitals access was not available. Another reason for not having access to medical files was in the hospitals were electronic data was not available. This challenges extent our study period and reduce the number of sources, exhaustiveness was not accomplished.

In order to identified ALS cases in the IESS and MSP hospitals we used the ICD-10th revision codes for ALS G12.0 and G12.2. However, we identified misclassification of cases in the MSP hospital. Only 37 medical files were found with the codes G12.0 and G12.2 from which only 4 were ALS cases. We identified that ALS cases were coded using the M34.0 code (progressive systemic sclerosis) 44 medical files were found from which 24 cases were ALS. Due to the Covid-19 pandemic we did not have the time to perform this searched in the IESS hospital. This represents a major problem for our study as the proportion of misclassified cases is unknown.

V.5.5. Conclusion

This study provide a description of ALS clinical characteristics in Cuenca Ecuador such as a young age at onset and diagnosis compared to European and North American countries. Nevertheless, different methodological issues make it difficult to draw firm conclusions. This study showed the different challenges in ALS research in Latin America to perform population-based studies, which could explain the predominance of Hospital-based studies in the region. However, this studies could be associated to different bias leading to important implications on ALS research such as lower case-ascertainment, and reliable assessment of clinical characteristics and survival that could explain ALS differences among geographical areas. There is a need for further studies performed in a prospective design and population-based approach to provide reliable evidence on ALS and future comparisons.

Chapter VI. General discussion

VI.1. Summary of thesis works and implication of findings

ALS heterogeneity among epidemiological indicators, clinical characteristics and frequency of genetic mutations has been observed between populations. Different researchers have proposed that certain populations could present a higher risk in developing the disease, as homogenous rates have been observed in countries with a common ancestral origin, but this has been showed only on populations from European origin. Studies in multi ethnic population in United States have showed higher incidence and mortality rates among non-Hispanic White populations compared to Hispanic populations. This has suggested that Caucasian populations could have a higher risk in developing the disease compare to other ethnics. Nevertheless, there is an underrepresentation of ALS literature in major regions of the world such as Asia, Africa and more specifically Latin America.

This thesis provides a systematic review of and three original investigations, of ALS in Latin America. Two original studies were performed in several Latin American countries and one study was performed in a specific country namely Cuenca, Ecuador. Throughout these studies we offer a wide description concerning ALS epidemiology and clinical characteristics in Latin America. More over a description of the clinical practices among Latin American neurologist on the diagnosis and management of ALS is provided.

Article 1: Amyotrophic lateral sclerosis in Latin America: a systematic review

Different studies have addressed ALS variability around the world. Global epidemiological studies have reported lower incidence rates for Latin America and the Caribbean, however these observations were based only in few Latin American studies. This under representation of Latin American studies could be explained as the quality of studies in the region is debatable or they present biases such as, selection bias due to the hospital-based approach, while international studies have evaluated worldwide incidence using high quality studies following a specific methodology, and the number of studies using this methodology are limited in Latin America.

Differences among clinical characteristics and frequency of genetic mutations have been also observed. Younger age at onset, lower proportion of bulbar cases and a lower proportion of C9orf72 repeat expansion has been showed in Latin American ALS

cases compared to European countries. But then again, these have been observed in limited studies.

Latin America is an interesting region for ALS research due to the ethnic diversity, a clear description of ALS epidemiology, clinical characteristics, and frequency of genetic mutations could provide important insights of ALS heterogeneity and the risk among certain populations. More over a description of the methodology of ALS studies in the region could help us identify the gaps and improvements for further research in the region. With this in mind we performed a systematic review of ALS literature in Latin America.

For this systematic review we included all observational studies performed in Latin American countries focusing in ALS epidemiology (Incidence, prevalence and mortality), clinical characteristics (age at onset and diagnosis, sex ratio, type of onset, form of ALS), Frequency of genetic mutations and survival. We also reported ALS distribution among ethnic groups in the region and we provided a description of the methodology followed by each study.

We found that ALS occurrence (incidence and mortality) was lower compared to reports in Europe and North America, and the rates were heterogeneous among Latin American countries (crude incidence rates of 0.2 to 3.1 per 100,000 PYFU). .

ALS cases in Latin America were predominantly male (sex ratio ranging from 1.0 to 2.8) and exhibit a younger age (mean age at onset 47 years to 58 years) compared to Europe and North America (mean age at onset between 63 and 65 years), bulbar onset proportion is similar to reports in other countries (35% to 46%), however Brazil showed a lower proportion (< 20%). C9ORF72 repeat expansion was the most frequent and was mostly found on Caucasian cases, the proportion of this mutation was lower compared to studies in Europe (1.7% of Cubans compared to 9.9% of Irish patients). ALS survival was variable, some studies reported a long survival (mean survival since onset 45 to 68 months) compared to Europe (median survival since onset 25 to 30 months).

However, studies performed in Latin America were mostly hospital based and performed in ALS or Motor neuron disease referral clinics. Retrospective data from hospital discharge data and medical files was the most common source, which are

associated to selection bias. Population-based studies were limited and were mostly performed using mortality data from national death registries.

Variability of ALS among ethnic groups was also found in Latin America. Studies in Cuba, Brazil and Ecuador found significant differences among ethnic groups, a higher mortality in the Caucasian population of Cuba was observed compared to Admixed and Blacks, similar results were found in Brazil.

This study provided important insights of a lower ALS occurrence, a younger age at onset, a lower proportion of C9orf72 in Latin America compared to Europe and North America. It also showed that ALS occurrence was variable among ethnic groups. However, we found that the methodology followed in each country was also heterogeneous and there were some issues, like a predominance of hospital based studies that make it difficult to compare to other studies in other regions as studies in European and North American countries are mostly population-based studies.

Article 2: ALS mortality in Latin America

Our previous systematic review, we found that studies in Latin America support a lower ALS occurrence, also differences among ethnic groups were reported. To best of our knowledge, there are no population-based registries for ALS in Latin America. On the other hand, the national mortality registries are a valuable source of information as every person that dies in a country should be registered by death certificates providing therefore a population-based source to investigate mortality. Due to the fatal outcome of ALS, mortality rates have been used as a proxy of incidence as we could assume that all ALS cases will eventually be identified in the mortality registers. Given the scientific interest to provide epidemiological data of ALS in Latin America, we performed a meta-analysis using population-based data from 10 Latin American countries. In addition, sources of heterogeneity were explored.

National mortality registries were used to identify ALS deaths through the ICD codes from the 9th and 10th revision for each country. A well-defined population at risk and from the same source (United Nations yearbook) was used for each country. Sex-and-age standardization was performed using the US 2010 population as reference.

To explore heterogeneity information was obtain from the same source for each key factor; proportion of Caucasian population was obtain from the same source (Latino Barometro) for each country. The importance of using the same source for the

Caucasian population was because this information is not provided by all countries, and the definitions of “Caucasian” varies among countries. Income classification according to the world bank, was performed using the mid-year period for each country, as different time periods were provided by each country, and income classification varies from each year. The age profile of ALS mortality was also determined.

Pooled standardized mortality confirm a lower ALS occurrence in Latin America compared to Europe and North America. Age-and-sex standardized mortality to the US 2010 population was 0.62 per 100,000 PYFU (95%CI: 0.49 -0.77). High heterogeneity was found in the region, sub-group analysis showed that countries with a higher proportion of Caucasian population presented a higher mortality rate compared to countries with a lower proportion of Caucasian population. Higher mortality rate was observed among upper-middle-income countries compared to lower-middle-income. The age profile of ALS mortality in the Latin America population suggest also a younger age at onset compared to Europe and North America.

This study confirmed a lower ALS mortality in Latin America, it also showed that ALS heterogeneity could be explained by socio-economic factors which was also showed in the Global Burden of Disease study, but also heterogeneity could be related to ancestral origin. Which supports the hypothesis of a higher risk among the Caucasian population.

Article 3: Clinical practices on the diagnosis and management of ALS among the neurologists in Latin America.

In order to have reliable ALS epidemiology data, it is of major importance to assure a common definition. Before the development of El Escorial criteria in 1994, ALS heterogeneity could be partly explained by different diagnosis. Since 1994, different revisions have been performed to the El Escorial, different sensibility has been observed between each diagnostic criteria. These differences among criteria could lead to potential variability.

Variations of ALS clinical characteristics and survival has been also observed among geographical areas, which could be explained by differences on diagnostic delay, for instance a longer diagnostic delay could lead to an older age at diagnosis and longer survival. ALS management can differ according to the different health systems, in countries where Riluzole is available and free of charge, it would be expected to

observe longer survival compare to other regions where the use of this medications is more restricted.

In this context we performed a survey among different Latin American countries to describe the clinical practices on the diagnosis and management of ALS among neurologist in the region.

We performed international collaborations with key neurology institutions in Latin America such as the PAFNS, which has a representation among 18 neurology societies in Latin American countries, and a network of neurologist in the region (IENT network).

A survey was performed based on the European and American guidelines. Diagnosis in Latin America was based on the Airlie House criteria, clinical evaluation and electromyography. Communication of diagnosis with the patients and a member of the family was preferred. Riluzole was prescribed by 80% of the neurologist, however some differences were observed between countries, all the neurologists from Argentina prescribed Riluzole while none of the neurologists in Peru prescribed it. This differences could probably due to the difficulties in access to Riluzole. Pneumologist and nutritionist referral was preferred to handle respiratory and nutritional complications, nevertheless working with other disciplines should be strengthened. Follow up by a palliative care team and discussion of terms in the end of life should be improved. We found, that a high proportion of neurologists with a neuromuscular sub-specialty participated in this survey which represents a selection bias found in our survey. A higher compliance with international guidelines was associated to neuromuscular sub-specialty.

This survey identified that neurologists in Latin America used the same diagnostic criteria as in European and North American countries. This survey also identified treatment gaps, an integration of a multidisciplinary team in ALS management should be strengthen. Latin American health systems faced different challenges which could make ALS management more difficult. There is a need for further studies with international collaboration to improve ALS management.

This study help to reinforced neurologists knowledge on ALS management according to international guidelines, which at the end can help improve quality of life of ALS patients.

Study 4: A pilot study in Cuenca

Lower rates of ALS incidence and mortality have been observed in Ecuador, a country with a predominantly Admixed population. ALS research is limited in the country, only two epidemiological studies have been performed. The methodology used in both publications make it difficult to draw firm conclusion. For instance, the hospital-based approach in the study by *Bucheli et al.* represent referral bias and other issues like, a non-defined population at risk, were found in the estimation of incidence rates. A population approach was conducted by *Luna et al.* using mortality data to estimate ALS mortality. Information of ALS clinical characteristics, survival and management has not been studied in the country.

In order to estimate ALS incidence rates and describe ALS clinical characteristics, survival and management, we performed an observational study in a predominantly Admixed population in Cuenca Ecuador.

Nevertheless, a population-based approach was not achieved, and for this reason incidence rates could not be assessed. Different challenges were found during this study, that did not allow us to estimate survival rates, and that bias our results of clinical characteristics.

A younger age at onset and diagnosis were also observed in Cuenca Ecuador similar to the results of other Latin American countries. Multidisciplinary approach in ALS cases was limited, and was mostly composed of rehabilitation physician. Respiratory and nutritional expertise was rarely reported. However due to the design of our study it is difficult to draw firm conclusions.

This study highlights the difficulties of ALS research in Latin America more specifically in performing population-based studies using multiple sources of case ascertainment. Several aspects of ALS research were not observed on medical files such as a classification according to a diagnostic criteria. We did not find information regarding ALS patients follow up such as: staging criteria, ALSFRS-R, weight or respiratory follow up. Further improvement is needed, as this characteristics could be of importance to promote ALS international research, which could benefit ALS patients in Latin America with inclusion of clinical trials.

VI.2. Potential factors associated to ALS occurrence in Latin America

We have showed evidence confirming a lower ALS occurrence in Latin America, and differences of clinical characteristics, genetic mutations and survival compared to Europe and North America. Differences of ALS have been also observed among ethnic groups in the region, suggesting a higher risk in Caucasian populations, supporting the hypothesis that ancestral origin could play a major role in ALS pathogenesis. Regardless, ALS epidemiological and clinical variability could be explained by other potential factors such as methodological issues, health care access and socio-economic status. Other determinants of risk such as environmental factors and genetic mutations should also be taken in consideration

VI.2.1. Methodological issues

In order to provide reliable comparisons of ALS epidemiological and clinical characteristics, studies should follow standard methodological framework. In this section, we describe several methodological designs and their implications on ALS research.

Study design

A retrospective design is one of the most common design used in research, as this is a practical approach in collecting information from hospital discharge data, medical records and databases. Nevertheless, this is limited by the quality of record and missing information. Systematic reviews of ALS global epidemiology have observed that prospective studies have shown higher estimates compare to retrospective studies (80,85). This could be explained as retrospective designs depend on the quality of the medical recorded information which can affect a well case identification and categorization of ALS patients according to diagnostic criteria. While prospective design provide accurate and standardized data and the long term collection helps categorized the disease progression (80,85).

Prospective designs implies a continues long-term data collection which represents an important logistic and specific funding, due to the different challenges of Latin America health systems, international collaboration could provide important benefits to improve ALS research in Latin America.

Hospital-based studies versus population-based studies

Hospital-based studies have been related to different bias, when compare to the general population, patients of referral centers have been younger and with a high proportion of spinal onset and familial ALS (70). This could have major implications in comparisons between countries. Patients with ALS characteristics such a young age at onset and spinal onset have been showed to have longer survival rates (59), leading to differences among geographical areas, which could be a result of referral bias.

Population-based studies with a recruitment of cases among multiple sources to assure complete exhaustiveness of a define geographical area has been recognized as gold standard methodology in ALS research (12). Population-based approach is the cornerstone to provide reliable data of a population and comparisons to other populations. ALS is a rare neurodegenerative disease, the use of multiple independent sources is fundamental to optimize case finding and allow us to provide precise estimates of epidemiological indicators (10).

The impact of methodology can be observed in the results in our systematic review, the country that reported the highest incidence rate was the study in Uruguay. Which is the only study that used different sources of case ascertainment and followed a prospective design. However, we need to acknowledge that Uruguay is high income country and there is a predominance of Caucasian population.

Case exhaustiveness

Another important characteristics to provide reliable information is case exhaustiveness. In France, a study performed in an ALS referral center estimated a crude incidence of 2.5/100,000 inhabitants for the Limousine region (133). A successive study years later, from a population-based register using information from three different sources (ALS referral center, public and private hospitals and health insurance data) in the same region, estimated a crude incidence as high of 3.19/100,000 PYFU and a standardized incidence of 2.58/100,000 PYFU. Using capture and recapture analysis the exhaustiveness of the register was estimated at 98.4% (122). Capture-recapture analysis have helped in estimating the number of missing cases, in another study in the same region, ALS mean annual incidence was reported as high of 4.9 per 100,000 PYFU (243).

Population structure

In order to provide reliable comparisons, we need to take in consideration that ALS is an age-related disease, with higher incidence among the 60 and 70 years of age in European population. The age and sex structure of populations varies across countries, and could affect ALS epidemiological indicators. To control this impact standardization using a common reference population can help provide reliable comparisons (12). US 2010 population is a common reference population used in several studies, in order to provide congruence we used this population in our meta-analysis of ALS mortality.

VI.2.2. Socio economic status

Differences on socio-economic status should be taken in consideration as potential factors of ALS variability. Different studies have shown that higher income countries have reported higher ALS estimates. This could be a result of a longer life expectancy in high income countries (244), and a better access to health (245).

A recent systematic review of ALS epidemiology reported higher crude prevalence (4.94/100,000 population) and incidence (1.79/100,000 PYFU) among developed countries compared to developing countries (prevalence: 2.15/100,000; incidence 0.63/100,000 PYFU) which could be partly explained by the differences in aging population, resulting with a higher prevalence and incidence in the elder population in developed countries (246). Some limits of the study should be discussed, there was an underrepresentation of studies in developing countries, for estimating prevalence, only five studies were taken in consideration for developing countries compare to 51 studies in developed countries; and for incidence estimates only nine studies of developing countries were used compared to 97 studies in developed countries (246).

A study in South Korea using nationwide data, analyzed the relationship between ALS and socioeconomic status, income was classified according to the income-based insurance contribution level, and highest income was considered as the population that paid the highest insurance. For the 2011-2015 period, the population with low income showed the higher incidence rates ranging from 1.19 to 1.53 per 100,000 population, compared to the high income population which ranged 1.09 -1.47 per 100,000 population; while the middle income group reported the lowest incidence rates 0.85 to 1.14 per 100,000 population (193)

The Global burden of disease study (GBD), coordinated by the Institute for Health Metrics and Evaluation estimated the burden of motor-neuron diseases from 195 countries and territories. In order to evaluate the development status and health outcomes of countries, GBD researchers used the Socio-demographic Index (SDI), which is a composite average of total fertility rate under the age of 25, mean education for ages 15 and older, and the ranking of the incomes per capita. This index is expressed on a scale from 0 to 1, a minimum level of development relevant to health would be around 0, and a maximum level near 1 (247). Considering 21 GBD regions in 2016, the highest age standardized prevalence was reported in high SDI regions such as high-income North America, Australasia and Western Europe. In contrast, high income Asia pacific, Southern Latin America, Eastern Europe and Central Europe reported the lowest age-standardized prevalence per 100,000 population (86). This results suggest that ALS heterogeneity could be explained by other factors rather than socio-economic status.

Our results of ALS mortality in Latin America reported a higher mortality rate on upper-middle-income countries compared to lower-middle-income countries. However, low mortality rates were reported in high-income countries, for instance Mexico and Ecuador upper-middle income countries reported one of the lowest mortality rates. While Costa Rica also an upper-middle income country, reported the second highest mortality rate (248).

Similar results are observed, according to the GBD 2017 SDI classification (249), Costa Rica which reported the second highest mortality rate is classified as middle SDI (0.66) along with Cuba (0.68), Ecuador (0.63), Colombia (0.63), Mexico (0.62), and Brazil (0.66). While Argentina, Chile and Uruguay are classified as high-middle SDI.

Socio-economic Status and ethnic groups

ALS differences among ethnic groups and SES in multiethnic populations from United States, may reflect under ascertainment of cases due to a poor access to health, lower insurance coverage and language differences among minorities (2,87). However, differences of ALS risk by SES could be also driven by factors associated to SES such as health behaviors and workplace exposures (2).

The National Longitudinal Mortality Study in United States, collected race/ethnicity and socioeconomic data to determine whether race/ethnicity and SES are associated to

ALS (2). Different indicators of SES were adjusted, as well the presence and type of health insurance coverage and indicators of immigrant status (birthplace). Adjusted models showed a lower hazard ratio among non-Hispanic Black, Hispanics and non-Hispanic other races compared to non-Hispanic White (2).

The study in Cuba, a country characterized by providing free access to health and no differences of SES among the population, reported higher mortality rates among the population identified as Caucasian compared to Blacks and Admixed populations (4).

The evidence suggest that SES could be an important factor, nevertheless, it does not explain the variability of ALS alone. Low income countries faced different challenges that could lead to a lower identification of cases leading to differences in ALS occurrence. Further studies are needed taking in consideration this factor.

VI.2.3. Life expectancy

ALS exhibits a specific age-related pattern, peak age-specific ALS incidence rates have ranged between 71.6 and 74.9 years in Europe, 77.4 years in North America and around 75 years in East Asia(13). Mortality rates in Latin America showed an age-related pattern, however peak standardized mortality was around 60 and 69 years age group.

Furthermore, mean age at onset has been reported between 63 and 65 years in Europe and New Zealand, and around 59 years in North America and East Asia (9). Younger ages have been reported in Latin America, reports from ALS studies in the region have showed mean age at onset ranging from 47.8 and 72 years.

This results suggest a younger age in Latin America ALS patients, which could be explain by differences in life expectancy at birth and the difficulties in access to health in the elderly population. Regression analysis have showed a positive correlation between mean age at onset and life expectancy ($r=0.91$, $p=001$) (250). Life expectancy is variable among regions, according to the World Bank in 2019, life expectancy at birth was 81.06 years for countries in the European Union, 79.12 years for North America, 76.26 for East Asia & the Pacific and 75.60 for Latin America and the Caribbean (251).

VI.2.4. Access to health

Differences of ALS across geographical areas and populations could be the result of under ascertainment of cases due to a poor access to health. As previously showed in this dissertation Latin America faces different difficulties in access to health.

According to the Global burden of Disease study 2016, national levels of personal health care access and quality can be approximated by measuring mortality rates from causes that should not be fatal in the presence of effective medical care (252). The health care quality and access index (HAQ index) was created with an overall scale from 0 to 100 (252). According to this index (figure 12), countries in the highest decile include most of European countries, Japan, Australia, New Zealand and North America, with the exception of Japan all countries have reported higher ALS occurrence (1). Similar results can be observed in Latin America, with Uruguay and Chile. However this is not the case for other countries with high HAQ index such as China, Israel and Cuba were lower ALS occurrence has been reported (1,4). Furthermore, Mexico, Ecuador and Colombia which have also reported low ALS mortality rates are classified in the same decile as Argentina and Brazil that have reported higher mortality rates.

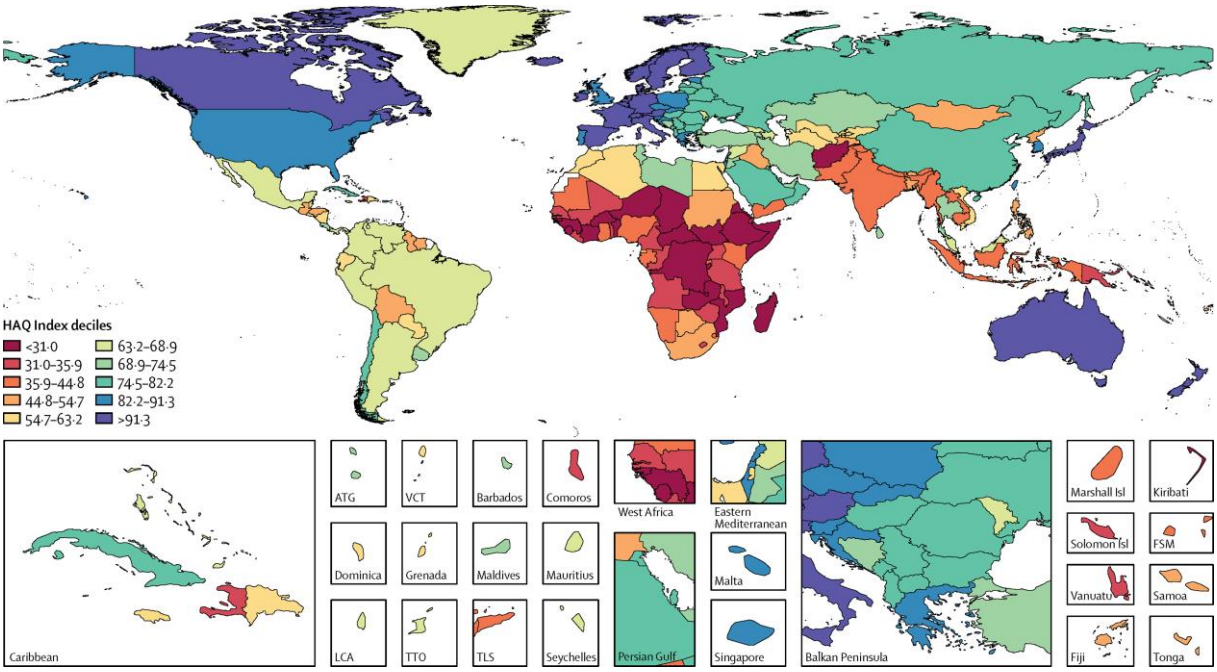

Figure 12. Geographical representation of HAQ index values by deciles.

Source: Fullman et al, 2018.

VI.2.4.1. Health care resources

Health care resources including infrastructure, material and human resources are fundamental for measuring quality of health care (108). Health workers are the fundamental pillar in providing health services and improving health outcomes. The World Health Organization considers having fewer than 23 health care professionals for every 10,000 inhabitants insufficient to provide adequate attention. The number of hospitals beds is one indicator of availability of tertiary attention Latin American and the Caribbean region shown significant deficiencies when compared to Europe or other high income regions (108). According to the OECD, on average, in Latin America there are two doctors per 1000 population and the number of hospital beds per capita is of 2.1 which is lower than the OECD average of 4.7 (109).

Medical resources are essential to ALS diagnosis and management. ALS is a complex disease, diagnosis is normally posed by neurologists and is based on clinical evaluation and complementary electro diagnostic studies and neuro-imaging. Countries that present less recourses could consequently report lower incidence as ALS cases would not be identified or would present long diagnostic delays. ALS management implies a multidisciplinary approach, countries with a lower rate of physicians could present a large proportion of patients without respiratory and nutritional expertise leading to a shorter survival.

Differences have been observed among income, the number of physicians and hospitals beds per 100,000 population for 2017 is higher among countries with a higher income compared to others. Nevertheless, Cuba an upper-middle income country have by far the highest number of physicians per 1000 population (8.29) more than the OECD average and higher than Chile and Uruguay and have showed a low ALS mortality rate.

Neurological resources

ALS is a neuro degenerative disease that poses a complex diagnostic that requires experienced neurologist to recognize signs and symptoms in early stages of the disease. There is an important shortage of neurologist around the world.A shortage of neurologist implies even longer waiting times and reducing access to care.

The department of mental health and substance abuse from the World Health Organization, produce a neurology atlas which is an assessment of the current health-

care resources around the world for people with mental, neurological and substance abuse. According to this, there are large inequalities in access to neurological care across different populations in particular in low and middle income countries (253). Median neurological workforce per 100,000 population in the America region (23 countries) was estimated at 2.3, from which median number of adult neurologist was 0.7 per 100,000 population. This gap is even greater when comparing by income, in lower-middle income countries, median neurological workforce was estimated at 1.4 while upper-middle-income countries was 3.1 and even higher for high-income countries, 7.1 per 100,000 population. Another difficulty in access to health, is the most of specialized care is often situated in the capital cities, in the America region 96% of countries have neurologists in the capital city, 78% of countries had a neurologist in other urban areas and only 17% of countries have neurologists in rural areas (253).

There is a shortage of neurologists in Latin American and the Caribbean and this ratio varies widely among countries in the region. The epilepsy report from the Pan American Health Organization (PAHO) in 2012, reported that the number of neurologists per 100,000 habitants in Central America and the Caribbean ranged as low of 0.01 in Haiti to 0.89 in Mexico, however this ratio was higher in Cuba 3.66 per 100,000 population. In South America, Bolivia and Colombia reported the lowest ratio 0.34 and 0.44 per 100,000 population, while the highest was reported in Chile (3.27), Uruguay (3.45) and Ecuador (3.53), no information was reported for Brazil and Argentina (254).

Sub-specialized neurological services are even more limited, according to the WHO report, from 105 countries participating only 20% of countries counted with specialist neurology units, 16% with neurorehabilitation services, and for other frequent neurological disorders only 18% of countries counted with stroke units and 16% with epilepsy surgery units (253).

Guidelines developed for neurological disorders help to provide evidence-based information for practitioners, according to the WHO, national guidelines help to develop quality standards and performance metrics for those providing and commissioning health and social care services. From 24 countries participating in the WHO report from the American region 58% of countries reported the existent of guidelines on the care of neurological disorders (253).

Latin American countries faced different challenges, especially low-middle income countries, difference of ALS occurrence could be a result of this large inequality.

ALS resources in Latin America

A report from the Esteban Bullrich foundation, a non-profit organization in Argentina, analyze the current public agenda of 18 Latin American and Caribbean countries, this report showed important differences among the countries.

As showed in table 15, only Brazil has an ordinance from the Ministry of Health that regulates ALS care protocols and treatment guidelines. This ordinance provides Riluzole and multidisciplinary consults free of charge. Brazil Ministry of health is one of the countries that foresees specific ALS financing. In terms of research, Brazil is one of the leading countries, as different research projects in different states of the country are planned. Also, this is one of the countries with the most ALS associations and different ALS referral centers.

ALS associations and referral centers are as well in Mexico, Costa Rica, Argentina Chile, Colombia and Uruguay, however this centers are mostly located in the Capital cities.

Table 15. ALS resources in Latin America

Subcontinent	Country	ALS research	ALS laws	MND laws	ALS associations	ALS referral center
North and Central America	Mexico	Yes	No	Yes	Yes	Yes
	Costa Rica	Yes	No	Yes	Yes	Yes
	El Salvador	No	No	No	No	No
	Guatemala	No	No	No	No	No
	Honduras	No	No	No	Yes	No
	Nicaragua	No	No	No	Yes	No
The Caribbean	Cuba	Yes	No	No	No	Yes
	Dominican Republic	No	No	No	No	No
South America	Argentina	Yes	No	Yes	Yes	Yes
	Brazil	Yes	Yes	Yes	Yes	Yes
	Chile	Yes	No	Yes	Yes	No
	Colombia	Yes	No	Yes	Yes	Yes
	Ecuador	Yes	No	No	Yes	No
	Paraguay	No	No	No	No	No
	Peru	No	No	Yes	Yes	No
	Uruguay	Yes	No	No	Yes	Yes

Source: Esteban Bullrich foundation

Motor neuron diseases cause severe disability with a high fatality rate and represents a high burden for families and health systems. The ageing population in Latin America is expected to increase as life expectancy in the region has increased around 4 years since 2000, and fertility has decreased from 2.6 to 2 births per woman (102). There has been a growth among the 65 and above years age group since 2010 to 2020, this age group increase from 6.87% to 8.97% of the total population (101). The burden of motor neuron diseases has increased from 1990 to 2016, and due to the increasing ageing population this is expected to increase even more (86). Therefore, the demand of people in need for neurological services will be important. The number of ALS cases is projected to increase around 50% in developing countries from 2015 to 2040, the weight of the disease will gradually shift from developed countries to developing countries (255). There is a need for future planning from governments and health-care providers to assure adequate and high-quality management for ALS patients.

VI.2.5. Ancestral origin

Our results have confirmed a lower occurrence of ALS in Latin America, and suggest that certain populations present a higher risk in developing the disease. The variability of ALS could be explained by the differences in socio-economic status and access to health. However, the results of Mexico, Ecuador and Colombia countries with a similar SDI as Costa Rica have reported the lowest ALS rates. Cuba a country with a better access to health have also reported a low incidence rate. Furthermore, countries from the Asian continent which present similar demographic characteristics (long life expectancy) and most of them high income countries, and with good access to health as European and North America countries, have presented lower incidence rates. For instance, Japan a high income county which provided subsidized public medicine and whose population has the longest life expectancy in the world showed lower incidence rates compared to European countries. This information could suggest that the differences of ALS might be due to ethnicities and ancestries rather than socio-economic status, under ascertainment of cases due to access to health and life-expectancy.

The interaction of genetic predisposition and ethnic groups has been found among other diseases. Factor V a genetic variant that increases risk of venous thromboembolic disease has been observed in 5% of white populations, while in East Asians and Africans this variant is rarely found. Similar observations has been found among susceptibility to Crohn's disease associated to the genetic variant CARD15 gene found in White patients but not in Japanese patients(256). Epidemiological variability has been also observed among other neurodegenerative disorders. In Alzheimer disease three different alleles —ε2, ε3, and ε4—have been described at the APOE locus on chromosome 19. A recent meta-analysis showed that the effect of APOE e4 on the risk for Alzheimer disease varies among ethnics, Japanese populations have shown a stronger risk (OR: 33.1, 95%CI: 13.6 – 80.5) than Caucasian populations (257). The reason of this variability is unclear, some researches have proposed there could be some genetic or environmental modifiers (256).

Homogenous epidemiological estimates has been observed among countries with a predominantly Caucasian populations and lower estimates of ALS occurrence have been observed in Admixed populations. It is hypothesized that European populations share common ancestral origins that share a variety of rare "at-risk" genes which can

increase susceptibility to the disease. Conversely, Admixed populations, could contain a wider variety of this at risk alleles leading to a protective factor with a lower risk in developing the disease (4).

A new study showed that genetic factors could play a major role in ALS pathogenesis, they found that approximately 17% of ALS cases could be due to a gene mutation (258). The heterogeneity of known ALS gene variants among populations could provide some important insights. Studies in South Korea have showed that the most common mutation among in the European population Co9rf72 was absent in the South Korean population as well as other common genes such as TARDBP and OPTN (193). Similar results were observed in Cuba, from 115 ALS patients only 5.2% had a known ALS genetic variant, the proportion of the C9orf72 repeat expansion in sporadic patients was significantly lower compared to the Irish ALS patients (Cuba: 1.7%, Ireland: 9.9%; p=0.004) (124) which are similar to studies in Brazil and Argentina (2.6%, 3.6% and 2.1%) (259–261). The proportion of C9orf72 repeat expansion in sporadic ALS observed in Latin American countries is higher than Asian countries (0.3%) (99), which could be associated to the high levels of European ancestry observed in Brazil and Argentina (table 5) hence an inheritability of the European ALS genetic background. These studies suggest that maybe other potentially ALS genes variants need to be discovered in Latin Americans populations.

Differences of clinical characteristics among populations could be also associated to genetic variants, for instance in Brazil a high proportion of a rare autosomal dominant subtype of FALS classified as ALS type 8 linked to the VAPB gene was identified in Southern Brazil (262). This mutation is highly prevalent in Brazilian FALS patients (259,263). ALS type 8 patients usually show a predominantly lower motor neuron phenotypes and prolonged disease coursed (263), as well a younger age at onset has been observed among ALS type 8 patients compare to non ALS type 8 patients (262).

The role of ancestral origin in ALS pathogenesis remains unclear, there is a need for further studies. This thesis have provided scientific evidence in an underrepresented region, with a large ethnic diversity. Our results support that there is a higher risk among the Caucasian population, however other factors such as Socio-economic status and access to health should be taken in consideration.

VI.2.6. Environmental factors

ALS etiology is still unknown, different research have shown advances on the implication of genetic factors in the pathogenesis of ALS, however the implication of environmental factors have been more difficult to assess. The difficulties in assess potentially modifiable risk factors could be due to different factors such as the difficulty in collecting enough number of cases to reach an adequate power, the poor representativeness of the source population and differences on the exposure definitions. In order to reduce these potential bias the EURO-MOTOR project was created with the aim to discover new causative and disease-modifying pathways to pave the way for novel therapies (264). The Euro-MOTOR project is a case-control study in three European countries (The Netherlands, Ireland and Italy) where ALS cases and controls have been identified in population-based design (264).

To our knowledge, studies evaluating environmental factors in Latin America have been performed.

VI.2.7. Gene and environmental interaction

Several authors have proposed a disease model in which ALS is a result of a pre-existing genetic condition present at birth and an accumulation through time of environmental risk (265). New research has proposed that ALS is a multi-step process in which several sequential steps are needed to develop the disease. Using a multistep model originally applied to cancer epidemiology in five European ALS registries (England, Ireland, Italy, the Netherlands and Scotland), researchers found a linear relationship between log incidence and log age at onset of ALS (r^2: 0.99) that is consistent with a multi-step process, an overall slope of 4.8 suggests that ALS is a six-step process (18). A similar study in Italy tested if whether carrying a large effect mutation might account for more than one step in the multi-step process of ALS model (266). A linear relationship (log incidence and log age at onset) was also found in the whole population with a slope of 4.65 consistent with the 6-step model. Analysis in cases that carried C9orf72 mutations showed a linear relationship and a slope estimate of 2.22 suggesting a 3-step process, similar results were found for SOD1 cases (2-step process) and TARDBP (4-step process) (266). This multi-step process was also confirmed in Japanese, Australian and South Korean ALS patients, similar slopes were observed for the three populations, 6-steps for the Japanese and Australian patients

and 5-steps in South Korea (267). Further studies in non-European and Admixed populations could help to identify gene-environment interactions among different populations and support this hypothesis.

VI.3. Amyotrophic Lateral Sclerosis in Asia and Africa compared to Latin America

We have showed the epidemiological differences of ALS in Latin America compared to European and North America countries, however other countries from other continents have also showed significant differences. In this section, we compare our results to those reported in Asian and African continents. The similarities and differences from these regions will provide further insights about ALS variability among geographical areas.

VI.3.1. Amyotrophic lateral sclerosis epidemiology in Asian and African continents compared to Latin America

ALS heterogeneity has been observed among subcontinents, lower standardized ALS incidence rates have been reported in countries from East Asia (China and Japan) with a pooled estimate of 0.83; 95%CI: 0.42 – 1.24 per 100,000 PYFU, and in South Asia (Iran) 0.73; 95%CI: 0.58 – 0.89 per 100,000 PYFU compared to North Europe with a pooled standardized estimate of 1.89; 95%CI: 1.46 – 2.32 per 100,000 PYFU (1). These results were reported from population-based studies using different sources of case ascertainment.

Recent studies in China have reported lower rates, a retrospective study in 2016 using data from Urban employee and residence insurance which covers around 95% of the China population reported a crude incidence of 1.65 per 100,000 PYFU (95%CI: 1.33 – 2.01), standardized incidence based in the 2010 Chinese population was 1.62 per 100,000 PYFU (95%CI: 1.58 – 1.67) (268).

Another study in Beijing from 2010 to 2015, using two different sources (Peking University third hospital and ALS care centers) estimated a crude annual incidence of 0.8 per 100,000 PYFU (95%CI: 0.7-0.9) (195).

Using nationwide health dataset in South Korea from 2011 and 2015, ALS mean annual crude incidence was 1.20 per 100,000 PYFU (95%CI: 1.10-1.29), age adjusted incidence to the WHO 200-2025 world standard population was 0.88 per 100,000 PYFU (95%CI: 0.81-0.95) (193), which was also consistent with another 5-year cohort for the same period study in South Korea using national health insurance data which reported a crude ALS incidence of 1.68 per 100,000 PYFU (269).

ALS incidence has also been low in other Asian countries, a prospective study in a multidisciplinary ALS clinic in Malaysia estimated a crude ALS incidence of 0.53 per 100,000 for 2019 (270). A retrospective study in Israel using healthcare services databases estimated an average annual incidence of 1.8 per 100,000 population (271).

ALS standardized incidence rate to the 2000 US population in Japan was estimated at 2.3; 95%CI: 2.2 – 2.4 per 100,000 people, from 2009 to 2010 (272). This was a retrospective study, information was collected from a nationwide survey sent to all 47 prefectural offices(272). Incidence standardized rates of Japan has been higher compared to South Korea but lower compare to Australia (2.9; 95%CI: 2.5 – 3.4) (267).

Epidemiologic ALS studies in Africa are limited, a recent 4-year prospective incidence study in South Africa, using two sources (public ALS clinics and private neurologist) and the capture recapture method, estimated a crude annual incidence rate of 1.08 (95%CI: 0.94 – 1.24) per 100,000 person-years, ALS incidence rate through the capture-recapture method was of 1.11 (95%CI: 1.01 -1.22) per 100,000 person-years. Adjusted ALS incidence to the 2010 US population, was 1.67 (95%CI: 1.09 – 2.26) per 100,000 person-years (89).

Variability of ALS occurrence has been observed within Asian countries, lower rates have been observed in China, Beijing, South Korea, Malaysia and higher rates in Japan. Reports from Beijing, South Korea and Malaysia were similar to ALS mortality rates in Latin America. While the incidence reported in China, Israel and Japan were higher than incidences in Latin America, this could be explained by differences in access to health, information of health insurance was used among these studies, and a coverage of all the population was assured.

Incidence rates in South Africa were higher compared to Latin America, which could be explained by differences in the methodology of the studies, the capture-recapture method was used in the South African study which has been showed to assure a complete exhaustiveness. Nevertheless, higher mortality has been observed among Black populations, in the study by *Zaldivar et al.* ALS mortality rate was higher in the Black population, 0.87 per 100,000 PYFU (95%CI:0.62 – 1.17) compared to the Mixed population which was 0.55 per 100,000 PYFU (95%CI: 0.40- 0.72).

Incidence rates in Asian and African countries are still lower compare to European and North American countries. This evidence supports ALS heterogeneity among populations with a higher risk among the Caucasian populations.

VI.3.2. Clinical Characteristics of ALS in Asian and African continents compare to Latin America

Age at onset

ALS median age at onset in Asia countries has been, 46.2 years in India (273), around 51 and 53 years in China (195,274), 57 years in Malaysia (270) 61.2 years in Japan (275). Younger age at onset has also been observed in African countries, in the TROPALS study median age at onset was 53 years, significant differences were observed with a younger age reported in Western Africa (47 years), Northern African (54 years) and an older age in Southern Africa (59.5 years) (p=0.0003) (93). This was consisted with a prospective study in South Africa which reported a median age at onset of 58 years (89). The presence of a juvenile form has also been observed in Africa (92).

Younger age at onset has been also observed in Latin American countries, this could be explained by differences in life expectancy. According to the World Bank life expectancy at birth in 2019, in India and African countries (around 65 to 70 years) has been shorter than China, Malaysia and Latin American countries (around 76 years). While in Japan a longer life expectancy has been reported (84 years).

Younger age at onset could be also explained by referral bias, as younger age has been observed in hospital-based studies. Information from India came from a retrospective study performed in a single neurology center (273), in Malaysia a prospective study was performed in an ALS multidisciplinary clinic (270). Data reported from Africa was a hospital-based study (93). In Latin America younger age at onset has been observed in hospital-based studies. On the contrary, the study in Japan was a prospective multicenter study in 30 neurology facilities of Japan (275).

Age at onset differed in Germany and China, older age at onset was observed in Germany (66.6 years 95%CI: 65.7-67.5) compared to China (53.2 years 95%CI: 52.0-54.5), however data from China was from ALS clinics in Beijing and from national registry in Germany (274).

Significant differences were observed in a study that compared ALS patients from South Africa and Portuguese ALS patients. Median age at onset was younger in South African patients (59.4 IQR: 50.5 – 69.4 years) compared to Portuguese (66.4 IQR: 58.3 – 73.3 years) ($p< 0.001$) (276).

Significant differences were also observed among ancestral origin, in the prospective study in South Africa, a younger median age at onset was reported in the African ancestry population (47 years) compared to the European ancestry population (65 years) ($p< 0.001$). Differences were also reported between the Mixed ancestry population (54 years) compared to the European ancestry ($p< 0.001$) (89).

Site of onset

Lower incidence of bulbar onset has been reported in East Asia (0.15; 95%CI: 0.12-0.18) and Iran (0.11; 95%CI: 0.07 – 0.17) compared to subcontinents in Europe (Northern Europe 0.86, Eastern Europe 0.73, Southern Europe 0.68) (9). Proportion of bulbar onset among Asian countries varies between 20% and 30% (270,273,277). Higher proportion of bulbar onset was observed in Germany (35.9%) compared to China (22.8%) (274), but another study found that the prevalence of bulbar onset between these two countries was equally distributed (91).

Proportion of bulbar onset in Africa was 22.7% in the TROPALS study and a similar proportion was found in a latter study in South Africa (19.7%) (89,93). When compared, the Portuguese population showed a higher proportion (28%) than the South African population (18%) ($p=0.044$) (276).

Proportion of bulbar onset has been reported between 30 to 40% in Latin America studies, however most of the studies in the region has been hospital-based data, which present selection bias with a lower proportion of bulbar onset. However, higher proportion of bulbar onset has been observed in Northern Europe, this differences could be related to the frequency of genetic mutations, for instance C9orf72 has been common in European countries, this mutations has been showed to present a bulbar onset (278). While in Asian countries SOD1 mutation is more common (99). Studies in Latin America, have reported a low proportion of C9orf72 (124).

The differences of site of onset among geographical areas is not clear, further studies are needed in different populations to clarify these doubts.

Survival

Survival of ALS varies widely, in Asian countries survival since onset varies from 30 months in Malaysia (270) to around 50 months in Korea and China (193,195,274). While in Africa shorter survival has been reported in Africa (93). This differences could be explained by younger age of onset and differences in management and access to health.

VI.4. Ancestral origin Limitations

One of the major limitations in the assessment of ancestral origin and ALS, is the lack of a uniform definition of it for biomedical research. Race consist of personal self-identification and group identity facets on the basis of physical characteristics such as skin color or hair texture(279). While ethnicity, refers to cultural characteristics as language, religion, history and shared origin (279,280).

Race and ethnic definitions are heterogeneous among countries as there is no international consensus on the topic. The US census 2000, obtains this information through the respondent's self-identification. Individuals are allowed to choose multiple responses to the race item (White, Black or African American, Asian and Native America), while ethnic classification is based only in Hispanic or non-Hispanic (280). On the contrast, in Europe "the term race" is usually not considered, for instance, the French council forbid the processing for measuring personal data revealing directly or indirectly the racial or ethnic origin of people (281). In most European countries such as, Germany, France, UK and Sweden usually this information is operationalized as migration background referring usually to the country of birth.

In Latin America, racial and ethnicity identification is not performed systematically among all Latin American national statistics. This identification is relatively new and varies among the different census of each country. In the 2011 national census of Uruguay, race is based as social constructs, information was collected as the respondents self-identification to the question which ancestry you believe you are (White, Black, Asian, Indigenous or other)(282). In Ecuador 2010 national census, ethnicity is based on the self-identification on cultural and traditional customs(188). On the contrast in Cuba this classification is based on skin color (189). On the contrary, in the national census of Mexico, there is no information of race or ethnic, but a classification according to the linguistic language talked is performed (283). In Argentina, only statistics of Indigenous populations and Afro descendants populations is collected (284).

Race and ethnic classifications are normally used as proxies for ancestral origin. Race and ethnic are social constructs used to categorize seemingly distinct populations, and are not an objective assessment of ancestral origin. A study inferred the genetic ancestry of 5,269 self-reported African American, 8,663 Latinos and 148,789 European Americans across United States to understand the relationship between genetic

ancestry and self-reported ethnic and racial identity (285). Among the Latino population they found that this group encompass all possible combinations of African, Native American and European ancestries. On average they estimated that Latinos in the United States presented 65.1% of European ancestry, 18.0% of Native American ancestry and 6.2% of African ancestry. When stratified by self-reported population, they found that Latinos that reported being Hispanic, as well Mexican or Central American carry more Native American ancestry than other Latinos. Those that self-reported being Black, Puerto Rican or Dominican have higher African ancestry. Latinos that self-reported as White, Cuban or South American have higher levels of European ancestry (285). Which is consistent to the reports of self-identified ethnic from the Latino Barometro group and to the hypothesis of a higher risk among the Caucasian population as higher mortality was observed in Uruguay, Chile, and Argentina all South American countries with a more important proportion of European origin.

There is a need to use accurate and standard methods to assessed ancestral origin. An objective approach can help elucidate the role of ancestral origin and ALS, and it can also provide important insights between environmental risk and genetics. The study of differences among groups represent some conflicting matters. Many researchers have argument that the use of racial or ethnic categories should be reduced or eliminated, as this categorization could reinforce health inequities (286). Nonetheless, the benefits of evaluating the variations among populations could help us understand this fatal neurodegenerative disease. The identification of genetic and environmental risk factors would provide opportunities to develop preventive strategies among populations that present a higher risk. In addition, evaluating the severity of the disease and the responses to treatment could improve health outcomes and move forward to a personalized medicine.

VI.5. Perspectives

Through this thesis we have showed that ALS research in Latin America is limited. There are different challenges to overcome in Latin American countries, such as a double burden of disease which leads to a lower financing for rare neurodegenerative disease as this are not considered a public heath priority. The limited number of neurologist, the lack of healthcare structures and administrative health data make even more challenging ALS research.

To clarify ALS variability among geographical areas and populations, epidemiological studies with standard methodology is indispensable to provide reliable data. This information could help us move forward in the subject of ALS pathogenesis. In addition, accurate epidemiological and clinical data can help strengthen health systems by identifying the needs among ALS patients and the difficulties in access to health.

Different initiatives have started in Latin America, through this thesis we identified few epidemiological studies that followed a strong scientific approach and provide reliable data that can help clarify ALS. Also, along the years we observed that creation of ALS referral centers increased in the region as well of ALS associations. These could be the starting steps to move forward and improve ALS research in the region.

Epidemiological studies of ALS in Latin America

Some projects have started in Latin America, in Brazil the revELA project that emerged as a series of assistive technologies to improve quality of life in ALS patients was developed by a partnership between the Laboratory for Technological Innovation in Health at the Federal University of Rio Grande do Norte (LAIS/UFRN) and the Ministry of Health (287). This project lead to the creation of an ALS population-based registry in Brazil in 2020 with the aim to determine ALS incidence and prevalence in Brazil, and to describe demographic factors associated to the disease. Registration of ALS cases will be performed by participating neurologists and patient's self-registration (288).

In Argentina an ALS registry (ReNELA) was created in a pilot study between 2015-2016, this registry is based on the model of the CDC National registry of ALS in United States (289). This registry is coordinated by the Ministry of health of Argentina, the National Service of Rehabilitation (SNR), the ALS association and members of the Argentinian Neurology Society. The innovation of this registry is that persons living with ALS and, or their families can add their information into the registry. As well the

physicians and health workers implicated in the study. The complete protocol of this registry can be found in the ALS association website (290).

International collaborations

In order to test the hypothesis of differences of ALS risk and phenotype among populations of Admixed ancestry, The Latin American Epidemiology Network of ALS (LAENALS), will perform comparative analysis between large scale population-based data from three Latin American countries Uruguay, Chile and Cuba. These comparisons will provide important insights towards new therapeutic approaches and personalized medicine. The difference in the level of admixture between the populations will also provide insights to clarify the role of ancestral origin and ALS (291)

Epidemiological studies of ALS in Ecuador

The team EpiMACT INSERM UMR 1094, developed a robust research project in Ecuador. First data have been reported in Ecuador from a population-based study estimating mortality rates, and other have been adopted through this thesis including a description of ALS clinical practices on the diagnosis and management among neurologist in Latin America. Followed by, a retrospective study describing ALS clinical data (Cuenca study). In the near future, a pioneer prospective study will be implemented, with the aim to describe ALS clinical characteristics, phenotype and genetics. The innovation of this project lies on the description of the frequency and type of ALS genetic mutations in Ecuador, and the identification of the ancestral geographical origin of the genome regions associated with ALS.

This study will provide original information on the clinical and genetic profile of ALS patients in Ecuador which could help improve the management of ALS patients in the country.

Conclusion

The works of this dissertation have contributed to the improvement of the knowledge on the epidemiology of Amyotrophic Lateral Sclerosis in Latin America. This thesis provides original studies conducted evaluating numerous parameters such as the epidemiology of ALS, clinical characteristics, the frequency of known genetic mutations and the clinical practices among neurologist of the diagnosis and management of ALS. The original studies presented in this thesis contribute to improve our understanding of ALS variability among geographical areas and populations. Our findings supports the hypothesis that some populations could present a higher risk in developing the disease.

A systematic review of ALS research in Latin America, suggested a low ALS occurrence in the region, heterogeneity of ALS among Latin American countries and among populations. It also showed a younger age at onset and provided data on the frequency of genetic mutations in Latin America.

The meta-analysis of ALS mortality in Latin America confirmed the low ALS occurrence in the region, and explained that heterogeneity among countries could be related to the proportion of Caucasian population and income country classification.

A cross-sectional study of the clinical practices of ALS diagnosis and management, showed that diagnosis criteria in Latin America is consistent with other regions. It also showed the management gaps in ALS management, improvement of a multidisciplinary team was recommended.

This thesis has also described the methodological challenges of ALS research as well the difficulties in access to health, which could be the basis for recommendations for future studies.

Further studies are needed, implementing prospective and population-based designs, taking in considerations socio-economic status, standard definitions of ethnic groups and objective genetic approach as well of environmental risk. There is a need to strengthen international collaboration, as the comparisons of differences and similarities would improve our understanding of ALS pathogenic mechanisms.

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Appendix

Appendix 1. Methodological evaluation supplementary data: Epidemiological and genetic features of ALS in Latin America and the Caribbean: a systematic review

S1 Methodological characteristics of the epidemiologic studies

Author	Year	Country	Study area	Years of study	Design	Sources							Diagnosis criteria	EEDC				AH				ST	Population of reference	Standardization group
						H	N	SP	DC	RDC	PA	AC		D	Pr	P	S	D	Pr	LPr	P			
Incidence studies																								
Olivares et al	1972	Mexico	Mexico city	7	R	X	X	X					MR									X	US 1960	NS
Rodriguez et al	2006	Costa Rica	NS	3	R	X					X		Cf											
Vasquez et al	2008	Uruguay	Countrywide	1	P	X	X	X	X	X			EEDC	X	X							X	US 1990	45-74 age group Age and sex
Bettini et al	2013	Argentina	Buenos Aires	7	R	X							EEDC	X	X							X	US 1990	45-74 age group Age and sex
Bucheli et al	2013	Ecuador	Quito	12	R	X							EEDC	-	-	-	-					X	US 1990	> 15 years of age Age and sex
Zapata et al	2019	Colombia	Medellin	1	R	X	X	X					AH; Awaji*					X	X		X			
Prevalence studies																								
Linden- Junior et al	2013	Brazil	Porto Alegre	1	R	X	X	X			X		EEDC	X	X	X	-							
Mortality studies																								
Zaldivar et al	2009	Cuba	Countrywide	5	R				X				ICD codes									X	US 2000	> 15 years of age Age and sex
Matos et al	2011	Brazil	Sao Paulo	4	R				X				ICD codes									X	NS	Age adjusted
Valenzuela et al	2015	Chile	Countrywide	16	R				X				ICD codes									X	WHO 2000	NS
Moura et al	2016	Brazil	Countrywide	9	R				X				ICD codes									X	US 2010	> 20 years of age Age and sex
Luna et al	2019	Ecuador	Countrywide	26	R				X				ICD codes									X	US 2010	Age sex total population

ST: Standardization, H: Hospital discharge data; N: Neurologist; Sp: Specialist; DC: Death certificates; RDC: Riluzole dispense centers; PA: Patients association; HI: Health Insurance; MR: Medical record; Cf: Clinical file; NS: No Specified;
-:Classificaton was not specified EEDC: El Escorial diagnostic criteria; D: Definite, Pr: Probable; P: Possible, S: Suspected
AH: Airlie House; D: Definite, Pr: Probable; LPr: Probable Laboratory supported; P:Possible
*: Patients with possible, probable or definite ALS according to AH associated to Awaji-Shima were enrolled.

S2. Methodological characteristics of the genetic studies

Author	*Year*	*Country*	*Study area*	*Years of duration*	*Design*	*Sources*							*Diagnosis criteria*	*EEDC*				*AH*			
						H	*N*	*SP*	*DC*	*RDC*	*PA*	*AC*		*D*	*Pr*	*P*	*S*	D	Pr	LPr	P
Chadi et al	2016	Brazil	Sao Paulo	5	P	X							EEDC	X	X						
Itzcovich et al	2016	Argentina	Buenos Aires	NS	P	X						X	NS	-	-	-	-	-	-	-	-
Tavares de Andrade et al	2018	Brazil	Multiple centers	6	R	X							AH					X	X		
Cintra et al	2018	Brazil	Multiple centers	18	R	X							AH					-	-	-	-

H: Hospital discharge data; N: Neurologist; Sp: Specialist; DC: Death certificates; RDC: Riluzole dispense centers; PA: Patients association; HI: Health Insurance; MR: Medical record; Cf: Clinical file;; -: Classification was not specified

EEDC: El Escorial diagnostic criteria; D: Definite, Pr: Probable; P: Possible, S: Suspected

AH: Airlie House; D: Definite, Pr:Probable; LPr: Probable Laboratory supported; P: Possible

S3. Methodological characteristics of the clinical characteristics studies

Author	*Year*	*Country*	*Study area*	*Years of duration*	*Design*	*Sources*							*Diagnosis criteria*	*EEDC*				*AH*			
						H	*N*	*SP*	*DC*	*RDC*	*PA*	*AC*		*D*	*Pr*	*P*	*S*	*D*	*Pr*	*LPr*	*P*
Marco et al	1983	Puerto Rico	San Juan city	NS	R	X							Clinical								
Otero- Siliceo et al	1997	Mexico	Mexico city	30	R	X							EEDC	X							
Castro- Costa et al	2000	Fortaleza	Fortaleza	18	R	X							EEDC	X	X	X	X				
Dietrich- Neto et al	2000	Brazil	Countrywide	1	P		X	X					EEDC	X	X						
Werneck et al	2007	Brazil	Parana	27	R	X		X					EEDC	X	X	X	X				
Torres et al	2009	Peru	Lima	22	R	X							AH					X	X	X	X
Loureiro et al	2012	Brazil	Rio de Janeiro	7	R	X							AH					X			
Adry et al	2012	Brazil	Bahia	11	R	X							AH					-	-	-	-
Lannuzel et al	2015	Guadeloupe	West Indies Hospital	15	R	X		X					AH					-	-	-	-
Prado et al	2016	Brazil	State of Minas Gerais	1	P	X							Awaji								
Deliz et al	2018	Puerto Rico	Countrywide	10	R	X							AH					-	-	-	-
Ryan et al	2019	Cuba, Uruguay	Habana; Montevideo	21	R	X							AH					X	X		X

H: Hospital discharge data; N: Neurologist; Sp: Specialist; DC: Death certificates; RDC: Riluzole dispense centers; PA: Patients association; HI: Health Insurance; MR: Medical record; Cf: Clinical file ; NS: No specified; -: Classification was not specified

EEDC: El Escorial diagnostic criteria; D: Definite, Pr: Probable; P: Possible, S: Suspected

AH: Airlie House; D: Definite, Pr: Probable; LPr: Probable Laboratory supported; P: Possible

S4. Methodological characteristics of the survival prognosis studies

Author	*Year*	*Country*	*Study area*	*Years of duration*	*Design*	*Sources*							*Diagnosis criteria*	*EEDC*				*AH*			
						H	*N*	*SP*	*DC*	*RDC*	*PA*	*AC*		*D*	*Pr*	*P*	*S*	*D*	*Pr*	*LPr*	*P*
Sivori et al	2007	Argentina	Buenos Aires	4	R	X							AH					-	-	-	-
Gil et al	2009	Uruguay	Montevideo	2	P	X	X	X	X				EEDC	X	X						
Garguilo-Monachelli	2011	Argentina	Buenos Aires	6	R	X							AH					-	-	-	-
Martinez et al	2011	Mexico	Monterrey	5	R	X							AH					X			
Moura et al	2015	Brazil	Brazilia	9	R	X				X			EEDC	X	X	X	X				
Abadia-Cubillo	2015	Costa Rica	Countrywide	5	R	X							EEDC	X	X						
Favero et al	2017	Brazil	Sao Paolo	12	P	X							EEDC	-	-	-	-				
Sanchez et al	2019	Mexico	Mexico city	15	R	X							AH; Awaji*					X	X		

H: Hospital discharge data; N: Neurologist; Sp: Specialist; DC: Death certificates; RDC: Riluzole dispense centers; PA: Patients association; HI: Health Insurance; MR: Medical record; Cf: Clinical file; -: Classification was no specified

EEDC: El Escorial diagnostic criteria; D: Definite, Pr: Probable; P: Possible, S: Suspected

AH: Airlie House; D: Definite, Pr: Probable; LPr: Probable Laboratory supported; P:Possible

*: Both criteria were used, patients with clinical findings of probable and definitive according to AH, as well those with electrophysiological signs compatible with definite or probable ALS according to Awaji criteria.

Appendix 2. Number of ALS deaths and population at risk for each country

Argentina 1995 - 2018																	
ALS deaths																	
Group Age	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	15	10	17	23	79	129	194	242	321	407	440	381	267	183
Female	0	0	0	2	5	9	7	32	53	92	154	203	320	356	390	311	294
Total	0	0	0	17	15	26	30	111	182	286	396	524	727	796	771	578	477
Population at risk																	
Male	42341403	42054834	41754739	41342215	39802392	36951568	33833112	30845858	27855425	25179078	22821733	20095009	17182604	14103593	10880785	7553566	6804834
Female	40685952	40471524	40310624	40171445	39108708	36755766	34032489	31443085	28760520	26371754	24367596	21979453	19546815	17091013	14519783	11500224	13806948
Total	83027355	82526358	82065363	81513660	78911100	73707334	67865601	62288943	56615944	51550832	47189329	42074462	36729419	31194606	25400568	19053790	20611782

Brazil 2004 - 2013																	
ALS deaths																	
Group Ag	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	1	35	44	64	118	236	351	444	580	619	649	543	363	301
Female	0	0	0	0	12	20	29	71	117	207	334	431	529	596	533	430	379
Total	0	0	0	1	47	64	93	189	353	558	778	1011	1148	1245	1076	793	680
Population at risk																	
Male	81542489	83990748	85353271	86033852	87802850	83578296	75878130	68586365	63025525	55213304	45549747	36021817	27611382	20920338	15049731	10067973	10086371
Female	78798945	81261537	82844581	84273769	86938566	83950631	77108094	70984928	67051576	60035064	50326724	40474796	31847302	24902293	18910416	13591517	15238867
Total	160341434	165252285	168197852	170307621	174741416	167528927	152986224	139571293	130077101	115248368	95876471	76496613	59458684	45822631	33960147	23659490	25325238

Chile 1990 - 2017																	
ALS deaths																	
Group Ag	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	4	3	6	14	47	93	145	206	201	240	241	205	145	113
Female	0	0	0	4	0	1	4	14	42	64	96	166	200	218	199	187	145
Total	0	0	0	8	3	7	18	61	135	209	302	367	440	459	404	332	258
Population at risk																	
Male	19025646	19007722	18970766	18992733	18709056	18078325	17216566	16284867	15146316	13674483	11727737	9530205	7561265	5796513	4225162	2813158	2536288
Female	18334607	18333287	18313214	18376427	18238234	17812222	17121026	16362107	15364350	14030411	12236247	10201975	8436738	6844203	5410966	4026714	4588332
Total	37360253	37341011	37283980	37369159	36947290	35890547	34337591	32646973	30510666	27704894	23963983	19732180	15998003	12640716	9636129	6839873	7124620

Colombia 1992 - 2015																	
ALS deaths																	
Group Ag	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	5	11	9	19	52	85	113	159	154	193	224	161	101	84
Female	0	0	0	2	7	9	12	20	38	93	111	153	149	158	166	108	82
Total	0	0	0	7	18	18	31	72	123	206	270	307	342	382	327	209	166
Population at risk																	
Male	53385981	53229762	52536728	49809725	46103001	41886939	37750670	33671078	29830481	25782626	21071404	16366764	12671110	9539081	7059682	4799344	4489609
Female	51127459	51109250	50531789	48269141	45625885	42847489	39581934	35983223	32211710	28136515	23064069	17984694	14095353	10954839	8468254	6057811	6339092
Total	104513440	104339012	103068517	98078866	91728886	84734428	77332604	69654302	62042191	53919141	44135473	34351457	26766463	20493920	15527936	10857155	10828701

Ecuador 1990 - 2019																	
ALS deaths																	
Group Ag	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	3	2	0	7	15	24	31	54	52	49	56	33	34	28
Female	0	0	0	0	1	6	1	8	16	23	32	53	39	41	41	36	37
Total	0	0	0	3	3	6	8	23	40	54	86	105	88	97	74	70	65
Population at risk																	
Male	22905480	22688802	22035445	20564080	18669784	16581375	14668533	12835473	11070702	9349161	7844861	6366098	5087829	3961054	2942202	2026002	2090475
Female	21995151	21850635	21259696	20064562	18482007	16652378	14931443	13273482	11509658	9765918	8214643	6699125	5413555	4303542	3286134	2346267	2586387
Total	44900631	44539437	43295141	40628642	37151791	33233753	29599976	26108955	22580360	19115079	16059504	13065223	10501384	8264596	6228336	4372269	4676862

Uruguay 1997 - 2019																	
ALS deaths																	
Group Ag	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	0	3	0	6	7	17	39	43	49	68	87	87	65	62
Female	0	0	0	0	1	1	3	1	3	11	31	39	54	67	78	79	61
Total	0	0	0	0	4	1	9	8	20	50	74	88	122	154	165	144	123
Population at risk																	
Male	2903948	3006029	3075786	3103621	2992458	2790549	2652334	2537377	2400223	2232393	2073585	1868720	1629871	1399570	1146925	845970	871055
Female	2781135	2884428	2955860	2994528	2934293	2790507	2699945	2624141	2509872	2360772	2233216	2063104	1871913	1711192	1537334	1273547	1779822
Total	5685083	5890457	6031646	6098149	5926751	5581056	5352279	5161518	4910095	4593165	4306801	3931824	3501784	3110762	2684259	2119517	2650877

Costa Rica 1999 - 2019																	
ALS deaths																	
Group Ag	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	1	0	4	5	8	18	45	42	55	57	63	57	46	29
Female	0	0	0	0	1	1	4	2	2	20	29	37	38	42	39	40	26
Total	0	0	0	1	1	5	9	10	20	65	71	92	95	105	96	86	55
Population at risk																	
Male	3609022	4041986	4448987	4619597	4374224	3722524	3436794	3271374	3052291	2656912	2395931	1871678	1460443	1113029	814074	618943	675019
Female	3425836	3843268	4152027	4438643	4255344	3823981	3656944	3518544	3299081	2881841	2619948	2057511	1630184	1287327	976990	716941	912717
Total	7034858	7885254	8601014	9058240	8629568	7546505	7093738	6789918	6351372	5538753	5015879	3929189	3090627	2400356	1791064	1335884	1587736

Cuba 2001 - 2006																	
ALS deaths																	
Group Ag	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	1	2	1	1	11	8	14	21	30	37	36	23	13	24
Female	0	0	0	0	0	0	0	4	6	8	17	26	23	37	23	22	39
Total	0	0	0	1	2	1	1	15	14	22	38	56	60	73	46	35	63
Population at risk																	
Male	2153783	2251011	2538888	2522196	2182175	2562453	3187941	3246362	2670573	1999185	1889432	1677131	1443865	1285316	893678	560142	670715
Female	2030546	2118294	2406652	2397108	2069426	2462391	3119130	3264382	2718539	2073995	1962955	1764694	1487910	1338892	971765	631868	849823
Total	4184329	4369305	4945540	4919304	4251601	5024844	6307071	6510744	5389112	4073180	3852387	3441825	2931775	2624208	1865443	1192010	1520538

Guatemala 2009 - 2016																	
ALS deaths																	
Group Ag	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	0	1	0	2	1	2	6	12	5	4	9	7	2	5
Female	0	0	0	0	0	1	0	1	2	0	2	9	3	5	5	1	3
Total	0	0	0	0	1	1	2	2	4	6	14	14	7	14	12	3	8
Population at risk																	
Male	9020861	8422695	7657602	6751011	5682827	4656704	3748998	2915944	2288796	1861472	1560865	1357852	1175209	902196	713583	524693	414274
Female	8680119	8151489	7486991	6710584	5835487	5012667	4302279	3557054	2874974	2304335	1863411	1554058	1311364	982145	780822	607023	526752
Total	17700980	16574184	15144593	13461595	11518314	9669371	8051277	6472998	5163770	4165807	3424276	2911910	2486573	1884341	1494405	1131716	941026

Mexico 1990 - 2019																	
ALS deaths																	
Group Ag	0-4 year	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	>80 years
Sex																	
Male	0	0	0	47	40	34	58	156	287	381	492	555	544	528	393	280	204
Female	0	0	0	15	21	30	43	62	149	255	353	448	456	470	413	267	204
Total	0	0	0	62	61	64	101	218	436	636	845	1003	1000	998	806	547	408
Population at risk																	
Male	163130294	168215393	166146788	158740152	143255987	126093276	113028105	102286450	88634813	74904955	61610659	48757916	38795146	28971272	21208069	14219674	15809037
Female	156915128	162198492	161009348	158111425	148864337	134520865	122294670	111184988	96123629	81260641	67060976	53358529	43184762	32868929	24664124	16992151	20853188
Total	320045422	330413885	327156136	316851577	292120324	260614141	235322775	213471438	184758442	156165596	128671635	102116445	81979908	61840201	45872193	31211825	36662225

Appendix 3. Clinical practices on the diagnosis and management of ALS among neurologists in Latin America survey

Estudio: Proyecto ELA.LA **Julio- Septiembre 2020**

Anexo 1: Cuestionario de las prácticas clínicas de la esclerosis lateral amiotrófica (ELA) en Latino America, de acuerdo a las guías por las academias americana y europea.

Identificación
Fecha de respuesta: __/___/_____
Código de identificación: ☐ ☐ ☐ ☐
Nombre (si lo desea): _____
País donde trabaja_____

Sección 1: Información general		
1.1 Hace cuánto tiempo ejerce la neurología: ☐<5 años ☐5-10 años ☐>10 años		
1.2 ¿Actualmente donde trabaja? Sector Publico: Si ☐ No☐ -Tipo de hospital: ☐ Básico ☐ Especializado Otro:_____	Sector Privado:☐Si ☐No -Tipo de institución: ☐ Consulta Privada ☐ Hospital Privado ☐ Compañía de Seguro privada	**1.2.1** Si trabaja en ambos Sectores, público y privado, ¿normalmente donde evalúa la mayor parte de pacientes con ELA? ☐ Publico ☐ Privado ☐ Ambos
1.3 ¿Tiene usted una sub especialidad en neurología? ☐ Sí ☐No **1.3B** ¿Ha recibido usted una formación o taller sobre ELA? ☐ Sí Hace cuanto____ Tiempo de formación_____ ☐ No	**1.3.1** Si su respuesta es afirmativa, cuál es su especialidad? ☐Neuro-vascular ☐Movimientos anormales y extra piramidales ☐Neuro-muscular ☐Epileptología ☐Medicina del sueño ☐Cognitivo Otro_____	
1.4 ¿Ha diagnosticado usted, ELA en los últimos 5 años? ☐Sí ☐No	**1.4.1** Si su respuesta es afirmativa, ¿Cuantos casos ha diagnosticado? _____	

1.5 De acuerdo a su experiencia, ¿Quién normalmente le refiere a usted pacientes que padecen ELA?

☐ Medico general ☐ Otro neurólogo

☐ Especialista (Internista, Neumólogo, otorrinolaringólogo)

☐ Otro _____

1.6 En su práctica clínica, ¿Al tener un paciente sospechoso de ELA usted continua con el diagnóstico y manejo o prefiere referir el paciente?

☐ Continuo yo mismo el diagnóstico y manejo

☐ Refiero el paciente a otro Hospital ya que hay mayor accesibilidad de efectuar los exámenes

☐ Refiero el paciente a otro colega ya que ha tenido mayor experiencia con esta enfermedad

☐ Refiero el paciente ya que el paciente así lo desea

Otro_____

Sección 2: Diagnostico

2.1. De acuerdo con su experiencia, ¿Utiliza usted uno de los siguientes criterios?

Awaji criteria Sí ☐ No ☐

El Escorial criteria (Airlie house) Sí ☐ No ☐

Otros criterios_____

2.2. De acuerdo con su experiencia, ¿Cuál de los siguientes exámenes solicita o realiza usted, para descartar otras causas en una paciente con sospecha de ELA?

Examen clínico solamente	☐ Si	☐ No	☐ Dudoso
Electromiografía	☐ Sí	☐ No	☐ Dudoso
Sistemáticamente neuro imágenes (TAC, IRM)	☐ Sí	☐ No	☐ Dudoso
Exámenes laboratoriales/ punción lumbar	☐ Sí	☐ No	☐ Dudoso
Bio-marcadores / biopsia	☐ Sí	☐ No	☐ Dudoso

2.3. ¿Qué diagnóstico diferencial investiga usted en un caso sospechoso de ELA? (Múltiples posibles respuestas)

☐ Causas infecciosas ☐ Síndromes auto-inmunes ☐ Síndrome post polio

☐ Radiculopatías ☐ Neuropatía motora multifocal ☐ Miastenia gravis

Otro_____

2.4 De acuerdo con su experiencia, ¿Cuál de los siguientes exámenes considera usted el más importante para confirmar el diagnóstico de ELA? (Múltiples posibles respuestas)

☐ Examen clínico solamente
☐ Electromiografía
☐ Sistemáticamente neuro imágenes (TAC, IRM)
☐ Exámenes laboratoriales/ punción lumbar
☐ Bio-marcadores / biopsia

Otro_____

2.5. De acuerdo con su experiencia, ¿Cómo comunica usted el diagnostico a sus pacientes?

☐ Frente a frente con el paciente solamente
☐ Frente a frente con el paciente y un miembro de la familia
☐ Le doy la noticia solamente a la persona que cuida el paciente
☐ Con la presencia de un psicólogo
☐ Otra persona brinda la información (Medico general, enfermera, estudiante de medicina…)

Otro_____

2.5.1. ¿Qué información brinda usted acerca de la enfermedad?

☐ El nombre de la enfermedad
☐ El pronóstico en términos de supervivencia
☐ Las posibles complicaciones (insuficiencia respiratoria)
☐ La ausencia de un medicamento que cure la enfermedad
☐ El posible rol genético
☐ Ninguno de los anteriores

Otro_____

2.6 Otra práctica (o comentario) que usted realice en el diagnóstico de ELA:_____

Sección 3: Cuidado

3.1. . ¿Qué medicamento prescribe usted en los pacientes con ELA?

_____

3.2. En el cuidado de pacientes con ELA usted brinda: (Múltiples posibles respuestas)

☐ Provee tratamiento sintomático
☐ Provee un cuidado con un equipo de múltiples disciplinas
☐ Provee el cuidado de acuerdo a la disponibilidad de medicamentos o equipo en su centro de trabajo
☐ Provee el cuidado de acuerdo a guías clínicas
☐ Solamente brinda cuidado paliativo

Otro_____

3.3 De acuerdo con su experiencia, ¿Con quién normalmente trabaja en el cuidado de pacientes con ELA? (Múltiples posibles respuestas)

☐ Neurólogo	☐ Médico rehabilitador	☐ Gastroenterólogo
☐ Neumólogo	☐ Nutricionista	☐ Ortofonista
☐ Psicólogo	☐ Terapista del habla	☐ Enfermera especializada
☐ Consejero social	☐ Medico cuidados paliativos	☐ Dentista
☐ Ninguna de las anteriores	☐ Otro_____	

3.4. De acuerdo con su experiencia, ¿Cómo maneja los aspectos nutricionales en pacientes con ELA?

-Refiere a un nutricionista Sí ☐ No ☐

-Indica suplementos nutricionales Sí ☐ No ☐

-Alimentación por sonda nasogástrica Sí ☐ No ☐

-Indica una gastrostomía si el paciente presente problemas severos para deglutir Sí ☐ No ☐

3.4.1. Si no indica gastrostomía, ¿puede justificar por qué?

☐ El paciente no puede pagarla

☐ No hay forma de realizarla en el centro donde usted trabaja

☐ Los pacientes rehúsan la gastrostomía

☐ La gastrostomía no beneficiara al paciente

Otro_____

3.5. De acuerdo con su experiencia, ¿Cómo maneja usted un paciente que inicia con signos o síntomas de insuficiencia respiratoria?

☐ Indico terapia con oxígeno solamente

☐ Indico ventilación no invasiva

☐ Indico ventilación invasiva (Traqueotomía)

☐ Refiero el paciente a un neumólogo

☐ Otro: _____

3.5.1. De acuerdo con su respuesta anterior, ¿Porque indica esa opción?

☐ Es la única terapia disponible en el centro donde trabajo

☐ Es lo que las guías clínicas sugieren

☐ Es la que representa el mejor beneficio para el paciente

☐ Es la opción que el paciente puede pagar

☐ Es lo que el paciente prefiere

☐ Otro: _____

3.6 Utiliza usted alguna guía para el manejo de pacientes con ELA?

☐ Sí ☐ NO

3.6.1. Si su respuesta es afirmativa, ¿Cuál es la guía que utiliza? _____

3.7 Otra práctica (o comentario) que usted realice en el cuidado de ELA: _____

Sección 4: Seguimiento de pacientes
4.1. Después del diagnóstico de ELA, ¿Cada cuánto les da cita a sus pacientes? ☐ Cada vez que el paciente necesite ☐ Cada 3 meses ☐ Cada 6 meses ☐ Una vez al año ☐ Cuando el paciente presenta una complicacion solamente ☐ Posterior al diagnóstico los pacientes no regresan a consulta
4.2. En cada visita de seguimiento, ¿Usted evalúa? (Múltiples posibles respuestas) Testing Muscular Sí ☐ No ☐ ☐ Dudoso Escala revisada de la calificación de la función de ELA Por sus siglas en Ingles (ALS-FRS-R) Sí ☐ No ☐ ☐ Dudoso
4.3. De acuerdo con su experiencia, ¿Que examen solicita usted para diagnosticar insuficiencia respiratoria en pacientes con ELA? Espirometria Sí ☐ No ☐ Dudoso ☐ Oximetría nocturna Sí ☐ No ☐ Dudoso ☐
4.4. De acuerdo con su experiencia, ¿Evalúa usted la pérdida de peso en pacientes con ELA comparándolo con su peso usual antes del inicio de la enfermedad? ☐ Sí ☐ No
4.5 Otra práctica (o comentario) que usted realice en el seguimiento de ELA: _____

Sección 5: Final de la vida	
5.1. De acuerdo con su experiencia, ¿Dónde normalmente mueren los pacientes que padecen de ELA?	☐ Mueren en casa ☐ Mueren en hospital
5.2 De acuerdo con su experiencia, ¿Los pacientes tienen seguimiento por un equipo paliativo?	☐ Sí ☐ No
5.3 De acuerdo con su experiencia, ¿Los pacientes han previamente definido sus deseos para el final de vida? (Es decir consentimientos de no reanimación, no traqueotomía)	☐ Sí ☐ No
5.4 Otra práctica (o comentario) que usted realicen final de vida: _____	

De acuerdo a su experiencia o su práctica clínica con pacientes de ELA como se evalúa en	
Conocimientos en:	Prácticas en:
Diagnostico 1 2 3 4 5 6 7 8 9 10	Diagnostico 1 2 3 4 5 6 7 8 9 10
Cuidado y manejo 1 2 3 4 5 6 7 8 9 10	Cuidado y manejo 1 2 3 4 5 6 7 8 9 10

Amyotrophic Lateral Sclerosis in Latin America: Epidemiology, clinical features, and clinical practices on the diagnosis and management of ALS among neurologists

Amyotrophic Lateral sclerosis is a neurodegenerative disease with a poor survival. ALS heterogeneity has been observed among epidemiological indicators and clinical characteristics between geographic areas and populations. Recent evidence has suggested a lower ALS occurrence in Latin America. However, ALS research is limited in the region. In order to provide scientific evidence, we aim to describe ALS epidemiology, clinical characteristics and the clinical practices of ALS diagnosis and management in Latin America. This thesis offers an updated review of ALS literature in Latin America and two original epidemiological studies in Latin America. First, a meta-analysis that provided a pooled ALS mortality of 10 Latin American countries and identified key factors of ALS heterogeneity in the region. A low ALS mortality was found in Latin America, and heterogeneity of ALS mortality was observed among Latin American countries. Higher mortality rates were observed among countries with a higher proportion of Caucasian population and in countries with a high income. A second study, described the clinical practices of neurologists in Latin America on the diagnosis and management of ALS. Diagnosis in Latin America is based on the Airlie House criteria. Riluzole is prescribed in the region but this varies between Latin American countries. Further improvement is needed on ALS management such as integrating a multidisciplinary team, early introduction of non-invasive ventilation and gastrostomy. This scientific evidence provides original and reliable data of an under represented region. Further research is needed to understand ALS heterogeneity.

Keywords: Amyotrophic lateral sclerosis, Latin America, heterogeneity, mortality, clinical characteristics, clinical practices, neurologists.

La sclérose latérale amyotrophique en Amérique latine : Épidémiologie, caractéristiques cliniques et pratiques cliniques sur le diagnostic et la gestion de la SLA chez les neurologues.

La sclérose latérale amyotrophique est une maladie neurodégénérative dont la survie est faible. L'hétérogénéité de la SLA a été observée parmi les indicateurs épidémiologiques et les caractéristiques cliniques entre les zones géographiques et les populations. Des données récentes ont suggéré que la fréquence de la SLA est plus faible en Amérique latine. Cependant, la recherche sur la SLA est limitée dans cette région. Afin d'apporter des preuves scientifiques, nous souhaitons décrire l'épidémiologie de la SLA, ses caractéristiques cliniques et les pratiques cliniques de diagnostic et de prise en charge de la SLA en Amérique latine. Cette thèse propose une revue actualisée de la littérature sur la SLA en Amérique latine et deux études épidémiologiques originales en Amérique latine. Tout d'abord, une méta-analyse qui a fourni une mortalité poolée de la SLA dans 10 pays d'Amérique latine et a identifié les facteurs clés de l'hétérogénéité de la SLA dans la région. Une faible mortalité liée à la SLA a été constatée en Amérique latine et une hétérogénéité de la mortalité liée à la SLA a été observée entre les pays d'Amérique latine. Des taux de mortalité plus élevés ont été observés dans les pays ayant une proportion plus élevée de population caucasienne et dans les pays à revenu élevé. Une deuxième étude a décrit les pratiques cliniques des neurologues d'Amérique latine en matière de diagnostic et de gestion de la SLA. Le diagnostic en Amérique latine est basé sur les critères d'Airlie House. Le Riluzole est prescrit dans la région mais cela varie entre les pays d'Amérique latine. Des améliorations sont nécessaires dans la prise en charge de la SLA, comme l'intégration d'une équipe multidisciplinaire, l'introduction précoce de la ventilation non invasive et de la gastrostomie. Ces preuves scientifiques fournissent des données originales et fiables sur une région sous-représentée. Des recherches supplémentaires sont nécessaires pour comprendre l'hétérogénéité de la SLA.

Keywords Sclérose latérale amyotrophique, Amérique Latine, hétérogénéité, mortalité, caractéristiques cliniques, pratiques cliniques, neurologues