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Epidemiological and clinical variability of amyotrophic lateral sclerosis between geographic areas and populations: focus on Africa and Latin America

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“A mis raíces: a mi familia,
a mis amigos y a mi amada.”

“Truth has had to be fought for every step of the way, almost everything else dear to our hearts, on which our love and our trust in life depend, has had to be sacrificed to it. Greatness of soul is needed for it, the service of truth is the hardest service.”

Friedrich Nietzsche

“Let us keep looking in spite of everything.
Let us keep searching for it is indeed the best method for finding.
And perhaps, thanks to our efforts, the verdict we will give such a patient tomorrow will not be the same as we must give him today.”

Jean-Martin Charcot

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Rights

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Introduction

Amyotrophic lateral sclerosis (ALS) is a rare disorder, which means that the condition affects less than five per 10,000 people in the general population (Office of the European Union, 2008). Despite that, it is the most common form of adult onset motor neuron degeneration. This fatal disease is defined by a combination of upper motor neuron (UMN) and lower motor neuron (LMN) degeneration. The etiology and physiopathology involved are not fully understood. Some researchers have suggested that it is caused by multiple susceptibility genes interacting with a variety of environmental risk factors.

Recently, epidemiological and clinical data has led researchers to propose ALS variability in terms of incidence, mortality and clinical characteristics between geographic areas and populations. The evidence is based on original investigations, multiethnic studies and meta-analyses. However, it is difficult to obtain firm conclusions because most of the scientific literature available is from Europe and North America and therefore from Caucasian populations. ALS variability could be associated with different factors, such as environmental exposures or genetic variants. Nevertheless, these findings may reflect variability between studies design, differences in case ascertainment and health care access.

Given the importance of this subject, it is crucial to furnish reliable data using standardized methods in different populations around the globe that might bring new answers to understand ALS heterogeneity.

Chapter I. Amyotrophic lateral sclerosis: A general overview

Amyotrophic lateral sclerosis is an incurable, fatal neurodegenerative disease that affects the motor neuron system. Motor neuron degeneration extends from the cortex to the anterior horns of the spinal cord (Figure 1). Traditionally, the classic ALS form is characterized by a combination of upper motor neuron and lower motor neuron signs and symptoms in the same body regions with subsequent evidence of progression to other regions (Kiernan et al., 2011).

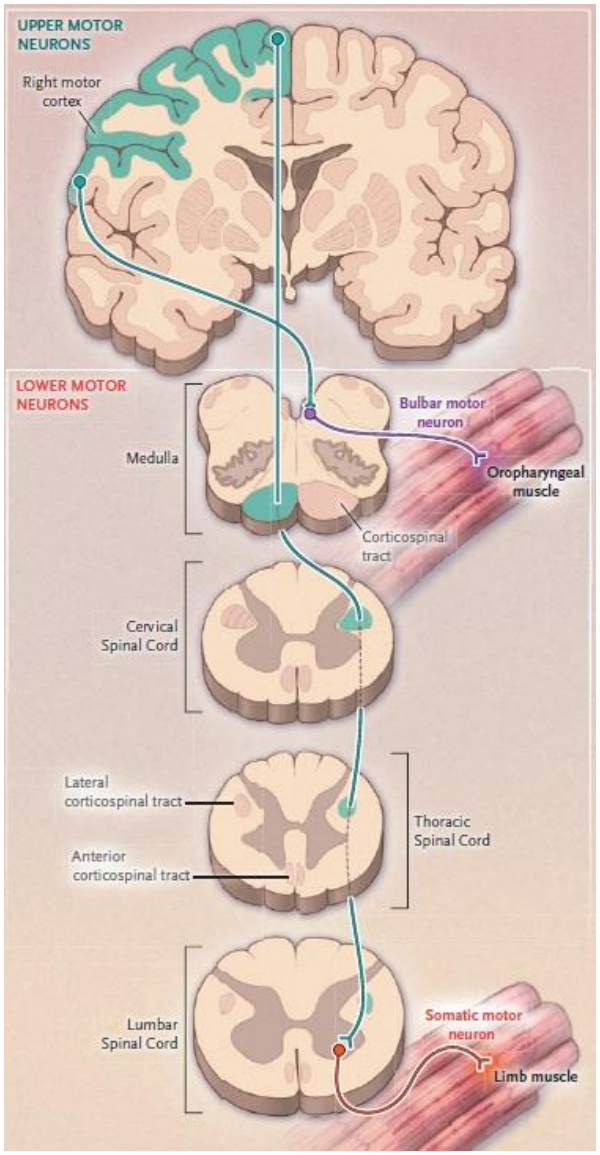

Figure 1 : Motor neuron system
Source: (Brown and Al-Chalabi, 2017)

The father of modern neurology, Jean-Martin Charcot, firstly described ALS using the anatomo-clinical method in the 19th century. The term “amyotrophic lateral sclerosis” denotes the combination of clinical findings of muscular atrophy and the pathological observation of bilateral and symmetric sclerosis of the lateral spinal cord columns (Goetz, 2000). Although much has been learned over the last 150 years since Charcot’s description, much remains to be done to understand the complexity of this disease.

I.1. Epidemiology: A brief introduction

Amyotrophic lateral sclerosis is the most common adult-onset motor neuron disorder. The worldwide standardized ALS incidence is 1.68 (95% CI, 1.50 – 1.85) per 100 000 person-years of follow-up (PYFU) (Marin et al., 2017). The number of ALS prevalent cases worldwide has been estimated at around 200,000 to 300,000 in recent years (Arthur et al., 2016; Logroscino et al., 2018b). It appears however, according to new evidence, that ALS displays an epidemiological variability between geographic areas and populations. This is precisely the subject that we are going to explore in this dissertation. A detailed description of ALS epidemiology will be presented in the next chapter.

I.2. Etiology

The majority of ALS cases appears sporadically with no apparent heritability. Sporadic ALS (sALS) refers to patients with no known family history of the disease. sALS accounts for 90% to 95% of all ALS cases (Rowland and Shneider, 2001). Familial ALS (fALS) is established in patients who have at least a family member affected with ALS. fALS is reported to range from 5% in population-based studies to 10% in hospital-based studies (Byrne et al., 2011).

Several genetic variants have been described to play a prominent role in the etiology of ALS, while the contribution of environmental, occupational and lifestyle factors have been more difficult to assess. ALS is considered to be a complex disease, multiple genetic polymorphisms

and environmental factors may eventually lead to motor neuron degeneration (Van Vught et al., 2005).

I.2.1. Genetics

Since the first gene associated with ALS was identified in the early nineties (Rosen et al., 1993), more than 30 different genes have been linked to the disease mostly for fALS (Chia et al., 2018). These mutations affect basically three pathophysiological processes: RNA metabolism, protein turnover, and axonal transport (Robberecht and Philips, 2013) (Figure 2).

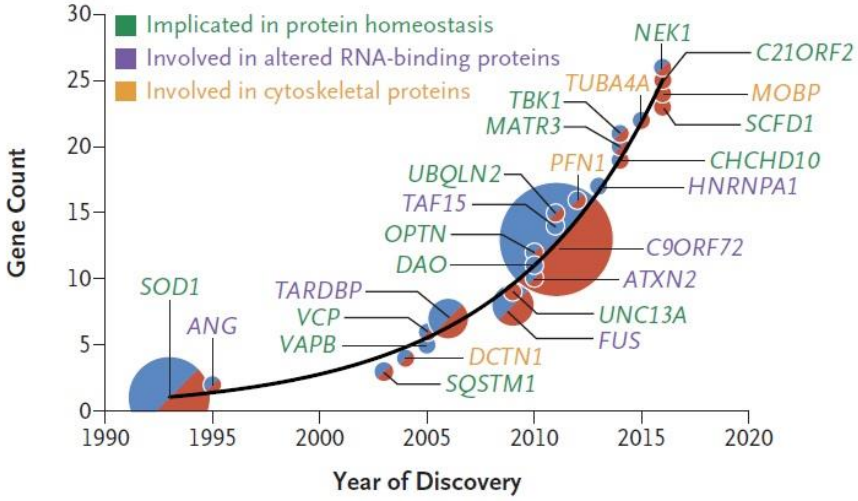

Figure 2 : Genetic mutations associated with ALS
Source: (Brown and Al-Chalabi, 2017)

A genetic mutation can be identified among 60% to 80% of fALS cases with a predominantly autosomal dominant pattern of inheritance for several mutations (van Es et al., 2017). The most common mutation in familial ALS is the hexanucleotide repeat expansion in C9orf72 (40%), followed by superoxide dismutase 1 (SOD1) (20%), fused in sarcoma (FUS) (1–5%), and TAR DNA-binding protein (TARDBP) (1–5%) (Renton et al., 2014). The same gene mutations described in fALS can be found in 10% of sporadic cases. In fact, the repeat expansion in C9orf72 is also the most frequent gene in sporadic ALS (around 7% in Western countries) (Majounie et al., 2012). Researchers are beginning to postulate that the genetic

architectures between familial and sporadic ALS could be similar (van Es et al., 2017). Figure 3 showed the genetic mutation associated with familial and sporadic ALS.

Figure 3 : Genetic mutation proportions associated with familial and sporadic ALS.
Source: (Renton et al., 2014)

It should be noted that the frequency of genetic variants are variable between different populations, which we will discuss later.

I.2.2. Potential risk factors

Environmental, occupational and lifestyle factors have been studied extensively as potential risk factors in ALS. The scientific evidence in this area is not conclusive, although there is research that supports a potential association between ALS and environmental exposure to metals (e.g. lead (Kamel et al., 2005), selenium (Vinceti et al., 2010, 1997)), pesticides (e.g. organochlorine compounds, herbicides and fumigants (Malek et al., 2012)), b-methylamino-L-alanine (BMAA) (Bradley and Mash, 2009; Delzor et al., 2014), electromagnetic fields (Huss et al., 2009), and viruses (Douville et al., 2011). Certain occupations have greater risk to develop ALS including professional athletes (e.g. soccer players (Chiò et al., 2005), football players (Lehman et al., 2012), cross-country skiers (Fang et al., 2016)), military (Weisskopf et al., 2005), farmers (Chió et al., 1991; Furby et al., 2010), and electrical workers (Gawel et al., 1983; Savitz et al., 1998; Zhou et al., 2012). Researchers have also investigated lifestyle factors as potential ALS risks, among them we can mention intense physical activity (Gallo et

al., 2016; Hamidou et al., 2014; Huisman et al., 2013), head trauma (Chen et al., 2007), diet (Fitzgerald et al., 2014; Veldink et al., 2007), and smoking (Alonso et al., 2010; Armon, 2009).

The assessment of risk factors in ALS is challenging mainly due to the problem of accurately estimate exposure throughout life and the retrospective designs of the studies. Evidence is still conflicting. For instance, smoking has been shown to increase the ALS risk in several studies (Armon, 2009; de Jong et al., 2012; Nelson et al., 2000; Wang et al., 2011), while other studies have failed to demonstrate this association (Fang et al., 2006).

I.3. Diagnosis

Amyotrophic lateral sclerosis diagnosis relies on El Escorial criteria since its publication in 1994. The initiative to establish standardized criteria on ALS diagnosis was led by the subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases in order to provide higher homogeneity in randomized therapeutic trials. El Escorial criteria assess diagnostic certainty based on the presence of signs of lower motor neuron degeneration and upper motor neuron degeneration combined with the progressive spread of signs within a region or to other regions (Brooks, 1994). Signs are evaluated from four body regions: bulbar, cervical, thoracic and lumbosacral. El Escorial criteria is mainly founded on the clinical judgement of upper and lower motor neuron involvement. Differential diagnosis is required to exclude other diseases that might explain the motor neuron degeneration. Four categories are proposed according to the clinical findings: suspected, possible, probable or definite ALS (table 1). A revised version, El Escorial revised or Airlie House criteria, was subsequently published in order to include electromyography (EMG) evidence of acute denervation and exclude suspected cases (Brooks et al., 2000). In line with these new criteria, patients are categorized as possible, probable laboratory-supported, probable and definite ALS (table 1).

Table 1 : Diagnosis criteria for ALS

Diagnosis criteria		
El Escorial criteria	**Definite**	Clinical presence of UMN and LMN signs in three regions
	Probable	Clinical presence of UMN and LMN signs in at least two regions
	Possible	Clinical presence of UMN and LMN signs in one region or UMN signs in two or more regions or LMN signs rostral to UMN signs
	Suspected	LMN signs only in two or more regions
El Escorial revised or Airlie House criteria	**Definite**	Clinical presence of UMN and LMN signs in three regions
	Probable	Clinical presence of UMN and LMN signs in at least two regions
	Probable laboratory-supported	Clinical presence of UMN and LMN signs in one region or UMN signs in one region and LMN signs in at least two regions defined by EMG criteria.
	Possible	Clinical presence of UMN and LMN in one region or UMN signs in two or more regions or LMN signs rostral to UMN signs

EMG, Electromyography; UMN, upper motor neuron; LMN, lower motor neuron.

The use of electro-clinical criteria for ALS diagnosis was proposed following a consensus conference in Awaji Island, Japan with the aim of promoting earlier entry of patients into clinical trials (de Carvalho et al., 2008). The Awaji criteria recommend that abnormalities required for the diagnosis of ALS may be derived from either clinical or neurophysiological approach (Costa et al., 2012).

There is often a long delay before diagnosis is reached, partly because of the insidious onset of symptoms. The median time to diagnosis is about 10 to 12 months (Marin et al., 2016b).

I.4. Clinical features and phenotypes

The clinical presentation in ALS denotes the motor neuron degeneration course. UMN symptoms and signs represent the degeneration of the frontal motor neurons located in the motor strip and their axons, while LMN degeneration in the brainstem and spinal cord producing muscle denervation (Marin et al., 2018a).

I.4.1. Disease onset

The first clinical manifestation could appear in bulbar, cervical, thoracic or lumbosacral region with upper or lower motor neuron symptoms and signs. In general, the onset of the disease is

categorized as either spinal or bulbar depending on the affected muscle territories and related clinical symptoms. The most common manifestation is asymmetric limb weakness for the spinal onset and dysarthria or dysphagia for the bulbar onset (Mitchell and Borasio, 2007).

It is unclear which factors are involved in the development of the different types of onset. Nevertheless, their impact in survival is better understood. Bulbar onset is associated with a worse prognosis than spinal onset (Chiò et al., 2009; Marin et al., 2016a).

I.4.2. Symptoms and signs

ALS symptoms and signs are the clinical expression of motor neuron degeneration.

I.4.2.1. Upper motor neuron symptoms and signs

Upper motor neuron symptoms in the limbs are stiffness, slowness and incoordination of movement. Spontaneous clonus and spasms could also occur. At the clinical examination, spasticity and increased reflexes are frequently present.

Upper motor neuron dysfunction in the bulbar region produces dysarthria and dysphagia accompanied by other symptoms such as jaw stiffness, spontaneous jaw clonus, laryngospasm, pseudobulbar affect and sialorrhea. Upper motor neuron signs may be present such as increased jaw reflex, jaw spasticity and slow tongue movement.

I.4.2.2. Lower motor neuron symptoms and signs

Patients with lower motor neuron limb involvement usually show weakness and atrophy together with cramps and fasciculations. Lower motor neuron signs are similarly identified such as reduced reflexes, weakness, muscle atrophy and fasciculations.

Lower motor neuron bulbar dysfunction produces dysarthria and dysphagia. Other symptoms include difficulty to open and close the jaw, and incomplete eye closure. Examination can

reveal masseter muscular weakness, difficulty maintaining jaw closure, poor palatal elevation, tongue weakness, muscle atrophy and fasciculations.

I.4.3. Phenotypes

The classic ALS form requires both upper and lower motor neuron degeneration at the same time. Nevertheless, ALS spectrum includes different clinical phenotypes that are mainly determined by the degree of UMN and LMN involvement.

Phenotypes will be presented in the next section including classic ALS, bulbar phenotype, primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), flail arm syndrome (FA), flail leg syndrome (FL) and ALS-plus syndrome (Figure 4). Primary lateral sclerosis and progressive muscular atrophy, in a strict sense, are classified as motor neuron disorders according to the International Classification of Diseases, tenth revision (ICD-10). However, some authors suggest that they may be ALS variants or represent different patterns of ALS course (Kim et al., 2009; Swinnen and Robberecht, 2014).

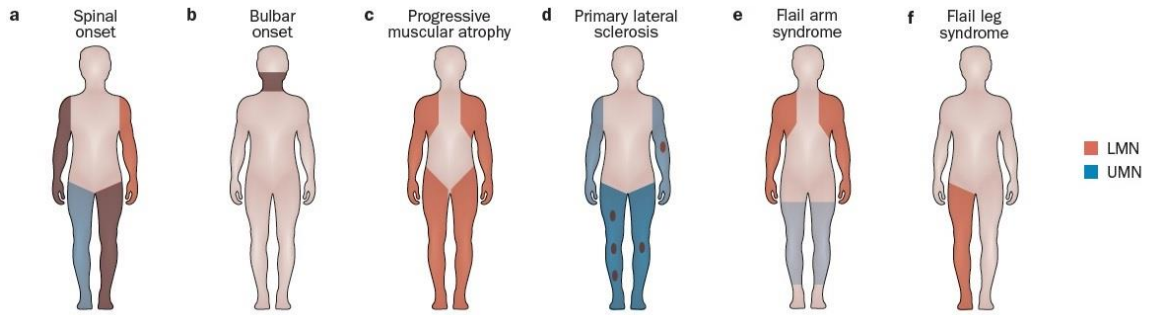

Figure 4 : ALS phenotypes
Adapted from: (Swinnen and Robberecht, 2014)

I.4.3.1. Classic ALS

The archetypal clinical characteristics of classic ALS are the symptoms and signs of UMN and LMN involvement with a progressive course until the fatal outcome approximately in 15 to 20 months after diagnosis.

I.4.3.2. Bulbar phenotype

Patients with a bulbar involvement experience difficulties with speech, mastication and swallowing. Spinal involvement usually appears after 6 months of the symptoms onset (Chiò et al., 2011b). A related phenotype named progressive bulbar palsy has been also identified. Progressive bulbar palsy presents a progressive UMN and LMN degeneration with cranial muscles involvement (Karam et al., 2010).

I.4.3.3. Primary lateral sclerosis

Primary lateral sclerosis (PLS) represents around 5% of all cases of motor neuron disease (MND) (D'Amico et al., 2013). There is selective involvement of corticospinal and corticopontine motor neurons (Gordon et al., 2006). The main characteristic is a dominant upper motor neuron involvement, combined with a slow disease progression and absence of lower motor neuron findings after at least four years of the onset (Gordon et al., 2009). Evidence showed that approximately one third of PLS patients develop lower motor neuron signs in the course of the disease (D'Amico et al., 2013; Gordon et al., 2006). A longer survival has been observed in patients with PLS compared to patients with classic ALS (median survival 9.88 years vs 2.76 years, $p<0.001$) (Tartaglia et al., 2007).

I.4.3.4. Progressive muscular atrophy

Progressive muscular atrophy (PMA) denotes a progressive lower motor neuron involvement accounting for 5% of all MND (Rowland, 2010). Clinical PMA is characterized by evidence of LMN degeneration including decreased deep tendon reflexes and muscle atrophy (Visser et al., 2007). Around one third of patients develop an upper motor neuron dysfunction in the disease course, which can be called lower motor neuron-onset ALS. PMA prognosis is better than classic ALS (48 months vs 36 months, $p = 0.01$) (Kim et al., 2009).

I.4.3.5. Flail arm syndrome

Flail arm (FA) syndrome is mostly described in males by a lower motor neuron involvement with progressive and predominant proximal weakness and wasting in the upper limbs for at least 12 months (Wijesekera et al., 2009). FA syndrome affects predominantly the proximal arm (Couratier et al., 2000; Hu et al., 1998). It is characterized by slow rate of progression to other body regions leading to a widespread form around 20 months (Chiò et al., 2011b). Symptoms remain confined to the arms for 18 months in 56% of cases, for 24 months in 46% of cases, and for 36 months in 27% cases (Wijesekera et al., 2009). Prognosis is significantly better than classic ALS. The median survival of FA syndrome is around 66 months (Wijesekera et al., 2009).

I.4.3.6. Flail leg syndrome

Flail leg (FL) syndrome patients present a lower motor neuron involvement in the lower limbs for at least 12 months (Wijesekera et al., 2009). FL syndrome is characterized by a progressive distal weakness and wasting of the legs that is often asymmetric (Chiò et al., 2011b), with a slow rate of progression. Symptoms were confined to the legs for 18 months in 63% of cases, for 24 months in 48% of cases, and for 36 months in 28% of cases. Survival is longer in FL syndrome patients (around 71 months) compared to classic ALS (Wijesekera et al., 2009).

I.4.3.7. ALS-plus syndrome

According to World Federation of Neurology Research Committee, ALS-plus syndrome is defined by clinical features of other neurological diseases in addition to the phenotype of ALS (Brooks et al., 2000). ALS-plus syndrome combines signs of upper and lower motor neuron involvement along with a widespread degeneration including frontotemporal dementia, autonomic insufficiency, Parkinsonism, and sensory loss. In a cohort study from the US, ALS-plus syndrome was identified around 14% of cases. Among them, the most common feature was ocular motility abnormality (84%), followed by extrapyramidal signs (22.7%), autonomic

dysfunction (5.3%) and cerebellar disorder (1.3%). A statistically significant shorter survival was observed in ALS-plus patients compared with those without ALS-plus (29.66 months vs 42.50 months, p=0.02) (McCluskey et al., 2014).

I.4.4. Cognitive impairment

It was thought that cognitive functions in patients with ALS were preserved. New evidence has shown that the disease involves a wide range of cognitive impairment. Almost half of patients with ALS have some cognitive impairment ranging from mild to severe (Couratier et al., 2017; Neary et al., 2000). In addition, approximately 10% of cases reach criteria for frontotemporal dementia diagnosis (Couratier et al., 2017; Ringholz and Greene, 2006).

The cognitive profile of patients with ALS is characterized by deficits in fluency, language, social cognition, executive functions and verbal memory (Beeldman et al., 2016). Patients with cognitive involvement could also present personality change, irritability, obsessions, poor insight, and pervasive deficits in frontal executive tests. These features could go together with behavioral impairment such as changes to character, social conduct, and executive function in frontotemporal dementia (Phukan et al., 2007).

I.4.5. Overview of the clinical spectrum in ALS

Despite the fact that classic ALS is well-recognized disorder with specifics clinical features, several patients exhibit a wide spectrum of clinical expressions. Some patients could have an exclusive predominance of upper or lower motor neuron signs, while others could present cognitive and behavioral impairment and multisystem degeneration. Figure 5 represents the broad clinical expression of ALS concerning motor neuron involvement, cognitive and behavioral impairment, and multisystem degeneration.

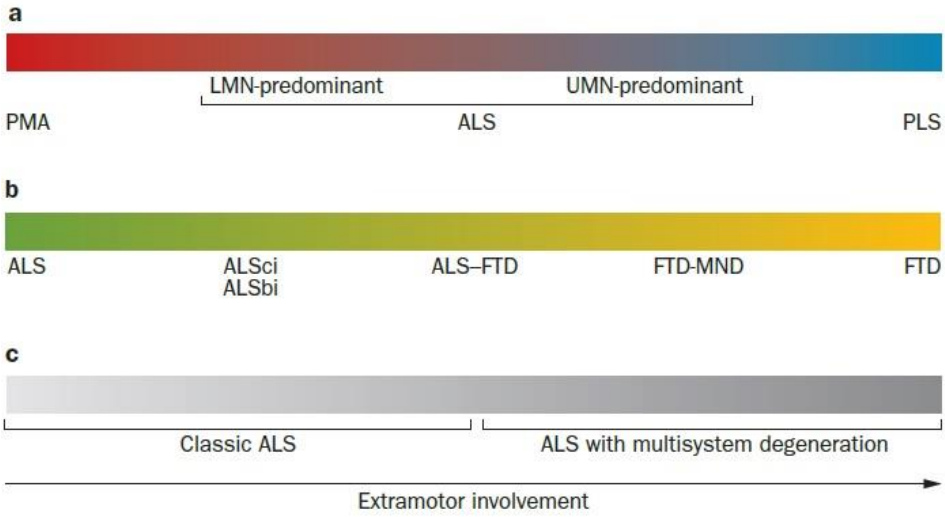

Figure 5 : ALS clinical spectrum
ALSbi, ALS with behavioral impairment; ALSci, ALS with cognitive impairment; FTD, frontemporal dementia; LMN, lower motor neuron; MND, motor neuron disease; PLS, primary lateral sclerosis; PMA, progressive muscular atrophy; UMN, upper motor neuron (in alphabetical order).
Source: (Swinnen and Robberecht, 2014)

I.5. Survival and prognosis

The neurodegeneration in ALS leads to an irreversible fatal outcome usually from respiratory failure. The median survival time is around 25 to 35 months since onset and around 15 to 20 months since diagnosis (Marin et al., 2016b). Several factors have been associated with survival including demographic characteristics, clinical features, treatment and management.

I.5.1. Demographic factors

Age: Most of the studies have identified constantly that age is an independent prognostic factor in ALS. A shorter survival is associated with an increased age (Chiò et al., 2002; del Aguila et al., 2003; Preux et al., 1996). A population-based study found a higher risk of dying for every 5-year increment of age with an adjusted hazard ratio (aHR) of 1.29 (95 % CI 1.17 to 1.43) (Marin et al., 2016a). Another study showed statistically significant differences in median survival times between patients older than 80 years compared with those below 80 years (7.4 months, 95% CI 4.4 to 10.2 vs. 17.4 months, 95% CI 15.1 to 19.4, $p < 0.0001$) (Dandaba et al., 2017).

I.5.2. Clinical factors

Site of onset: Patients with bulbar onset have a worse prognosis compared to patients with spinal onset (Chiò et al., 2002; del Aguila et al., 2003; Preux et al., 1996; Testa et al., 2004). This finding has been not completely explained by age or sex differences (Chiò et al., 2009; Tysnes et al., 1991). Moreover, prognosis is extremely poor in patients with respiratory involvement at onset (Couratier et al., 2016; de Carvalho et al., 1996; Shoesmith et al., 2007).

Diagnosis delay: Studies have shown that a longer time from symptoms onset to diagnosis is associated with a better prognosis (Haverkamp et al., 1995; Thijs et al., 2000). This could indicates that patients seeking medical attention more rapidly probability have a more aggressive progression that leads to shorter diagnosis delay (del Aguila et al., 2003).

Rate of disease progression: The rate of disease progression, assess by the Revised ALS Functional Rating Scale (ALSFRS-R) score, was significantly related to prognosis (Kimura et al., 2006; Kollewe et al., 2008). ALSFRS-R is a validated rating instrument for monitoring the progression of disability in patients with ALS (Cedarbaum et al., 1999). ALSFRS-R slope has also been evaluated as a prognosis predictor (Marin et al., 2016a). ALSFRS-R slope is the ratio of the difference between the ALSFRS-R score obtained at diagnosis and a presumed normal score just before symptom onset to the diagnostic delay.

Cognitive impairment: The prognosis appears to be worse in ALS patients with cognitive impairment. This seems to be related to the impairment severity. For instance, a study found that mild cognitive impairment was no associated with survival in multivariate analyses (Rippon et al., 2006), while several studies reported that ALS patients with frontotemporal dementia (FTD) have significantly shorter survival compared to those without cognitive or behavior impairment (Crockford et al., 2018; Elamin et al., 2011). This could be due to poor compliance for health care management such as non-invasive ventilation and percutaneous endoscopic gastrostomy (Chiò et al., 2012). A study showed that patients with ALS-FTD were more likely to be noncompliant for NPPV compared to patients with classic ALS (relative risk for

noncompliance 2.00, CI 1.1 to 3.6; $p = 0.013$) (Olney et al., 2005). Nevertheless, patients with ALS-FTD had a shorter survival even after NPPV initiation with an adjusted hazard ratio of 2.70 (95 % CI 1.04 - 4.67, $p = 0.04$) according to a recent study (Govaarts et al., 2016).

Nutritional status: The nutritional status is a prognostic factor in ALS. A prospective study showed that patients with malnutrition, assessed by body mass index, presented a higher risk of dying in the multivariate analysis (relative risk = 7.4, 95% CI, 1.7 to 32.1, $p < 0.01$) (Desport et al., 1999). A higher risk of death was observed in patients with a weight loss from 5% and over of usual at the time of diagnosis compared to those whose weight remained stable or dropped by less than 5% (median survival time: 20.6 months (95% CI 12.4 to 29.0) vs 29.0 months (95% CI 21.2 to 38.5) (Marin et al., 2011b)

Respiratory status: Respiratory function is a relevant factor for ALS prognosis. Studies have described an association between forced vital capacity (FVC%) at time of diagnosis and survival (Chiò et al., 2002; Shoesmith et al., 2007; Stambler et al., 1998). A cohort study found that median survival for ALS patients with baseline FVC <75% was statistically shorter compared to patients with baseline FVC >75% (2.91 years vs 4.08 years, $p < 0.001$) (Czaplinski et al., 2006). Other indicators of respiratory function have been significantly correlated with survival such as per cent predicted vital capacity (VC%) and sniff nasal inspiratory pressure (SNIP) (Lyall et al., 2001; Schiffman and Belsh, 1993).

I.5.3. Treatment and management

Riluzole: This neuroprotective drug that blocks glutamatergic neurotransmission in the central nervous system is the only available disease-modifying therapy for ALS. Evidence from randomized controlled trials showed a reduced relative risk of dying at 12 months in patients with riluzole compared to patients with placebo (relative risk = 0.78, 95% CI 0.65 to 0.92) (Miller et al., 2012).

ALS centers and multidisciplinary care: Two population-based studies have found that survival was longer in ALS patients attending a multidisciplinary clinic or tertiary ALS centers compared to those attending to hospital facilities or general neurology clinic (Chiò et al., 2006; Traynor et al., 2003). The median survival was 7.5 months longer in patients attending an ALS clinic than for patients in the general neurology cohort ($p < 0.0001$) (Traynor et al., 2003). However, another prospective population-based study found no survival differences in patients attending multidisciplinary clinics (Zoccolella et al., 2007).

A recent study compared survival times between patients with ALS attending to referral centers and the entire ALS population in the same geographic area (Logroscino et al., 2018a). Four European ALS registers were considered in the analysis: Ireland (Irish ALS register), Italy (Piedmont and Puglia) and France (Limousin). A longer survival was observed in patients referred to ALS centers ranging from 11% to 15%. This observation could be explained by differences in age and clinical characteristics of patients (e.g. type of onset) along with a positive effect of the multidisciplinary care.

I.6. Management

Several key points have been recommended by the European Federation of Neurological Societies guideline on treatment and management of ALS (EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis: et al., 2012) including the following points:

- Riluzole treatment should be offered as early as possible after diagnosis in patients with ALS.

- Symptoms should be treated such as sialorrhea, bronchial secretions, pseudobulbar emotional lability, cramps, spasticity, insomnia, fatigue, depression and anxiety.

- Multidisciplinary care should be available for ALS patients with the following specialists and health care staff: neurologist, respiratory physician, gastroenterologist, rehabilitation medicine physician, social worker, occupational therapist, speech

therapist, respiratory therapist, specialized nurse, physiotherapist, dietitian, psychologist, dentist and palliative care physician.

- Patient follow-up should be performed every 2–3 months.
- Symptoms or signs of respiratory insufficiency should be checked at each visit and proper intervention is necessary.
- Patients should be referred to a dietitian as soon as dysphagia appears. Early and appropriate interventions need to be considered.
- It is recommended to initiate discussions on palliative care and end-of-life decisions.

Chapter II. Epidemiological and clinical variability of amyotrophic lateral sclerosis

The standardized amyotrophic lateral sclerosis incidence worldwide has been estimated at 1.68 (95% CI, 1.50 – 1.85) per 100,000 PYFU based on population-based studies (Marin et al., 2017). In the recent decades, studies suggest that ALS presents a broad range of variability in terms of epidemiological indicators and clinical features between geographic areas and populations. Improving our understanding of ALS heterogeneity will provide new clues on potential determinant factors to develop the disease and the different clinical expressions. In an effort to better understand ALS variability, evidence needs to be addressed in a comprehensive way, in order to gain more insights of their potential implications and future directions. Here, we have performed a review to put into perspective epidemiological and clinical data of ALS.

II.1. Research objectives

General objective

- To assess ALS variability in terms of incidence, mortality and clinical characteristics between geographic areas and populations.

Specific objectives

- To describe ALS variability based on the scientific evidence available concerning epidemiological and clinical characteristics between geographic areas and populations.

- To describe and compare the clinical characteristics and survival of patients with ALS in Africa.

- To describe and compare ALS mortality among ethnic groups in Ecuador, a predominant admixed population from Latin America.

II.2. Epidemiological variability of ALS among geographic areas

Over the last decades, the evidence suggests that ALS distribution might not be uniform around the world. This scientific query has raised interest due to their potential implications. A heterogeneous pattern worldwide could imply that certain populations are at higher risk to develop ALS due to environmental or genetic factors. Nevertheless, it is complicated to find evidence for this issue since epidemiological data are mainly restricted to certain geographic regions and there are methodological concerns in several studies. In this context, relevant evidence will be presented to put into perspective ALS variation worldwide.

II.2.1. Worldwide distribution of ALS

In the nineties, a systematic review provided some clues of the worldwide distribution of motor neuron disease (Chancellor and Warlow, 1992). The authors described mortality and incidence of the disease since 1950. A wide variability of epidemiological indicators was observed. The review considered mainly retrospective studies from Europe. Incidence rates were based on nine studies that used multiple sources of case ascertainment (Europe n=6, North America n=2, Asia n=1). The crude retrospective incidence per 100,000/year ranged from 0.6 (95% CI, 0.5 – 0.7) in Sardinia, Italy from 1965 to 1974 (Rosati et al., 1977) to 2.6 (95% CI, 2.1 – 3.2) in Sweden from 1970 to 1981 (Gunnarsson and Palm, 1984). There was a similar variation in ALS mortality. Based on 12 mortality studies, the crude mortality rate per 100,000 ranged from 0.4 to 0.6 in Japan between 1952 and 1971 (Kondo and Tsubaki, 1977) and from 1.0 to 2.5 Sweden between 1961 and 1985 (Gunnarsson et al., 1990). Nevertheless, it was difficult to draw conclusions due to several limitations. The principal limitation was the scarce data outside Europe, which made it difficult to establish a reliable picture of the worldwide ALS distribution. At that time, there was no standardized diagnosis criteria for ALS, since the El Escorial criteria was not launched before 1994 by the World Federation of Neurology Research Group on Neuromuscular Diseases (Brooks, 1994). Methodological concerns were also expressed such as case ascertainment exhaustiveness and quality of certain studies.

A further systematic review based on 37 studies (hospital-based and population-based) reported ALS incidence and prevalence worldwide (Chiò et al., 2013). Once again, most of the literature available consisted of European studies (Europe n=25, North America n=5, Asia n=6, South America n=1). The median incidence was 1.90/100,000 PYFU (inter-quartile ranges (IQR) 1.37 – 2.40) considering all studies. A wide range of prevalence and incidence was observed between geographical areas. The lower crude incidence were reported in China (0.3/100,000 person-year) (Fong et al., 1996) and Iran (0.4/100,000 person-year) (Sajjadi et al., 2010). In Europe, incidence varied from 0.5/100,000 in former Yugoslavia (Alcaz et al., 1996) to 3.6 in the Faroe Islands (Joensen, 2012). The analysis considering different geographical regions showed that the median ALS incidence rate was 2.08 (IQR 1.47 – 2.43) in Europe, 1.80 (IQR 1.75 – 2.02) in North America and 0.46 (IQR 0.38 – 0.53) in Asia. Researchers estimated that overall median prevalence was 4.48 (IQR 3.03 – 6.70) per 100,000 people. Prevalence also varied between geographic areas with an estimate of 5.40 (IQR 4.06 – 7.89) in Europe, 3.40 (IQR 3.15 – 3.65) in North America and 2.01 (IQR 1.48 – 2.54) in Asia. These findings support the hypothesis of a heterogeneity distribution of ALS. However, the authors recognized that low incidence rates could also be related to methodological differences between the studies (e.g. prospective versus retrospective design, one or multiple sources of case ascertainment).

To further clarify the global ALS incidence, a meta-analysis was performed to control potential biases and explore potential factors of heterogeneity. The authors included only population-based studies of newly diagnosed cases using multiple sources of case ascertainment (gold standard methodology). The age population structure was considered to provide crude and standardized incidence (Marin et al., 2017). Overall, 44 studies were included covering 45 geographical areas (Europe n = 24, North America n = 10, South America n = 2, Asia n = 5, Africa n = 1, Oceania n = 1, Hawaii n = 1, and Caribbean n = 1). The pooled crude incidence per 100,000 PYFU was estimated at 1.75 (95% CI, 1.55 – 1.96). Standardized incidence based on the US 2010 population was reported for 42 geographical areas (Europe n = 22, North

America n = 10, South America n = 2, Asia n = 5, Africa n = 1, Oceania n = 1, and Caribbean n = 1) due to data availability (number of ALS cases by age and sex groups). The pooled worldwide standardized incidence was 1.68 (95% CI, 1.50 – 1.85) per 100,000 PYFU (Figure 6). A subgroup analysis was performed considering different geographic areas based on subcontinents' classifications according to the United Nations Statistics Division (United Nations, 1999). The meta-analysis showed a homogenous incidence in Europe, North America and New Zealand with a pooled standardized incidence of 1.81 (95% CI 1.66 – 1.97) per 100,000 PYFU. There were statistically significant differences on ALS standardized incidence rates between Northern Europe (1.89, 95 CI, 1.46 – 2.32) and Eastern Asia (0.83, 95% CI 0.42 – 1.24, *p*=0.001), and Southern Asia (0.73, 95% CI 0.58 – 0.89, *p*= 0.02). ALS worldwide distribution is shown in figure 6. A meta-regression was performed to assess the potential sources of heterogeneity such as study population characteristics (life expectancy after 50 years in men and women and sex ratio of the study population), study design (prospective/retrospective), diagnosis criteria, period and duration of the study, person-years of follow up. The subcontinent was identified as a significant source of heterogeneity. This finding supports the hypothesis of a heterogeneous ALS distribution between geographic areas.

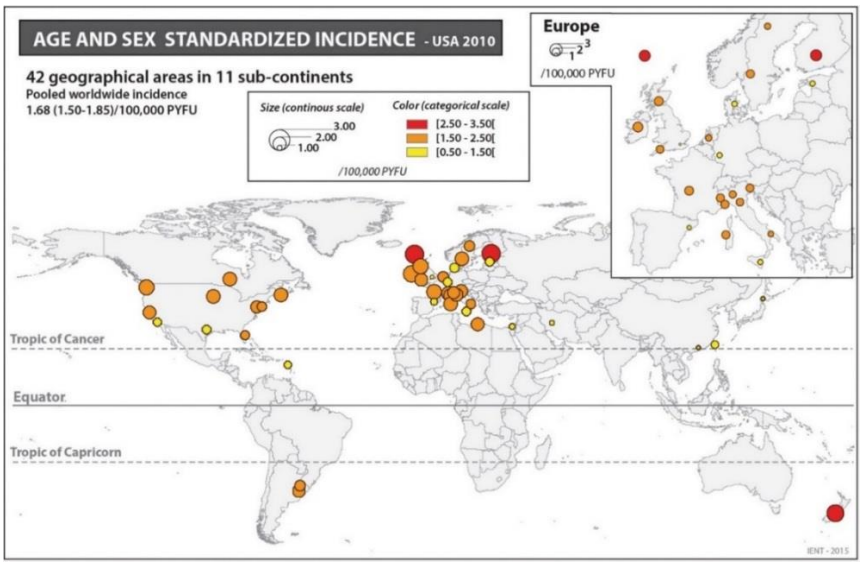

Figure 6 : Distribution of ALS worldwide: standardized incidence based on 2010 US population

Source: (Marin et al., 2017)

The Global Burden of Diseases (GBD) has recently published a systematic analysis to estimate epidemiological indicators of motor neuron diseases for 195 countries and territories from 1990 to 2016. The study assessed the relationship between age-standardized rates of MND and the socio-demographic index (SDI), which is a measure of the social development of a country based on education, income, and fertility (Logroscino et al., 2018b). Age-standardized rates were based on the GBD reference population (Wang et al., 2017).

The results of this study showed that the worldwide prevalence was 4.5 (95% CI, 4.1 – 5.0) per 100,000 people. A heterogeneous geographic distribution was observed with the highest prevalence in high-income regions, such as North America (20.2, 95% CI 19.0 – 21.5), Australasia (17.7, 95% CI 16.2 – 19.2) and Western Europe (16.7, 95% CI 15.3 – 18.1). After age-standardization, the prevalence per 100,000 people remains higher at 16.8 (95% CI 15.8 – 17.9) in North America, 14.7 (95% CI 13.5 – 16.1) in Australasia, 12.9 (95% CI 11.7 – 14.1) in Western Europe. Interestingly, age-standardized prevalence was lower among regions with high SDI values such as Asia Pacific, southern Latin America, Eastern Europe and central Europe (Figure 7).

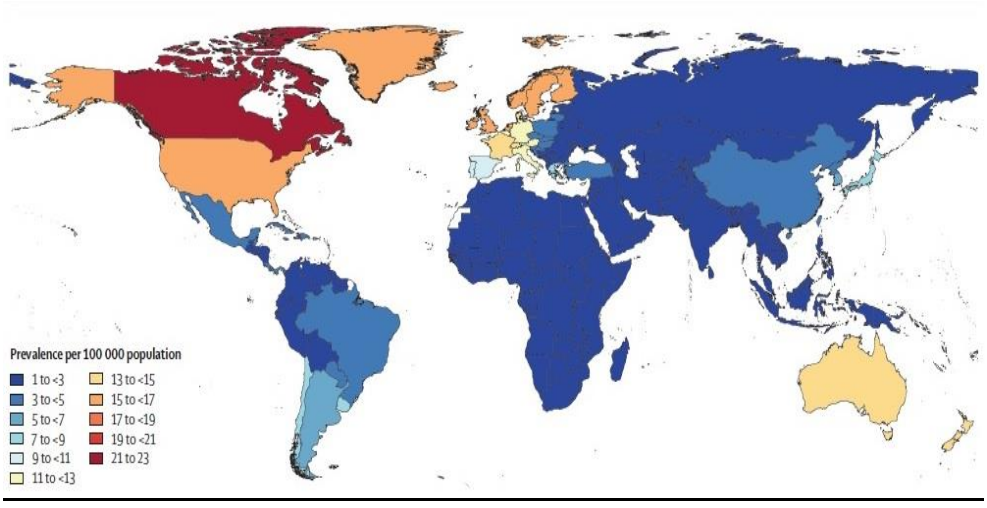

Figure 7 : Age-standardized prevalence of motor neuron disease worldwide

Source : (Logroscino et al., 2018b)

The GBD study also reported that the worldwide incidence was 0.78 (95% CI 0.71 – 0.86) per 100,000 person-years. The age-standardized incidence per 100,000 person-years was higher

in Australasia (2.77, 95% CI 2.63 – 2.91), North America (2.30, 95% CI 2.20 – 2.41) and Western Europe (2.00, 95% CI 1.89 – 2.11). The rates in high-income North America, Western Europe, and Australasia were higher than expected based on their SDI levels. Conversely, high SDI Asia Pacific region showed lower rates than expected based on the SDI level.

This study showed that age-standardized rates changed in each SDI level, which suggests that other factors than sociodemographic development are related to the geographical heterogeneity of the disease. In addition, GBD study assessed the relationship between several risk factors and geographical heterogeneity. No statistically significant association was found. Therefore, heterogeneity was not explained by any risk factors quantified in GBD. These results all suggest that other factors that have not yet been quantified might be related to the geographical variability.

Heterogeneity in the occurrence of ALS in different geographic regions could imply that genetic, ancestral origin and ethnicity of the populations might play a major role in the risk of developing the disease. This is supported by several ALS studies among different ethnic groups that repeatedly showed lower incidence, mortality and prevalence in certain populations (Cronin et al., 2007). In addition to this fact, evidence based on population-based studies (gold standard methodology) has shown that ALS incidence is homogenous among European origin populations from Europe, North America and New Zealand (Marin et al., 2017).

II.2.2. Historical geographic cluster

Geographic variability is a key subject to understand the risk of developing diseases. Important lessons have been learned from geographic areas with higher incidence of ALS. The most remarkable example includes the Guam Island located in the Western Pacific. The incidence of ALS-Parkinsonism dementia complex (ALS-PDC) was between 50 and 100 times higher than in the rest of the world in the 1950s (Arnold et al., 1953; Koerner, 1952). The highest peak was observed from 1950 to 1954 with an incidence of 73 per 100,000 PYFU in males and 41

per 100,000 PYFU in females (Kurland and Mulder, 1954). Incidence progressively declined in the 1980s (5 per 100,000 PYFU in male and 4 per 100,000 PYFU in female) until reaching similar incidence rates as other areas of the world (around 1 to 2 per 100,000 PYFU) (Plato et al., 2003). The higher incidence of ALS localized in a specific geographic area brought several etiological hypotheses including familial aggregation (however, no definitive inheritance pattern could be recognized) and environmental exposures. An interesting hypothesis involved the consumption of a neurotoxin, β-N-methylamino-L-alanine (L-BMAA) (Bradley and Mash, 2009; Delzor et al., 2014; S. J. Murch et al., 2004). L-BMAA could have been ingested by the local population, named Chamorro, through multiple dietary sources (cycad flour, flying foxes and animals that feed on cycad seeds) (Banack et al., 2006; Cox et al., 2003; Susan J. Murch et al., 2004). It has been suggested that the decrease in the number of cases could be due to lifestyle modifications in the last decades such as changes in place of residence, elimination of food supplies associated with toxins, and other exposures (Marin et al., 2018a; Pobocik et al., 1999).

II.3. Epidemiological variability of ALS among ethnic populations

Research in the field of genetics identified susceptibility genes for ALS. A certain number of potential risk variants were found only in certain populations. Angiogenin (ANG) gene was reported as a susceptibility gene for ALS in the Irish and Scottish populations (Greenway et al., 2004), although no association was observed in the populations from the USA, England or Sweden (Greenway et al., 2006). Several haplotypes in the vascular endothelial growth factor (VEGF) sequence were associated with increased risk of ALS in populations from Sweden, England and Belgium (Lambrechts et al., 2003). The association was no found in populations from England (Brockington et al., 2005), Netherlands (Van Vught et al., 2005), USA (Chen et al., 2006), Italy (Del Bo et al., 2008), Germany (Fernández-Santiago et al., 2006) and China (Zhang et al., 2006). These findings led researchers to suggest that ethnic background could play a role in the disease occurrence (Cronin et al., 2007).

II.3.1. Ancestral background: Epidemiological definitions

Prior to discussing the potential association between the ancestral origin background and ALS, it is necessary to mention certain definitions on ethnicity and "racial" background. The National Institutes of Health (NIH) in the USA categorized populations into "race" and ethnicity for biomedical research. This classification was set for standardized data collection of Federal statistics according to the Office of Management and Budget, Office of Information and Regulatory Affairs.

There are five categories for "race": i) American Indian or Alaska Native, ii) Asian, iii) Black or African American, iv) Native Hawaiian or Other Pacific Islander, and v) White. There are two categories for ethnicity: i) Hispanic or Latino and ii) Not Hispanic or Latino. Definitions of each category are shown in the table 2.

Table 2 : National Institutes of Health (USA) categories for “race” and ethnicity

	Categories	Definitions
“Race”	American Indian or Alaska Native	A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.
	Asian	A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent.
	Black or African American	A person having origins in any of the black racial groups of Africa.
	Native Hawaiian or Other Pacific Islander	A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
	White	A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.
Ethnicity	Hispanic or Latino	A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.
	Not Hispanic or Latino	Not Available

The federal institutions in the USA considered that these categories should not be interpreted as being primarily biological or genetic in reference. Instead, it could be understood in terms of social and cultural characteristics as well as ancestry. Emphasis is placed on the respect for individual dignity to guide the collection of this information. It is also important to highlight that this classification is mainly used in the USA.

At this point, the definition of admixed population also needs to be included in our discussion. Admixed ancestral origin is refer to mixed ancestral origin. Admixture refers to the process in which individuals from two or more geographically isolated populations with different allele frequencies mate and form a new mixed or “hybrid” population (Chakraborty, 1986; Redden et al., 2006).

The terminology used to classify populations is heterogeneous worldwide. As an illustration, Caucasian is another frequently used term to denote European ancestry origin. The term refers to a common origin in the distant past in the Caucasus region of Central Europe (Bhopal and Donaldson, 1998). In the UK, researchers classified cases based on their ancestral origin (e.g. European or African origin). In some geographic regions such as Latin America, people could be categorized in ethnic groups based on cultural aspects. The definition of ethnicity is therefore widely different around the world.

Heterogeneity of definitions raises a real problem for epidemiological comparison. Furthermore, another important issue that this matter raises is if ethnicity or “race” might genuinely be a proxy of ancestral origin. These limitations will be addressed in the following chapters.

II.3.2. Amyotrophic lateral sclerosis among ethnic populations

To return to the issue of ALS among different populations, it is necessary to begin describing the first systematic review that assessed epidemiological indicators among ethnic populations. Based on 61 studies, it was postulated a lower risk to develop ALS among African, Asian, and Hispanic populations compared to Caucasian populations (Cronin et al., 2007). The authors came to this conclusion by observing two facts: first, a geographic variability of epidemiological indicators. Second, a heterogeneity in terms of incidence and mortality among ethnic groups. However, studies in the review were heterogeneous with regard to methodology (e.g. population-based studies and hospital-based) and case ascertainment.

II.3.2.1. Data from multiethnic populations: ALS incidence

Data from multiethnic populations (mainly form the USA and the United Kingdom) have provided useful information to examine the variation of ALS epidemiology between ethnic groups within a given region. New evidence continues to support the hypothesis that populations of European origin or Caucasians exhibit a higher risk of developing ALS.

A retrospective study in California (USA) provided demographic profiles and incidence estimates in the San Francisco Bay Area (SFBA) and Los Angeles County (LA) using multiple sources of case-ascertainment. The results showed different incidence rates among ethnic groups. These areas were selected for their racial and ethnic diversity (categorizing “race” and ethnicity according to the NIH definition). The overall age-standardized incidence was 2.01 (95% CI 1.8 – 2.3) in SFBA and 1.17 (95% CI 1.0 – 1.3) in LA. In the San Francisco Bay Area, a higher age-standardized incidence was observed in whites (2.5, 95% CI 2.2 – 2.9) compared to blacks (1.52, 95% CI 0.9 – 2.4) and Asians (1.0, 95% CI 0.7 – 1.4). The variation among

“races” was consistent with incidence rates in Los Angeles County (whites (1.40, 95% CI 1.2 – 1.6), blacks (1.03, 95% CI 0.7 – 1.5) and Asians (0.66, 95% CI 0.5 – 0.9). Considering the ethnic groups in the areas, Hispanics presented a slightly lower standardized incidence compared to non-Hispanics in the San Francisco Bay Area (Hispanic 1.57 (95% CI 1.0 – 2.3) vs Non-Hispanic 1.89 (95% CI 1.7 – 2.2)) and Los Angeles County (Hispanic 0.66 (95% CI 0.5 – 0.9) vs Non-Hispanic 1.01 (95% CI 0.9 – 1.2)) (Valle et al., 2015).

Another study was interested in ALS prevalence and incidence between ethnicity and “race” in three states (Florida, New Jersey and Texas) and eight metropolitan areas (Atlanta, Baltimore, Chicago, Detroit, Las Vegas, Los Angeles, Philadelphia and San Francisco) of the USA. The study covered approximately 27% of the USA population. A total of 5,883 cases were identified (74.8% were white, 9.3% were African-American/black, 3.6% were Asian, 12.0% were of unknown race, and 0.3% were categorized as other race (e.g. American Indian, Caribbean, and multiple races)). According to ethnicity, most of them were non-Hispanics (77.5%). The crude incidence rate per 100,000 person-years was 1.79 (95% CI 1.68 – 1.91) in whites, 0.80 (95% CI 0.64 – 0.95) in African Americans and 0.76 (95% CI 0.53 – 0.99) in Asians. Differences remains after age standardization with higher incidence in whites (1.48, 95% CI 1.42 – 1.53) compared to African Americans (0.89, 95% CI 0.79 – 0.99) and Asians (0.78, 95% CI 0.64 – 0.92). Similarly, incidence rates were different between Hispanics (0.84, 95% CI 0.75 – 0.92) and non-Hispanics (1.36, 95% CI 1.31 – 1.41) (Rechtman et al., 2015).

A different population-based study compared ALS incidence rates among people of African ancestry and European ancestry in London. The age- and sex-standardized incidence was 1.97 (95% CI 1.55 – 2.48) in the European ancestry group and 1.35 (95% CI 0.72 – 2.30) in the African ancestry group. There was no statistically significant difference in the relative risk (1.45, 95% CI 0.74 – 2.89) between the European and African groups. However, the results were limited by a small proportion of cases with African ancestry (Rojas-Garcia et al., 2012).

To sum up, lower incidence has been reported consistently among Hispanics, Africans, and Asians populations compared to Caucasians. The differences in rates remain similar after population standardization. Studies reporting ALS standardized incidence rates among ethnicity and "race" groups are shown in table 3.

Table 3 : Studies reporting ALS standardized incidence per 100,000 person-years among ethnic and "race" groups

Subcontinent	Country	Authors	Study period	Race/ethnic group	Standardized incidence (95% CI)
Northern America	USA San Francisco Bay Area	(Valle et al., 2015)	2009 - 2011	White	2.49 (2.2 – 2.9)
				Black	1.52 (0.9 – 2.4)
				Asian	1.00 (0.7 – 1.4)
				Hispanic	1.57 (1.0 – 2.3)
				Non-Hispanic	1.89 (1.7 – 2.2)
	USA Los Angeles County	(Valle et al., 2015)	2009 - 2011	White	1.40 (1.2 – 1.6)
				Black	1.03 (0.7 – 1.5)
				Asian	0.66 (0.5 – 0.9)
				Hispanic	0.66 (0.5 – 0.9)
				Non-Hispanic	1.01 (0.9 – 1.2)
	USA	(Rechtman et al., 2015)	2009 – 2011	White	1.48 (1.42-1.53)
				African American	0.89 (0.79-0.99)
				Asian	0.78 (0.64-0.92)
				Non-Hispanics	1.36 (1.31-1.41)
				Hispanic	0.84 (0.75-0.92)
	USA	(McGuire et al., 1996)	1990 - 1995	Non-white	0.74 (0.00–1.96) m 0.53 (0.00–1.91) w
				Overall	2.11 (1.27–2.93) m 1.87 (1.08–2.66) w
	USA	(Annegers et al., 1991)	1985 - 1988	White	1.36 (0.96-1.87) m 1.25 (0.88-1.72) w
				Hispanic	1.27 (0.41–2.96) m 0.10 (0.00–0.46) w
				African American	1.10 (0.48–2.17) m 0.70 (0.28–1.44) w
Northern Europe	UK	(Rojas-Garcia et al., 2012)	2002 - 2008	European origin	1.97 (1.55 – 2.48)
				African origin	1.35 (0.72 – 2.30)

Table 3 has been adapted and updated from: "Current issues in ALS epidemiology: Variation of ALS occurrence between populations and physical activity as a risk factor" (Luna et al., 2017).
95% CI: 95% confidence interval; m, men; w, women.

A lower ALS incidence was not only found in studies that compare different ethnic groups but also in studies carried out in specific ethnic populations. For instance, a study was interested in determining incidence among American Indians and Alaska Natives (AI/ANs) in the USA. Using data from the Health Service, researchers found that the age-standardized incidence

was 0.92 per 100,000 person-years (Gordon et al., 2013). Therefore, the incidence among American Indians and Alaska Natives seems to be lower than reported for white population (close to 2/100,000).

II.3.2.2. Data from multiethnic populations: ALS mortality

Another epidemiological indicator used to estimate the occurrence of ALS is the mortality rates. It could be assumed that all patients diagnosed with the condition will eventually be identified via the death certificate given the invariable fatal outcome of the disease (Marin et al., 2011a). Therefore, mortality rates have been used as proxies to provide an estimate of incidence in ALS.

Studies among ethnic groups have repeatedly shown that ALS mortality was higher in white populations compared to Hispanic and African-American populations (Leone et al., 1987; Marin et al., 2011a; McCluskey L, 2004).

A study was performed using multiple-cause mortality files from the National Center for Health Statistics from 1969 to 1998 in the USA. The authors reported that the age-standardized mortality per 100,000 person years was 1.96 (95% CI 1.89 – 2.02) for non-Hispanic whites, 0.92 (0.75 – 1.08) for Hispanics and 1.06 (0.94 – 1.18) for African Americans. Hence, mortality rates among African Americans and Hispanics were approximately 50% lower than rates among non-Hispanic whites (Noonan et al., 2005).

Another retrospective study on ALS mortality was carried out using the national multiple cause-of-death from 1979 to 2001 in the USA. A higher mortality rate was observed in whites compared to blacks or other groups. The relative risk (RR) for blacks (RR = 0.62, 95% CI 0.60 – 0.64) and other groups (RR = 0.42, 95% CI 0.40 – 0.46) was lower than that for whites (Sejvar et al., 2005).

In the United Kingdom, a study among immigrants showed that ALS mortality rates was lower among Asian (standardized mortality ratio (SMR) = 37.6%), East African (SMR = 55.5%),

Caribbean (SMR = 73.6%), and West African (SMR = 76.9%) immigrants to London as compared to native English from 1979 to 1988 (Elian and Dean, 1993). However, the denominators of ethnic populations were not known for that time period and ethnicity was assigned based on the individual's name.

Variability of mortality rates among ethnic groups and populations could be related to socioeconomic status or differences in the access to health care or validity of death certificates information. To address most of these issues, a recent mortality study used an adjusted model for socioeconomic status, type of health insurance, and birthplace to estimate the ALS mortality risk in different ethnic groups in the USA. Within this adjusted model, higher rates were reported among whites compared to other populations (non-Hispanic black, HR 0.61 (95% CI 0.48 – 0.78); Hispanic, HR 0.64 (95% CI 0.46 – 0.88); other races, non-Hispanic, HR 0.52, (95% CI 0.31 – 0.86)) (Roberts et al., 2016).

If we are interested in ALS studies in geographic areas with admixed populations, we can highlight that two mortality studies have been conducted in ethnically admixed populations.

In Cuba, a population-based study described ALS mortality rates using multiple-cause mortality files from the Central Statistics office. The age-adjusted mortality rates were calculated over a 6-year period by sex, race/ethnicity, age, and geographic region at time of death. A lower adjusted mortality per 100,000 was observed in the admixed population (0.55, 95% CI 0.4 – 0.72) compared to white population (0.93, 95% CI 0.83 – 1.03) and black population (0.87, 95% CI 0.62 – 1.17). The differences in rates were statistically significant between white and admixed populations (rate ratio (RR), white as reference = 0.44, 95% CI 0.33 – 0.59), and black and admixed populations (RR, black as reference = 0.31, 95% CI 0.21 – 0.45). There was no significance differences between white and black populations (RR, white as reference = 0.88; 95% CI 0.64 – 1.2) (Zaldivar et al., 2009).

In Brazil, a retrospective epidemiological study determined ALS mortality rates using death certificates over 10 years. Overall, 8,942 ALS deaths were reported, of which 73.4% occurred

in Caucasians, 16.8% in admixed populations, 3.8% in blacks, 0.8% in Asians, and 0.1% in Indigenous. It was not possible to identify the ethnic population in 5.1% of deaths. The authors estimated the odds ratios (ORs) among ethnic groups compared to the general population. A higher risk of dying with ALS was observed in Caucasians (OR = 2.92, 95% CI 2.78 – 3.07). Conversely, a lower risk was found in admixed (OR = 0.27, 95% CI 0.26 – 0.29), Asians (OR = 0.05, 95% CI 0.04 – 0.07), Blacks (OR = 0.04, 95% CI 0.03 – 0.04) and Indigenous (OR = 0.02, 95% CI 0.01 – 0.04) (Moura et al., 2016).

The results found in admixed populations from Cuba and Brazil were similar to those in Hispanic populations in the USA, which represent a proxy of admixed populations. At this time, the epidemiological evidence supports the hypotheses that Caucasians have an increased risk of developing ALS compared to other ethnic groups. Further research is needed to clarify this issue and provide reliable data among different populations.

II.4. Clinical variability of ALS

The classic form of ALS is characterized by upper and lower motor neurons degeneration in an anatomic region with the subsequent progression to other regions (brainstem, cervical, thoracic, or lumbosacral spinal cord). The progression is irreversible, which leads to death usually from respiratory failure. The clinical features are not as straightforward as it seems since new evidence suggests that the clinical presentation is far greater than assumed previously. ALS presents a broad clinical expression with highly variable range of UMN and LMN involvement at onset and during the disease course. New findings give us a more insight into better understanding the complexity of the disease. The ALS conception is changing nowadays. This is illustrated for example by studies showing that cognitive impairment is more frequent than expected in patients with ALS (Couratier et al., 2017). This means that neurodegeneration spread beyond the motor neuron system. In the next section, we discuss the clinical spectrum and clinical variability of ALS.

II.4.1. Age and site at disease onset

ALS is the most frequent motor neuron disease in adults with a peak incidence among the sixth and seventh decades of life followed by a sharp decrease (Marin et al., 2018b). Juvenile forms and early-onset in young-adult have been described. Juvenile ALS is defined by an age at onset before 25 years (Orban et al., 2007). Young-adults could have an early-onset around the third or fourth decade of life (Ben Hamida et al., 1990; Sabatelli et al., 2008).

Recent original investigations reported variability of age at onset between geographic areas (Marin et al., 2016b). A younger age at onset (around 50 to 60 years) were reported in Israel (Kahana and Zilber, 1984) and Libya (Radhakrishnan et al., 1986). Conversely, age at onset was particularly homogenous in North America, Europe and New Zealand (around 60 to 65 years). These differences could be related to variations in demographic structures of populations. For instance, a study showed a positive correlation between mean age at onset and life expectancy in the general population ($r = 0.91$, $p = 0.01$) (Byrne et al., 2013).

Interestingly, age at onset differences have been also reported among populations in multiethnic studies. A hospital-based cohort of patients with ALS described a significantly lower age at onset in African Americans (around 55 years) compared to patients with an European background (around 61 years), p=0.011 (Kazamel et al., 2013). Selection bias could have played a major role in the systematic inclusion of young African patients with ALS in this study. A systematic review interested in the epidemiology of ALS among subjects of African origin concluded that those patients exhibited a higher proportion of juvenile form and younger age at onset for classic ALS (Marin et al., 2012). It is still difficult to provide firm conclusions on variability of age at onset due to the limited data available between different populations.

The spinal onset is the most common form in patients with ALS, while bulbar onset is described in approximately one third of cases (Marin et al., 2016b; Swinnen and Robberecht, 2014). A geographic variability of the type of onset has been suggested in recent studies. The proportion of bulbar onset was broadly variable between geographical areas worldwide. There was also a significant variation even within continents. In Europe, the pooled estimate of bulbar onset ALS was 45.4 % (95% CI, 38.1 – 52.8) in Northern Europe, 34.9 % (95% CI, 32.5 – 37.3) in Western Europe and 34.2 % (95% CI, 31.3 – 37.3) in Southern Europe. Bulbar onset seems to be lower in North America (28.6, 95% CI 24.3 – 33.4), East Asia (27.9, 95% CI 18.8 – 39.4), West Asia (22.0, 95% CI 17.6 – 26.9) and South Asia (26.5, 95% CI 18.1 – 36.4) (Marin et al., 2016b). These differences remain unexplored. Further clinical studies in different populations could provide insights to clarify this issue.

II.4.2. Sex ratio

ALS exhibits a slightly predominance of male cases. A male/female sex ratio (SR) of 1.3 has been reported in Western studies form Europe, North America and New Zealand. In other parts of the world, differences seems to be greater with a SR around 2 (Radhakrishnan et al., 1986; Sajjadi et al., 2010; Vázquez et al., 2008).

A high degree of SR variation was also observed in studies regarding multiethnic populations in specific geographic areas. A study in Hawaii described a SR of 1.8 for Caucasians, 2.5 for Japanese and 22.9 for Filipinos (Matsumoto et al., 1972). In a multiethnic Asian population study, the proportion of males with ALS was different between ethnic groups (51.1% Chinese, 78.6% Malays and 66.7% Indians) (Goh et al., 2011). It remains to be determined whether these differences on sex distribution are objectively genuine between populations or it could be explained by differences in terms of the population structure, accessibility to the health system or reduced case ascertainment in females. Differences in study design (retrospective vs prospective) and case ascertainment sources (hospital-based vs population-based) could also be related to this apparent disparity on sex distribution. The impact of these biases has been clearly illustrated in Western publications, for example, the SR was consistently reported around 2 before 1990 due to methodological issues (Højer-Pedersen et al., 1989; Rosati et al., 1977). Recent studies in Western countries based on population-based methodology have revealed a decrease SR closer to 1 (Logroscino et al., 2008; Marin et al., 2016b).

II.4.3. Familial ALS

Around 5% to 10% of ALS cases are familial (fALS), usually inherited as dominant traits. The remaining 90% to 95% of cases of ALS are sporadic (Brown and Al-Chalabi, 2017). A meta-analysis reported a pooled estimate for fALS at 5.1% (95% CI 4.1% to 6.1%) using prospective population-based registry data (Byrne et al., 2011).

It has been described a variation in the distribution of fALS between geographic areas. According to another meta-analysis considering 29 population-based studies, the overall proportion of fALS worldwide was 4.7 % (95 % CI 3.9 – 5.7) (Marin et al., 2016b). The proportion of familial ALS was higher in certain regions like North Europe (5.2, 95% CI 3.5 – 7.5, p= 0.09), Western Europe (5.4, 95% CI 4.3 – 6.7, p = 0.04) and North America (6.7, 95% CI 5.3 – 8.4) compared to Southern Europe (3.3, 95% CI 1.9 – 5.5). Furthermore, a lower proportion of fALS was observed in Asia (1.2%, 95% CI 0.0 – 6.5, in Hong Kong and 0.6 %,

95% CI 0.1 – 2.3, in Israel). These findings could imply the existence of a more important hereditary component in certain populations.

II.4.4. Genetics variants

Directly related to the previous topic, the latest studies point to the fact that the proportion of genetic variants associated to ALS are displayed differently among geographic areas and populations.

The hexanucleotide repeat expansion in C9orf72, which is the most frequent known ALS-associated genetic variant, is highly prevalent in Europe. C9orf72 exhibit a higher frequency in familial ALS ranging from 27.1% in Spain (García-Redondo et al., 2013) to 46.0% in Finland (Renton et al., 2011). In sporadic ALS, the repeat expansion ranges from 3.2% in Spain (García-Redondo et al., 2013) to 21.1% in Finland (Renton et al., 2011). The proportion of C9orf72 is far lower in Asia. A study of 563 Japanese patients with ALS found the repeat expansion only in two cases among 552 sporadic ALS cases (0.4%) and none over 11 patients with familial ALS (0.0%) (Ogaki et al., 2012). In the same manner, C9orf72 was investigated in 254 Korean patients with ALS, none of the cases presented the repeat expansion (Jang et al., 2013).

These findings have been supported by a large cross-sectional study that analyzed 4,448 patients with ALS in 17 regions worldwide. The repeat expansion was identified in 7.0% of white patients with sALS from the USA, Europe, the Middle East, and Australia. In this study, C9orf72 was identified in 4.1% of black, 8.3% of Hispanic and 0.0% of Native American patients from the USA. None patient from Asia, India and the Pacific Islands presented the repeat expansion (Majounie et al., 2012). These findings provide strong evidence that C9orf72 play an important role on ALS in patients with a European ancestral background but it might not be the case for other populations.

The frequency of superoxide dismutase 1 (SOD1) mutation in sporadic ALS seems to be similar in Europe (ranging from 0.4% in Netherlands (van Es et al., 2010) to 3.9% in Scandinavia (Andersen et al., 1997)) and Asia (ranging from 1.2% in Korea (Kwon et al., 2012) to 4.2% in Iran (Alavi et al., 2013)). In familial ALS, the SOD1 mutations appears to be more commonly identified in Asia (around 30%) compared to Europe (around 15%) according to a recent meta-analysis (Zou et al., 2017).

TARDBP accounts for 1% to 5% of ALS mutations. TARDBP gene has been not found in patients with ALS across numerous studies in Europe (e.g. Belgium (Gijselinck et al., 2009) and Finland (Mentula et al., 2012)), North America (Guerreiro et al., 2008) and Asia (e.g. Japan (Kamada et al., 2009) and Korea (Kwon et al., 2012)). Interestingly, 28.7% of patients with ALS carried TARDBP mutations in Italy (Sardinia) (Chiò et al., 2011a).

FUS mutation similarly represents around 1% to 5% of known ALS-associated genetic variants. It appears to exhibit a slightly higher predominance in Asian patients (Zou et al., 2017).

Other variants seem to be more specific in certain populations. For instance, optineurin mutations (OPTN) was firstly identified in Japanese patients (Maruyama et al., 2010). Studies from China (Li et al., 2015) and the UK (Johnson et al., 2012) suggest that the OPTN mutations are more common in Asian patients with ALS. The evidence illustrates once again the major role of certain mutations in certain populations.

In this sense, it is likely that ALS have a complex heterogeneous genetic architecture that differs between populations. A recent meta-analysis described the frequencies of C9orf72, SOD1, TARDBP and FUS mutations in ALS among populations (Zou et al., 2017). An overall of 111 studies were analyzed considering European and Asian populations. Mutation proportions were distinctly different between these two populations in familial and sporadic ALS (I^2: 44–95%, p<0.01). The multivariate meta-regression analyses showed a statistically significant association between populations and genetic variants like SOD1 (p < 0.0001), FUS

(p = 0.04) and C9orf72 (p < 0.0001) in familial ALS. The difference reached statistical significance between populations and C9orf72 (p < 0.0001) in sporadic ALS. The mutations frequencies between European and Asian patients with ALS are shown in table 4.

Table 4 : Frequency of ALS mutations between European and Asian patients with ALS

		Familial ALS		Sporadic ALS	
Gene mutation	**Population**	**Frequency**	**(95% CI)**	**Frequency**	**(95% CI)**
SOD1	European	14.8%	(11.5% to 18.5%)	1.2%	(0.7% to 1.9%)
	Asian	30.0%	(25.1% to 35.1%)	1.5%	(1.0% to 2.0%)
TARDBP	European	4.2%	(1.6% to 7.8%)	0.8%	(0.2% to 1.5%)
	Asian	1.5%	(0% to 6.0%)	0.2%	(0% to 0.3%)
FUS	European	2.8%	(2.1% to 3.5%)	0.3%	(0.1% to 0.5%)
	Asian	6.4%	(3.2% to 10.5%)	0.9%	(0.2% to 1.9%)
C9orf72	European	33.7%	(29.3% to 38.2%)	5.1%	(4.3% to 6.0%)
	Asian	2.3%	(0.3% to 6.3%)	0.3%	(0.1% to 0.6%)

Table 4 has been adapted from: “Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis” (Zou et al., 2017).

The proportions of ALS-related genes are different among European and Asian patients. Almost one third of familial ALS is associated to C9orf72 repetition expansion in Europeans and SOD1 mutations in Asians. Furthermore, C9orf72 is clearly the most frequent genetic variant in sporadic ALS among European cases.

Few studies have identified ALS-associated genes in other geographic regions like Latin America and the Caribbean. Only one recent multicenter hospital-based study assessed the frequency of genetic mutation between European and Hispanic or Latin-American patients (Ryan et al., 2019). Genetic mutations were analyzed in 115 Cuban and 832 Irish patients with ALS. A known ALS-associated genetic variant was found in 5.2% of Cuban cases. C9orf72 was identified only in two sporadic ALS cases, accounting for 1.7 % of all Cuban cases (95% CI 0.6 – 4.1). The two Cuban patients carrying C9orf72 repeat expansion were identified as ‘whites’. As might be expected, the repeat expansion exhibited a higher proportion in Irish

cases (9.9%, 95% CI 7.8 – 12.0) compared to Cuban cases (p=0.004). No SOD1, TARDBP or FUS mutations were found in Cuban cases (Ryan et al., 2019).

Another two studies have found low frequencies of C9orf72 repeat expansion in Latin-American populations from Argentina and Brazil. C9orf72 was found in 2% of Argentinian cases (Itzcovich et al., 2016) and 3.6% of Brazilian cases (Cintra et al., 2018). However, the ethnic background of the cases was not available. This could have an impact due to the great proportion of population with a European ancestral origin in these countries mainly in Argentina. For instance, a study on the genetic structure of the Argentine population showed that the mean European genetic contribution was 78% (Seldin et al., 2007).

Most of ALS genetic epidemiology is based on studies performed in North America, Europe and Asia. Genetic studies have not been performed yet in several regions of the world. Therefore, there is an evident need to promote epidemiological and genetic research in certain areas of the globe in order to define the genetic architecture of ALS among populations.

The diverse proportions of genetic mutations could explain the heterogeneous distribution of ALS worldwide. This also could imply a higher risk in certain populations that carry specifics mutations. Understanding the determinants of risk in genetic epidemiology could be a decisive step that might lead to move forward the development of new therapies for ALS.

II.4.5. Phenotypes

The classic form of ALS requires clinical evidence of upper and lower motor neuron degeneration at the same time. The clinical heterogeneity of the disease implies a wide spectrum of phenotypes that are mainly based in the predominance of UMN and LMN involvement. However, there is no consensus on phenotypes classification. This section discusses main clinical characteristics contributing to the ALS variability and some clues on clinical variability.

Patients with predominant upper motor neuron degeneration could be categorized into upper motor neuron-predominant ALS or primary lateral sclerosis (PLS). Primary lateral sclerosis is a motor neuron disorder. Diagnosis is established when the motor neuron signs stay restricted to the UMN after at least four years of the onset. Some authors suggested that PLS is part of the ALS spectrum due to the fact that approximately one third of cases develop LMN signs in the course of the disease and autopsy studies have shown LMN degeneration in patients with PLS (D'Amico et al., 2013). In the upper motor neuron-predominant ALS, patients exhibit UMN dysfunction with slow progression to LMN involvement. In both cases, prognosis is better than classic ALS.

Predominant LMN phenotypes could be observed in patients with flail arm syndrome, flail leg syndrome, lower motor neuron-predominant ALS and progressive muscular atrophy. Flail arm (FA) syndrome is characterized by proximal weakness in the upper limbs predominantly in the arms. Patients with flail leg (FL) syndrome show distal weakness in the lower limbs. FA and FL had significantly better survival than classic ALS. In lower motor neuron-predominant ALS, clinical signs of LMN dysfunction are evident with a slow progression that leads to UMN involvement in the disease course. Progressive muscular atrophy (PMA) represents a motor neuron disorder with predominant LMN degeneration. Survival is slightly longer compared to classic ALS. There is also a controversy considering PMA as part of the ALS spectrum. However, one third of PMA cases develop UMN signs during the disease progression and researchers have showed that patients with PMA exhibited ubiquitinated inclusions typical of ALS (Ince et al., 2003).

Besides, there are patients presenting upper and lower motor neuron involvement combined with non-motor neuron degeneration and multisystem involvement. Cognitive and behavioral abnormalities could be found. In fact, at least a quarter of ALS patients meet the criteria for frontotemporal dementia (FTD) (Rippon et al., 2006). The multisystem degeneration could involve extrapyramidal, cerebellar, sensory and autonomic systems.

The phenotypes are principally differentiated by the predominance of motor neuron involvement, non-motor neuron degeneration and survival. It therefore seems reasonable to propose that clinical forms with less widespread neurodegeneration are associated to better prognosis; however, the fatal outcome remains unchangeable.

There are few data of the distribution of phenotypes among geographic areas. Most of the studies compared general clinical characteristics (e.g. type of onset). It is more difficult to find studies describing specifics phenotypes. It seems a very interesting topic to explore it due to some clues of potential phenotypic variability among populations. A case-control study in the UK reported that Africans were at fourfold higher risk of presenting with the 'flail arm' variant of motor neuron disease compared with subjects of European background (Tomik et al., 2000).

There is a knowledge gap on the occurrence of non-motor degeneration symptoms and signs such as behavioral and cognitive impairment in several regions of the world. Prognosis factors are other neglected topic on the ALS literature outside Europe and the USA.

Nowadays, it is unclear whether the distribution of ALS phenotypes vary among populations. Further studies to describe clinical features and phenotypes using standardized criteria are needed in order to understand ALS clinical variability.

II.4.6. Potential factors involved to ALS clinical characteristics and their variability

The clinical variability remains other puzzling feature of ALS. It is unclear which factors play a role to determine phenotypic expression.

A study reported that ALS clinical characteristics are strongly associated with age and sex (Chiò et al., 2011b). In fact, certain phenotypes are more likely to occur in males. A predominance of male cases has been reported in classic ALS, flail arm syndrome and lower motor neuron-predominant ALS (Chiò et al., 2011b). Bulbar phenotype increases with age. Older patients are more likely to present a bulbar phenotype (Dandaba et al., 2017). Patients with bulbar onset under 40 years represents only 10% and the proportion increases up to 40%

in patients over 65 years (Hamidou et al., 2017). In the same line, a study described that young-adults with ALS were more likely to show a predominant upper motor neuron phenotype (Sabatelli et al., 2008). Moreover, the course of ALS progression is slow in young patients with a significant longer survival (Chiò et al., 2009; Pupillo et al., 2014).

The association between phenotype expression and genetic variants is another interesting topic. The most evident illustration is related to C9orf72 repeat expansion. ALS patients carrying C9orf72 present specific clinical characteristics (Couratier et al., 2017). Patients with the repeat expansion display younger age at onset and shorter disease duration compared to those without (García-Redondo et al., 2013). C9orf72 patients exhibit more frequently bulbar onset (Millecamps et al., 2012), co-morbid frontotemporal dementia (FTD) (Byrne et al., 2012), and psychiatric symptoms (Snowden et al., 2013). By the same time, patients carrying FUS mutations are younger with a rapid evolution (Millecamps et al., 2010).

It is still unknown the role that several factors (e.g. ethnicity, environmental exposures) play in terms of clinical expression. A clear understanding of clinical characteristics of ALS in relation with ancestral background is difficult to accomplish due to the scarcity of studies. Further research is needed to determine if certain populations are more likely to exhibit specific clinical characteristics or phenotypes. However, other potential explanation for clinical variability could be the difference of clinical practices and judgment among clinicians.

II.5. Methodological considerations for epidemiological and clinical studies on ALS

Methodology is essential to put into perspective the study findings. Understanding the implications of the methodological approaches allow us to build a critic view considering the strengths and the potential biases in research. The analysis of the methodology is a fundamental step to recognize accuracy and reliability of data and conclusions in the study. In the next section, several methodological issues will be discussed in epidemiological and clinical research of ALS.

II.5.1. Standardized diagnosis criteria

One of the first basic considerations is the use of standardized criteria for ALS diagnosis. It is crucial to assure a common definition framework to assess the same disease with similar features. El Escorial and Airlie House criteria are the diagnostic standard parameters recommended by the World Federation of Neurology consensus. Before these criteria were launched, ALS diagnosis relied on clinical judgement that might have been influenced by clinical subjectivity. This could account at least for a part of the heterogeneity observed in some studies performed before 1994.

II.5.2. Sources of case ascertainment

The case ascertainment source is another important methodological issue on ALS. The use of one source or multiple sources could have an impact on cases identification. Multiple independent sources of case ascertainment could allow us to provide a more precise estimation of epidemiological indicators. The reliability of the information is also crucial (e.g., diagnosis accuracy). Ideally, multiple independent sources with reliable data will assure complete ascertainment of cases in order to provide an accurate estimation of ALS occurrence and straightforward description of clinical characteristics.

II.5.3. Population-based vs hospital-based studies

In epidemiology, population representativeness is a key factor to provide conclusions with external validity. It is for that reason that population-based studies are taking the lead as the standard methodology on ALS research despite the complexity to put them into place.

Most of ALS literature is based on hospital-based studies or referral-based studies. These studies drive a selection bias. A recent study conducted in four European countries showed that patients referred to ALS centers exhibited specific characteristics like younger age, high proportion of familial ALS, less proportion of bulbar onset, and better prognosis compared to patients from ALS population-based registries (Logroscino et al., 2018a).

II.5.4. Incident vs prevalent cohorts

The clinical characteristics could also vary in prevalent and incident cases. A study showed that prevalence cohorts have different characteristics compared with incident cohorts. Prevalent cases were more likely to be younger and exhibited fewer bulbar onset than incident cases (O'Toole et al., 2008).

II.5.5. Retrospective vs prospective designs

A retrospective approach is a practical method to provide epidemiological and clinical descriptions using available data. However, this could be limited by poor quality of the record information. A prospective approach requires a continuous long-term data collection process, which involves a substantial logistic and financial investment. The reward is the collection of standardized data. This allows to provide more accurate description of the disease. Retrospective and prospective designs could have an impact in the study results. A study showed that ALS incidence rates in Europe were higher for the prospective studies (median 2.39, IQR 2.15 – 2.68) compared to retrospective studies (median 1.52, IQR 1.22 – 2.04) (Chiò et al., 2013).

II.5.6. Population structure

ALS is an age-related disease with a peak of incidence around 60 or 70 years, together with a slightly male predominance. The age and sex structure of the populations under study need to be taken into account because the population at risk could be extremely variable between geographic areas and populations. Standardization is commonly used to control this impact and provides reliable epidemiological data for comparison.

II.6. Synthesis

Recent studies, systematic reviews and meta-analyses led researchers to postulate the heterogeneity of ALS occurrence and clinical characteristics between geographic areas and populations. This query is rising interest in the scientific community due to the potential role of certain factors (e.g. genetic variants) in the occurrence of the disease and clinical expression.

Robust conclusions on the worldwide occurrence of ALS are difficult to achieve linked to the fact that the literature available mainly come from studies in Europe and North America. Studies from Asia have increased the information to support the heterogeneous distribution and clinical variability of ALS. However, relatively little is known about epidemiological indicators (e.g. incidence, mortality), genetic variants, clinical features and prognostic factors in certain global regions such as Africa and Latin America.

The ancestral origin of the populations has been proposed as a crucial factor in the role of ALS susceptibility. This is mainly supported by epidemiological evidence presented in this chapter. However, other potential aspects could explain ALS variability like access to health care, socioeconomic factors, case ascertainment and variability of study design. Genetic and physiopathological mechanisms potentially involved are ongoing to be understood and this improvement could open the door for future research (e.g. new therapy treatment).

Further studies with strong methodological framework need to be encouraged in diverse geographic areas and populations to clarify these issues. The epidemiological and clinical evidence discussed in this chapter was the starting point to carry out well-designed and relevant studies for this dissertation.

II.7. Article 1 - Variation of ALS occurrence between populations

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Motor neuron diseases

Current issues in ALS epidemiology: Variation of ALS occurrence between populations and physical activity as a risk factor

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease with a fatal outcome. This review aims to report key epidemiological features of ALS in relation to the hypothesis of variation between populations, to summarize environmental hypothesis and to highlight current issues that deserve much considerations. Epidemiological ALS studies have shown a variation of incidence, mortality and prevalence between geographical areas and different populations. These data could support the notion that genetic factors, especially populations' ancestries, along with environmental and lifestyle factors, play a significant role in the occurrence of the disease. To date, there is no strong evidence to confirm an association between a particular environmental factor and ALS. Physical activity (PA) has been extensively evaluated. Recent studies support with the best evidence level that PA in general population is not a risk factor for ALS. However, further research is needed to clarify the association of PA in some occupations and some athletic activities. Epidemiological research based on multicenter international collaboration is essential to provide new data on ALS especially in some regions of the world that are to date poorly represented in the ALS literature.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neuromuscular disorder characterized by a progressive degeneration of the brainstem, corticospinal tract, and spinal anterior horn. The diagnosis of ALS is primarily clinical and is based on the evidence of involvement of the central and peripheral neuron in different territories [1]. El Escorial diagnostic criteria [2] were developed to estimate the certainty of ALS diagnosis and to

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standardize the inclusion criteria in clinical trials. A revised version has subsequently been published to include Electromyography (EMG) evidence of acute denervation [3].

The onset of the disease is categorized as either spinal or bulbar depending on the affected muscle territories and related clinical symptoms. Recent studies described that ALS displays a variety of clinical phenotypes [4]. Recently the presence of non-motor symptoms and the extension to other areas of the brain has been increasingly recognized [5–7]. The disease is invariably lethal and the median survival time since diagnosis is around 15–20 months [8]. Death is usually from respiratory failure.

ALS is one of the most puzzling diseases in terms of understanding of its pathogenesis [9], which might combines environmental and genetic factors [10]. Genetic variants associated with ALS have been described [11–14], while the contribution of environmental factors has been more difficult to assess. To date, none definitive replicable environmental risk factor has been identified.

Accurate description of epidemiological profile and determinants of ALS occurrence may provide clues around its etiology and potentially to other neurodegenerative diseases.

This review aimed to report key epidemiological features (incidence, mortality, prevalence) of ALS in relation to the hypothesis of variation between populations, to summarize environmental hypothesis and to highlight current issues that deserve much considerations.

2. ALS occurrence – variation between populations

2.1. *Seminal reviews*

In 2007, Cronin et al. published a review focused on "ethnic variation in ALS incidence", along with prevalence and mortality [15]. Based on 61 studies the authors postulated a reduced occurrence of ALS among Asian, African and Amerindian populations as compared to Caucasian populations. A stability of ALS incidence rates was identified within Europe and North America. This paper was nevertheless limited by the methodological heterogeneities between the included studies (hospital-based and population-based) that rendered firm conclusions challenging.

In 2013, Chio et al. focused on the "global epidemiology" of ALS [16]. Based on 38 studies (hospital-based and population-based), it confirmed the wide range of ALS incidence rates between populations (from 0.5/100,000 in Belgrade [17] to 3.6/100,000 in the Faroe Island [18]), the stability of ALS rates displayed in Europe (around 2/100,000 Person-Years of Follow-Up (PYFU)) or issued from North America. Also, examined rates from Asia were found lower.

2.2. *Methodological issues while examining ALS incidence between populations*

Variation in the incidence of amyotrophic lateral sclerosis (ALS) between geographical areas could support the notion that genetic factors, especially populations' ancestries, along with environmental and lifestyle factors, play a significant role in the occurrence of the disease. Given the importance and prospects of this hypothesis, it is important to control for potential bias due to selection or to confusion that might obscure the answers to this question.

2.2.1. *Population-based versus referral-based studies*

High standard in terms of case ascertainment is mandatory to report accurate ALS rates. Nevertheless, a significant part of the ALS epidemiological literature is founded on cases series from hospital or referral center (e.g. based on the recruitment of ALS cases in a single center). Hospital-series are known to drive a selection bias [19] whose extent induces the unrepresentativeness of the included patients (that present with a younger age, with a lower proportion of bulbar onset and with a more favorable prognosis) as compared to the overall population. This is related to the fact that the oldest patients, those with worse clinical status and pejorative prognostic factors are less likely to reach or to be referred to a referral center [20]. As a result, data founded on hospital series drive a high probability to underestimate ALS incidence.

A population-based study, instead, implies using an appropriate methodology, an epidemiological investigation of a sample or the entire population, within defined geographical and time boundaries [21]. Gold standard methodology for ALS incidence description relies on registers that are sustained population-based investigation of ALS in a given region, with a recruitment of cases that relies on multiple sources of cases ascertainment (referral centers, hospitals, neurologists, other specialists, health insurance data (exemption fees, riluzole reimbursement), general practitioner, ALS patient's associations, in some cases mortality data). The use of multiple sources of case ascertainment allows researcher to evaluate exhaustiveness of case ascertainment through the use of capture-recapture method. Based on the cross matching between sources, a log-linear model allows estimation of the number and proportion of missed cases. This method was used for the first time in ALS field in Limousin region [22] and then applied by other researchers in the field in Italy, Scotland, Ireland, Uruguay and France [23–26] with exhaustiveness of 97.9, 97.9, 100.0, 96.7 and 98.4% respectively. The presence of a registry improves over time the completeness of the identification of cases and decreases the referral bias.

2.2.2. *Age-structure of the population understudy*

ALS crude incidence is an important data for public health needs estimations about ALS care planning within a given country. Nevertheless, for comparisons between areas, given the age-related nature of ALS incidence, the age structure of the populations under-study need to be taken into account and controlled for. By definition ALS crude rates are not comparable when populations display different age-structure distribution. In this context, prerequisite is to standardize, using the same given reference populations, the rates to be compared. Impact of standardization might be important, for example, in Lybia, a country characterized by a low proportion of subjects aged 50 and over (namely 12% at the time of the study), crude incidence rates published by Radhakrishnan et al. were 0.89/100,000 [27] while after standardization on the 2010 US population it reached 2.03/100,000 PYFU [28].

2.3. *Recent clues about ALS incidence variation*

A recent meta-analysis tried to control for these latter two issues (selection and confusion led by a third covariate, for example: age). Founded on 44 population-based investigation of ALS using multiple sources of case ascertainment, the meta-analysis reported an overall pooled worldwide crude ALS incidence of 1.75 (1.55–1.96)/100,000 person-years of follow up (PYFU) and 1.68 (1.50–1.85)/100,000 PYFU after standardization on the US population [28]. Subcontinent was identified in this work as a significant source of rates heterogeneity, allowing researchers to strengthen the hypothesis of a heterogeneous worldwide distribution of ALS. While homogeneous incidence rates have been reported from populations of European origin from Europe, North America and New Zealand, leading to the estimation of a pooled ALS standardized incidence of 1.81 (1.66–1.97)/100,000 PYFU), incidence rates from Eastern Asia (Japan, China) have been found significantly lower in this work 0.83 (0.42–1.24)/100,000 PYFU as well as rates from South Asia (Iran, 0.73 (0.58–0.89)/100,000 PYFU) [28].

2.3.1. *Data from multiethnic populations*

The main body of literature on ALS epidemiology is large but limited geographically [16]. Most population-based studies to date have been performed in Europe and North America [24,29–33] and several regions of the world such as in Asia, Africa and South America remain with limited data. Due to the lacking studies in some geographic regions, data from multiethnic populations in UK or US are useful to examine variation of ALS epidemiology between ethnic groups within a given region. However, it is important to consider that the terminology used to classify populations is heterogeneous. While in the US, several researchers categorized patients in races (white, black/African American and Asian) and ethnicities (Hispanic and non-Hispanic) [34,35], some studies in the UK distinguish between origins (e.g. European and African origin) [36].

2.3.1.1. Incidence data. In the literature, Hispanics, African Americans and Asians populations display lower crude incidence compared to Caucasians (Table 1). The differences in rates remain similar after population standardization.

In the US, for example, Valle et al. conducted a retrospective study to identify ALS cases in the San Francisco Bay Area (SFBA) and Los Angeles County (LA) [34]. These areas were selected for their racial and ethnic diversity. The incidence rates were higher among whites compared to blacks and Asians. Within SFBA, the rates were 2.5 among whites, 1.5 among blacks and 1.0 among Asians. This pattern was similar in LA: 1.4 whites, 1.03 blacks and 0.66 Asians. Furthermore, Hispanics showed slightly lower rates compared

Table 1 – ALS incidence in multiethnic populations.

Country	Reference	Race/ethnic group	Crude incidence (95% CI)	Standardized incidence (95% CI)
US (SFBA)	Valle (2015) [34]	White		2.49 (2.2–2.9)
		Black		1.52 (0.9–2.4)
		Asian		1.00 (0.7–1.4)
		Hispanic		1.57 (1.0–2.3)
		Non-Hispanic		1.89 (1.7–2.2)
US (LA)	Valle (2015) [34]	White		1.4 (1.2–1.6)
		Black		1.03 (0.7–1.5)
		Asian		0.66 (0.5–0.9)
		Hispanic		0.66 (0.5–0.9)
		Non-Hispanic		1.01 (0.9–1.2)
US	Rechtman (2015) [35]	White	1.79	1.48 (1.42–1.53)
		African American	0.80	0.89 (0.79–0.99)
		Asian	0.76	0.78 (0.64–0.92)
		Non-Hispanics	1.65	1.36 (1.31–1.41)
		Hispanic	0.57	0.84 (0.75–0.92)
UK	Rojas-Garcia (2012) [36]	European origin	1.97 (1.55–2.48)	
		African origin	1.35 (0.72–2.30)	
US	McGuire (1996) [29]	Nonwhite		0.74 (0.00–1.96) m
				0.53 (0.00–1.91) w
		Overall		2.11 (1.27–2.93) m
				1.87 (1.08–2.66) w
US	Annegers (1991) [86]	White		1.36 (0.96–1.87) m
				1.25 (0.88–1.72) w
		Hispanic		1.27 (0.41–2.96) m
				0.10 (0.00–0.46) w
		African American		1.10 (0.48–2.17) m
				0.70 (0.28–1.44) w

SFBA: San Francisco Bay Area; LA: Los Angeles County; m: men; w: women; 95% CI: 95% confidence interval.

to non-Hispanics in both areas. In addition, Rechtman et al. found a crude incidence of 1.79 among whites, 0.80 among African Americans and 0.76 among Asians in the US. After standardization, the incidence remains higher in whites compared to African Americans and Asians [35].

2.3.1.2. *Prevalence data*. Prevalence is the proportion of a population that is affected with a particular disease at a given time point. Prevalence is determined by the incidence and duration of illness. In Europe, ALS crude prevalence has been reported from 1.1 per 100,000 (95% CI, 0.71–1.71) in Yugoslavia [17] to 8.2 per 100,000 (95% CI 2.1–20) in the Faroe Islands [18]. In the US, the rates range from 2.94 [37] to 5.0 per 100,000 [38]. One study in South America (Uruguay) showed a crude prevalence of 1.9 per 100,000 [25]. In Asia, a wide variation has been described between 0.95/100,000 in China [39] to 11.31/100,000 in Japan [40].

Few researchers reported prevalence rates in multiethnic populations [35,36,41]. The studies with available ethnic group data usually described other epidemiological features (e.g. incidence, mortality) [42–44] or only mentioned that ALS was more common in one ethnic group (generally white population) [38]. In the UK, the prevalence was 5.79 per 100,000 population (95% CI 4.97–6.92) for the European ancestry group and 4.94 (95% CI 3.68–6.5) for the African ancestry group [36]. A study, using a population-based design, investigated the racial variations in ALS prevalence and incidence in three states (Florida, New Jersey and Texas) and eight metropolitan areas (Atlanta, Baltimore, Chicago, Detroit, Las Vegas, Los Angeles, Philadelphia and San Francisco) of the US. The areas represented approximately 27% of the US population. An overall of 5883 cases were collected. Of these cases, 4401 (74.8%) were white, 546 (9.3%) were African American/black, 214 (3.6%) were Asian, 704 (12.0%) were of unknown race, and 18 (0.3%) were categorized as other race [35,41].

2.3.1.3. *Clues from mortality rates*. Mortality rates have been used as proxies to provide an estimate of incidence in ALS. Death certificates (DC) are popular sources of information because, in most countries, they carry a record of the causes of death and are readily available [45]. It could be assumed that all patients diagnosed with the condition will eventually be identified via a DC associated to the invariable fatal outcome of the disease. However, problems in the accuracy of DC certificates should be considered [46].

Mortality data are of particular value when investigating changes in ALS over time in a particular country. Good practice epidemiological criteria have been proposed to consider ALS mortality rates as reliable proxies of incidence rates [46]. Nevertheless, only few studies on mortality data published to date followed a high-quality methodology.

Mortality studies in this field reported consistently that ALS mortality was higher among white people (close to 2/100,000 PYFU) [46] than among Hispanic (0.8–0.9 per 100,000 PYFU) [42,47] and African American people (1.1 per 100,000 PYFU) [42]. In the US, Noonan et al. reported a mortality variation in different ethnic groups: Hispanic 0.9/100,000 PYFU (95% CI 0.8–1.1), African American 1.1/100,000 (95% CI 0.9–1.2) and Non-Hispanic 2.0/100,000 PYFU (95% CI 1.9–2.0). McCluskey et al. described lower mortality rate among non-white 1.0/100,000 (95% CI 0.9–1.1) as compared with white 2.1/100,000 (95% CI 2.0–2.2) [48]. Furthermore, an immigrant study performed in the UK (1979–1988) showed ALS mortality rates to be lower among Asian (standardized mortality ratio (SMR) = 37.6%) East African (SMR = 55.5%), Caribbean (SMR = 73.6%), and West African (SMR = 76.9%) immigrants to London as compared to native English. However, the denominators of ethnic populations were not known for that time period and ethnicity was assigned based on the individual's name [49]. The variation in reported mortality rates among populations could be related to the access to health care among ethnic groups [50], to the impact of socioeconomic status on access to diagnosis or environmental and to genetic variation related to the populations ancestry. A recent mortality study in US (2016) tried to control these issues using a model that was adjusted for socioeconomic status, type of health insurance, and birthplace to estimate the ALS mortality risk in different ethnic groups [44]. Within this adjusted model, higher rates of ALS were reported among whites compared to other populations (non-Hispanic black, HR 0.61 (0.48–0.78); Hispanic, HR 0.64 (0.46–0.88); other races, non-Hispanic, HR 0.52, (0.31–0.86)).

Only one study was conducted to address ALS mortality in an ethnically mixed population in Cuba (including an admixed group). The total mortality rate was 0.83 per 100,000 PYFU. The adjusted mortality rate was considerably lower in the mixed population: 0.55 (95% CI 0.4–0.72) than in whites (0.93/100,000 PYFU; 95% CI 0.83–1.03) and blacks (0.87/100,000 PYFU; 95% CI 0.62–1.17) [47]. These results were similar to those found in Hispanic populations in the US [42,43]. The evidence supports the hypotheses that admixed populations are characterized by a lower risk of developing ALS. ALS is considered as a complex genetic disease caused by multiple susceptibility genes interacting with a variety of environmental risks [51]. Admixed populations, containing a much wider variety and different combinations of at-risk alleles, might experience a lower overall risk of developing the disease [47].

At this stage, an international research collaboration, it is essential to perform an investigation of ALS incidence, prevalence and mortality in several countries (including ethnically mixed and admixed populations) with homogeneous and standardized methodology.

2.4. *Sex ratio time trend and variation*

There is a discreet male predominance in ALS. While age-related bulbar onset appears similar in male and female, the spinal form is more common in male [52].

Some authors postulated a recent decrease in the male/female sex ratio compared with the oldest publications (before 1990s). For example in Sardinia, Italy in the 70s [53] the male/female SR was 2.6:1 and 1.8:1 was reported in Scotland for 1989 [54]. In Norway, the SR changed from 1.58 in the 1960s to 1.32 in the early 1990s [55]. Conversely a joint analysis of 6 European registers for the period 1998–1999 reported a SR of 1.16 [52]. This apparent trend of SR could be explained in part by difference in study design (retrospective in the oldest and prospective in the most recent studies), difference in case ascertainment and by the different geographic distribution of the studies. Nevertheless, this variation might also be

explained by the changing lifestyle of women, which has become more similar to that of men, socioeconomic changes during the last century in women with an increase exposure to occupational and environmental risk factors [56].

The SR seems to vary between populations. A recent meta-analysis based on population-based studies reported pooled estimates of the SR at 1.29 (95% CI 1.15–1.45), 1.27 (95% CI 1.08–1.48) and 1.24 (95% CI 1.15–1.34) in Northern, Western and Southern Europe, respectively. Similar SR were also found in North America and New Zealand [57]. Conversely, SR reached a value higher than 2 for Uruguay [25], Libya [27], Iran [58] and Hawaii [59].

From multiethnic populations, high degree of variation of SR has been reported between groups of different ancestries for example in East Asia, Israel and Hawaii [59–61]. In a multiethnic Asian population study SR was 1.43. However, the percentage of males with ALS was different between each ethnic group (51.1% Chinese, 78.6% Malays and 66.7% Indians). This information is useful to exemplify the variation of SR between different ancestral groups sharing the same environment [61]. However, these data are from small groups and further research is needed to estimate the SR in multiethnic populations.

2.5. *Age-related ALS incidence*

Population-based studies have consistently shown an age-related profile of ALS that is consistent with an age-related disorder (occurring within a specific age-range) rather than an aging-related disorders (whose incidence increases with age). Indeed, the incidence of ALS increases after the age of 40 years, reaching a peak in the late sixties or early seventies, followed by a rapid decline [19].

Age-related disease pattern suggests that ALS occurs within a susceptible group within the population [52]. It is possible that subjects who survive beyond the age of 80 are protected against motor neuron damage either because they are genetically unsusceptible to the putative causative influence or the exposure occurred after a critical age [62]. Besides, some authors postulated that the pattern of ALS incidence among the elderly may rather arise from problems with the case ascertainment among this age group. Difficulties in diagnosing ALS among the elderly might be related to comorbidities, difficult access to specialized care (the elderly are less likely to encounter neurological services) [56] or a more rapid and aggressive disease that cause elderly patients to die in some case before the diagnosis of ALS is reached has been described [19].

2.6. *ALS incidence time trends*

Data from Denmark reported that ALS incidence increased by 2% per year in the last 30 years [63]. In New Zealand, the overall incidence of ALS steadily increased from 1985 to 2006, increasing on average by 3.3% per year from 1.6 per 100,000 in 1985 to 3.3 per 100,000 in 2006 [64]. In US, the mortality rates increased from 1.25 per 100,000 to 1.82 per 100,000 from 1969 – 1998, representing a 46% increase during the 30-year period. Explanations for this apparent increase might be attributed to improved case ascertainment for example due to the refinement of the algorithm used to identify definite ALS cases, along with an increased public awareness of the ALS Registry [38] and decreasing mortality from other causes, resulting in a growing proportion of the susceptible subpopulation that survives long enough to develop the disease [65].

2.7. *Risk factors*

2.7.1. *General view in ALS risk factors*

The environmental risk factors in ALS have been studied extensively. To date, there is no strong evidence to support an association between a particular factor and ALS. A general classification of potential risk factors in ALS is shown in Table 2.

Environmental, occupational and life style factors have been evaluated. The evidence is conflicting and difficult to interpret. For example smoking has been shown to increase the risk in several studies [66–69]. Controversially, others researchers found that smoking was associated with ALS risk and worse survival in women only [70] while other studies have failed to demonstrate this association [71]. The same contrasting results have been found with other associated factors.

Evaluation of the environmental factors in a rare neurodegenerative disease is challenging. Most of the evidence is based on case-control studies and retrospective cohort studies. Furthermore, the problem to accurately estimate exposures throughout life is one obstacle to ALS risk factors research [72].

2.7.2. *Physical activity as a risk factor*

Physical activity (PA) has been extensively evaluated as a risk factor of ALS. Discordant results have been published as regards the association between PA and ALS. Some aspects have to be considered as potential explanation for these variations: (1) PA definition used in most studies is heterogeneous and there are no standardized criteria to measure or categorize the amount of PA in each patient. (2) An accurate PA measure is also complicated since the data arise mostly from retrospective studies. (3) Several studies distinguished

Table 2 – Potential risk factors in ALS.

Factors classification	Specific factor	References
Environmental	β-Methylaminoalanine (BMAA)	[87–89]
	Metals	[90–92]
	Pesticides and Solvent	[93,94]
	Electromagnetic fields (EMFs)	[95,96]
	Viruses	[97,98]
Occupations	Professional athletes	[74–76]
	Military	[99,100]
	Farmers	[101–103]
	Electrical occupations	[104,105]
Life style	Physical activity	[73,78,80]
	Trauma – head trauma	[106,107]
	Smoking	[66,70,71]
	Diet	[108,109]

recreational, work-related and sports physical activity; some of them have analyzed the association to these difference PA categories and others summarized exposures. (4) Given the fact that ALS is a rare disorder, most of the analytical studies are case control studies that might determine some specific biases (information bias on the exposure (Physical activity years before disease onset), selection bias related (i) to the difficulty to recruit control sample representative of the general population and (ii) to the inclusion of prevalent ALS cases instead of incident cases). Furthermore, small sample size and inadequate control of confounders are also limiting factors [73].

Physical activity is a composite cause being the intersection of multiples factors. For example, head trauma could be present in some sports (e.g. American Football), the characteristics (aerobic/anaerobic) and amount of physical activity could be different depending on the type of sport (soccer, biking, etc.), or occupation (e.g. farmers, military, etc.) and the intensity of the activity also could be broadly diverse between high level athletes, amateurs and people who practice recreational sports. Some of these factors could interact with each other and some could act as confounding factors. Moreover, there are no studies concerning PA and genetics allowing to test gene-environment interactions in the risk of ALS.

The hypothesis that intense physical activity (PA) could be a risk factor for developing ALS, was supported by the observation that ALS incidence was increased among football players [74] and American Football players [75] in Italy and in the US, respectively. A recent study in cross-country skiers in Sweden found a higher risk of ALS in long distance cross-country skiing, but only among the best skiers [76]. This association is biologically plausible, because vigorous exercise may induce oxidative stress and glutamate excitotoxicity [77]. ALS studies on professional athletes have the advantage of including large numbers of participants, but are by definition limited to a highly selected group (selected on physical performance and underlying biological characteristics), and studies did not fully accounted for potential confounders [78] such as trauma, possible use of drugs (anabolic steroids, non-steroidal anti-inflammatory drugs), drugs of abuse (cocaine, methamphetamine), dietary supplements (branched amino acids), exposure to toxins on the pitch (e.g. pesticides) [79] or amount and type of PA (for example, position in the field for soccer players: goalkeeper, defenders, midfields, forwards). Some author postulate that a small amount of PA could be protective against ALS whereas more PA could suppress the protective effect or even be a risk factor [80].

2.7.3. *Recent evidence – reviews and meta-analysis*

In 2014, a review of epidemiological studies was conducted by Hamidou et al. according to the meta-analysis of Observational Studies in Epidemiology Guidelines [79]. Thirty-seven epidemiological studies were included in the review. The level of evidence was examined and synthetized using Armon's classification for exogenous risk factors for ALS [81]. Results were stratified according to type of exposure into categories: PA related to (i) sport and work, (ii) soccer and American football, (iii) occupation and (iv) proxies of PA. The analysis concluded: (1) studies with the highest evidence level – two class I studies [73,80] and one class II study [82] – did not found a positive association between PA and ALS in the general population. This led the authors to conclude with the best evidence level (level A) that PA is not a risk factor for ALS among the general population. (2) Physical activity in the professional category (agriculture, forestry, fishing and mason) as a risk factor for ALS remains unknown. (3) Football/soccer may be considered as a possible risk factor for ALS.

In 2016, a systematic review/meta-analysis was published to identify additional putative risk factors associated with the onset and progression of ALS. Six case-control studies between PA or participating in sports and ALS were included. Estimates showed that participating in recreational sports or other physical activities was not associated with an increased risk of ALS (OR = 0.90, 0.78–1.03), but ever participating in an organized athletic club in high school or college, or in professional sports, was associated with ALS (OR = 1.35, 1.11–1.65) [83].

2.7.4. *Prospective cohort study*

A prospective cohort study, best level of evidence in this field, was published in 2016 to evaluate the association between physical activity and risk of death from ALS [78]. Data from the European Prospective Investigation into Cancer and Nutrition was used. The main exposure factor was total PA estimated at cohort entry with the Cambridge Physical Activity Index (CPAI). The result showed that total PA was inversely associated with ALS mortality ($P = 0.042$). The result did not appear to be confounded or modified by age, gender, body mass index, smoking and the highest level of education attained. Also, according to the authors, the association was unlikely to be explained by reverse causation as the exclusion of events occurring during the first 5 years of follow-up lead to stronger association. Those physically active (corresponding to a level of PA $\geq$ 75% of the PA distribution) were less likely to die from ALS compared to those inactive: HR = 0.67 (95% CI 0.42–1.06), while this result did not reach statistical significance. Occupational, household, recreational, potentially traumatic, sportive, and vigorous PAs were not associated with ALS mortality. The main strengths in this study remain in the prospective cohort design, the use of a standardized index to measure PA and adjustment to confounded factors. This cohort study supports the inverse association reported by Pupillo et al. in the European population-based case–control study between total PA and ALS (OR 0.65, 0.48–0.89) [73] and the conclusion given by Hamidou et al. in their review [78].

3. Conclusion

Epidemiological research based on multicenter international collaboration is essential to provide new data on ALS especially in some regions of the world that are to date poorly represented in the ALS literature. Several questions need to be resolved concerning the variation of the occurrence of the disease between populations and the relation between those variations and population ancestral origin along with environmental factors. In addition, estimate the burden of neurodegenerative diseases including ALS across geographies

and time can assess epidemiological patterns to improve our understanding of the variability. Initiatives as the Global Burden of Disease (GBD) Collaboration are crucial to prioritize investments in research and estimate the levels of health around the world [84,85].

Recent studies have addressed the association between physical activity and ALS. The best level of evidence supports that PA in general population is not a risk factor for ALS. However, further research is needed to clarify the association of PA in some occupations and some athletic activities (including extreme levels of PA).

Population-based studies, using standardized methods will be optimal to provide good quality evidence and increase the understanding of amyotrophic lateral sclerosis.

Disclosure of interest

The authors declare that they have no competing interest.

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Chapter III. Amyotrophic lateral sclerosis in Africa

III.1. Framework of ALS in Africa

The first African cases of ALS were reported from Kenya in the 1950s (Harries, 1955). Back then, the general idea was that ALS did not occur among Africans (Gelfand, 1948). Even until today, just few studies have been focused in Africa and its population. The literature is mainly founded on case series with heterogeneous methodology. Therefore, it remains difficult to draw conclusions on ALS in Africa.

III.1.1. Epidemiology of ALS in Africa

There is scarce information on the epidemiology of ALS in Africa. Only one population-based study investigated the incidence in Africa (Libya). Overall, 23 patients with MND were identified in Benghazi, Libya, from 1980 to 1985. Case ascertainment was performed through polyclinics, hospitals and the center for the handicapped with a subsequent centralized diagnosis confirmation. The crude incidence was 0.89 per 100,000 person-years. After standardization, ALS incidence was 2.03 per 100,000 PYFU (Radhakrishnan et al., 1986).

A systematic review of neurodegenerative diseases in sub-Saharan Africa found only two community-based studies on ALS (Lekoubou et al., 2014). The prevalence was 5 per 100,000 in Ethiopia (Tekle-Haimanot et al., 1990) and 15 per 100,000 in Nigeria (Osuntokun et al., 1987). To the best of our knowledge, there are no studies describing MND or ALS mortality in Africa.

According to the Global Burden of Disease (GBD) 2016 study, a low prevalence of MND per 100,000 population was reported in sub-Saharan Africa, particularly in central sub-Saharan Africa (0.9, 95% CI 0.8 – 1.1), eastern sub-Saharan Africa (1.0, 95% CI 0.8 – 1.1) and western sub-Saharan Africa (1.0, 95% CI 0.9 – 1.2). Age-standardized prevalence per 100,000 people was 1.2 (95% CI, 1.1 – 1.4) in central sub-Saharan Africa, 1.3 (95% CI, 1.1 – 1.4) in eastern sub-Saharan Africa, and 1.3 (95% CI, 1.2 – 1.5) in western sub-Saharan Africa. In addition,

age-standardized incidence per 100,000 was 0.36 (95% CI, 0.31 – 0.41) in western sub-Saharan Africa, 0.37 (95% CI, 0.32 – 0.43) in southern sub-Saharan Africa, 0.39 (95% CI, 0.33 – 0.44) in central sub-Saharan Africa and 0.39 (95% CI, 0.34 – 0.45) in eastern sub-Saharan Africa (Logroscino et al., 2018b). However, the GBD study estimations are limited by scarce data mainly from sub-Saharan Africa.

III.1.2. Clinical characteristics of ALS in Africa

The clinical features of ALS have been described in 21 studies across African countries. Studies were performed in Western Africa (n=7), Eastern Africa (n=6), Northern Africa (n=5), Middle Africa (n=2) and Southern Africa (n=1). Most of them were hospital-based studies with a retrospective design. The number of ALS cases ranged from two to 276 with a median sample size of 28 cases (IQR 13 – 80 cases). Diagnosis was mainly established on clinical grounds and electromyoneurography was used in few studies. El Escorial criteria has been applied in recent publications.

A higher proportion of male cases was described with a male/female SR ranging from 1.4 to 17.0. The age of disease onset was described between 40 and 50 years. There were no reports of familial forms in most studies (Collomb et al., 1968; Imam and Ogunniyi, 2004; Ndiaye et al., 1986; Sene Diouf et al., 2004; Wall and Gelfand, 1972), while fALS accounted for 1.2% and 2% of cases in Tunisia and Nigeria, respectively (Ben Hamida and Hentati, 1984; Osuntokun et al., 1974). In contrast, a study reported 14.3% of fALS in Sudan (Abdulla et al., 1997). The diagnosis delay varied from 14 months to 42 months (Ben Hamida and Hentati, 1984; Radhakrishnan et al., 1986). Survival was rarely reported mostly due to difficulties following patients. There are no studies investigating prognostic factors in patients with ALS in Africa. However, some studies suggested that African patients experienced a better prognosis (Abdulla et al., 1997; Osuntokun et al., 1974; Radhakrishnan et al., 1986).

The demographic and clinical characteristics reported in African studies are shown in table 5.

A systematic review conducted to assess clinical features among patients with ALS in Africa suggested that specific characteristics are exhibited in African cases compared to European cases including: i) higher predominance of male cases, ii) presence of juvenile form of the disease, iii) younger age at onset (Marin et al., 2012).

It is still difficult to drawn clear conclusions on these characteristics due to heterogeneous methodological approaches (e.g. diagnosis criteria) and potential biases (e.g. selection bias) in several studies in Africa.

Table 5 : Studies reporting demographics and clinical characteristics of patients with ALS in Africa by study period according to subcontinents

Subcontinent	Country	Authors	Study period	Study design	Setting	Number of ALS cases	Male/Female sex ratio	Mean age ± SD (years)	Familial forms	Diagnosis	Diagnosis delay (month)	Mean survival (months)
Northern Africa	Morocco	(Imounan et al., 2015)	2008 – 2012	Retrospective	Hospital-based	60	1.5	50.0 ± 11.7		El Escorial		
	Sudan	(Abdulla et al., 1997)	1993 – 1998	Retrospective	Hospital-based	28	1.8	40.1	14.3%	Clinical + EMNG		§
	Morocco	(Bougteba et al., 2005)	1986 – 2003	Retrospective	Hospital-based	276	2.0	46.0		Clinical + EMNG		
	Libya	(Radhakrishnan et al., 1986)	1980 – 1985	Retrospective	Population-based	23	2.3	50.9 ± 2.3		Clinical + EMNG	42.0	42∫
	Tunisia	(Ben Hamida and Hentati, 1984)	1974 – 1980	Retrospective	ND	102 (82cl; 20j)	2.7	53.3cl; 21.3j	1.2%	Clinical + EMNG	14.0cl; 55.3j	35.2cl
Eastern Africa	Tanzania	(Dekker et al., 2018)	1984–1992 2007–2015	ND	Hospital-based	116	1.6	53.7		El Escorial		
	Zimbabwe	(Mielke and Adamolekun, 1996)	ND	ND	Hospital-based	13 (7b; 6w)	ND	37.0b; 68.0w		ND		
	Ethiopia	(Tekle-Haimanot et al., 1990)	1986 – 1988	Door-to-door survey	Population-based	3	2.0	28, 38, and 42		Clinical		
	Kenya	(Adam, 1992)	1978 – 1988	Retrospective	Hospital-based	46	2.8	r: 13 to 80		Clinical		r: 5 to 48
	Zimbabwe	(Wall and Gelfand, 1972)	1967 – 1971	Retrospective	Hospital-based	13	3.3	36.0	0.0%	Clinical	17.0	
	Kenya	(Harries, 1955)	1954	Retrospective	Hospital-based	2	NC	26 and 30		Clinical		
Middle Africa	Cameroon	(Kengne et al., 2006)	1993 – 2001	Retrospective	Hospital-based	10	4.0	50.9 ± 3.3		Clinical		
	Gabon	(Le Bigot, 1993)	1980 – 1985	Retrospective	Hospital-based	2	ND	ND		Clinical		
Western Africa	Senegal	(Sene Diouf et al., 2004)	1993 – 2000	Retrospective	Hospital-based	33	1.4	50.0≠	0.0%	El Escorial	r: 6.0 – 60.0	
	Nigeria	(Imam and Ogunniyi, 2004)	1980 – 1999	Retrospective	Hospital-based	16	15.0	38.6	0.0%	El Escorial		11.5
	Côte d'Ivoire	(Piquemal et al., 1982)	1971 – 1980	Retrospective	Hospital-based	30 (15cl; 15j)	3.0	47.6cl; 21.4j		Clinical	16.9cl; 12.1j	
	Senegal	(Ndiaye et al., 1986)	1960 – 1985	Retrospective	Hospital-based	74 (64cl; 10j)	4.0	44.0	0.0%	Clinical + EMNG		
	Senegal	(Jacquin-Cotton et al., 1970)	1960 – 1969	Retrospective	Hospital-based	18	8.0	r: 25 to 70		Clinical		
	Senegal	(Collomb et al., 1968)	1960 – 1968	Retrospective	Hospital-based	18	17.0	47.7	0.0%	Clinical	24.1	
	Nigeria	(Osuntokun et al., 1974)	1958 – 1973	Prospective	Hospital-based	92	3.0	37.6 ± 1.5	2.0%	Clinical + EMNG		72
Southern Africa	South Africa	(Cosnett et al., 1989)	<1989	Retrospective	Hospital-based	86	3.2	47.4b; 54.0w; 54.0i		Clinical		

Table 5 has been adapted and updated from the chapter 13: "Other neurocognitive disorders in tropical health" in the Neuroepidemiology in tropical health book (Marin et al., 2018a).
b, black; cl, classic ALS; EMNG, electromyoneurography; i, Indian; j, juvenile ALS; NC, calculated; ND, not determined; r, range; w, white. ∫, median; §, Durations of illness for three familial ALS cases were 2, 8 and 10 years

Crucial questions remain to be answered on ALS in Africa. Epidemiological studies must to be carried out to determine incidence and mortality in most regions of the continent. The particularity of certain demographic and clinical features need to be confirmed among African cases. Further studies will also clarify the role of genetic and environmental determinants on ALS in African population.

Several issues should to be addressed to provide more reliable picture of ALS in Africa. As was pointed out earlier, it is of crucial importance to generate data in different geographic areas and populations to understand the variability of the disease.

III.2. The epidemiological study of ALS in the tropics (TROPALS): focus on Africa

Our research team INSERM UMR 1094 Tropical Neuroepidemiology unit in Limoges (France) invited hospital centers across Africa to participate in the epidemiological study of ALS in the tropics' (TROPALS) collaboration. The project was a teamwork made of epidemiologists, neurologists and clinical researchers, the aim was to describe and compare the sociodemographic and clinical features, treatments, prognoses and survival times of patients with ALS in Africa.

III.2.1. Methodological design: The TROPALS study

From this standpoint, a multicenter hospital-based cohort study was carried out using a standardized methodology. All patients diagnosed with ALS were included from the neurology department of each participating hospital center. Exhaustive and continuous recruitment was conducted including all incident and prevalent cases from 2005 to 2017. Neurologists and clinical researchers in each hospital center performed standard clinical examination and data collection.

An ALS expert neurologist (Pr. Philippe Couratier), clinical coordinator of the ALS referral center of Limoges teaching hospital (CHU Limoges), reviewed all medical records and complementary test including electromyoneurography (EMNG) in order to confirm the ALS diagnosis and categorize diagnosis certainty according the Airlie House criteria.

Baseline sociodemographic and clinical data were collected at the time of ALS diagnosis of the incident cases, and medical records were used to collect the baseline data of the prevalent cases. A standardized questionnaire was developed (Appendix 1). The following data were recorded with the close collaboration of the Centre of Biostatistics and Methodology of Research (CEBIMER) of the Limoges teaching hospital:

- Date of the first symptom
- Type of onset

- Symptoms
- Signs of involvement of the upper and lower motor neurons
- Regional distributions of the signs
- Cognitive impairment
- Extra-motor involvement (extrapyramidal, cerebellar, sensory, autonomic, urinary or oculomotor)
- ALS Functional Rating Scale Revised (ALSFRS-R) score
- Complementary tests
- The type of treatment (disease modifying therapy, symptomatic and/or traditional medicine)

Patient follow-up was performed every three months, if possible depending on the capabilities of the participating centers. Disease progression was assessed during the follow-up. If more than 6 months elapsed without patient contact, the researcher in charge contacted the patient or the family to assess the vital status of the patient.

All findings were reported using the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Vandenbroucke et al., 2007) and Standards of Reporting of Neurological Disorders (STROND) (Bennett et al., 2015).

Statistical analyses were conducted using IBM SPSS® Statistics ver. 22 and SAS software ver. 9.3 (SAS Institute, Cary, NC, USA). Quantitative variables were described as medians with interquartile ranges (IQRs). The Shapiro–Wilk test was used to explore the normal distributions of continuous variables. Qualitative variables were shown as frequencies with percentages. The subcontinental regions were defined according to the United Nations Statistics Division (United Nations, 1999).

Means were compared by analysis of variance or Kruskal–Wallis test, depending on the conditions of application. Percentages were compared using the Pearson X^2 test. For post-hoc analysis, X^2 post-hoc test or one-way ANOVA followed by the Scheffe or Kruskal–Wallis post-

hoc test were employed, depending on the conditions of application. The Bonferroni correction for multiple tests was applied in post-hoc tests. All missing data were reported.

The survival and prognostic analyses included patients for whom at least 1 month of follow- up data were available and those who died in the first month. All analyses were performed from the date of diagnosis or onset until the date of death or censoring. Survival was analyzed using the Kaplan–Meier method and the Breslow and log-rank tests, depending on the conditions of application. Kaplan-Meier survival curves were shown for the factors associated with survival. Cox proportional hazards modelling was performed. The interaction-with-time method was used to assess proportional hazard assumption. Variables with non-proportional hazards were considered as time-dependent variables. Variables with p-values <0.20 in univariate analysis were selected for entry into a multivariate model. The full model was simplified via a backward selection procedure considering potential confounding at each step (Vittinghoff et al., 2012). Hazard ratios with 95% confidence intervals (CIs) were estimated. A p-value <0.05 was considered as statistically significant.

III.2.2. Results: Sociodemographic, clinical features, prognoses and survival of ALS patients - The TROPALS study

Nine hospital centers participated in the TROPALS collaboration from the following eight African countries:

- Algeria (Centre Hospitalier Universitaire Mustapha in Alger)
- Benin (Centre National Hospitalier Universitaire Hubert Koutoukou MAGA in Cotonou)
- Burkina Faso (Centre Hospitalier Universitaire Sourô Sanou in Bobo-Dioulasso)
- Mauritania (Centre Hospitalier des Spécialités in Nouakchott)
- Senegal (Centre Hospitalier Universitaire de Fann in Dakar)
- South Africa (Tygerberg Academic Hospital in Cape Town)
- Togo (Centre Hospitalier Universitaire CAMPUS in Lomé and Centre Hospitalier Universitaire Sylvanus Olympio in Lomé)
- Tunisia (Centre Hospitalier Universitaire RAZI in Manouba)

Overall, 185 ALS patients were included: 114 from Northern Africa (NA), 41 from Western Africa (WA) and 30 from Southern Africa (SA). The African countries and the number of ALS patients included in each country are shown in figure 8.

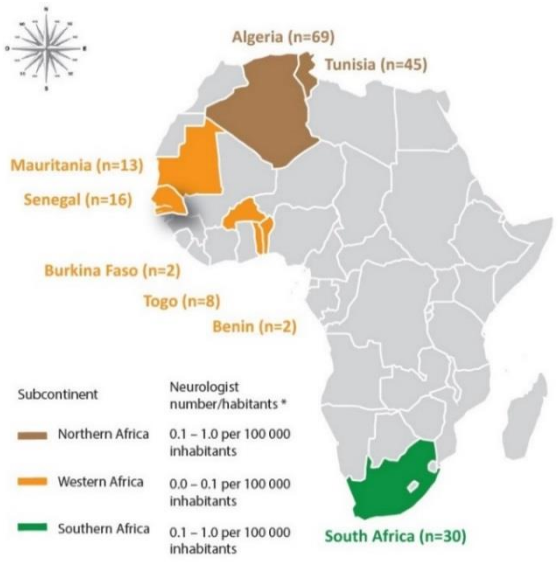


Figure 8 : The African countries and numbers of ALS patients included in the TROPALS study.
*World Health Organization. Atlas: Country resources for neurological disorders. 2004

III.2.2.1. Sociodemographic characteristics: The TROPALS study

A male predominance was observed with a male/female sex ratio (SR) of 2.9. The overall median age at onset was 53.0 years (IQR 44.5 – 64.0 years). Eight cases (4.3%) described a juvenile form with a disease onset before age 30 (four before 25 years of age). WA patients were significantly younger at onset (47.0 years) compared to NA (54.0 years) and SA (59.5 years) patients (p = 0.0003) (figure 9). The median age at diagnosis was 55.0 years (IQR 46.0 – 66.5 years), with significant differences among the subcontinents (p = 0.0003) (figure 9).

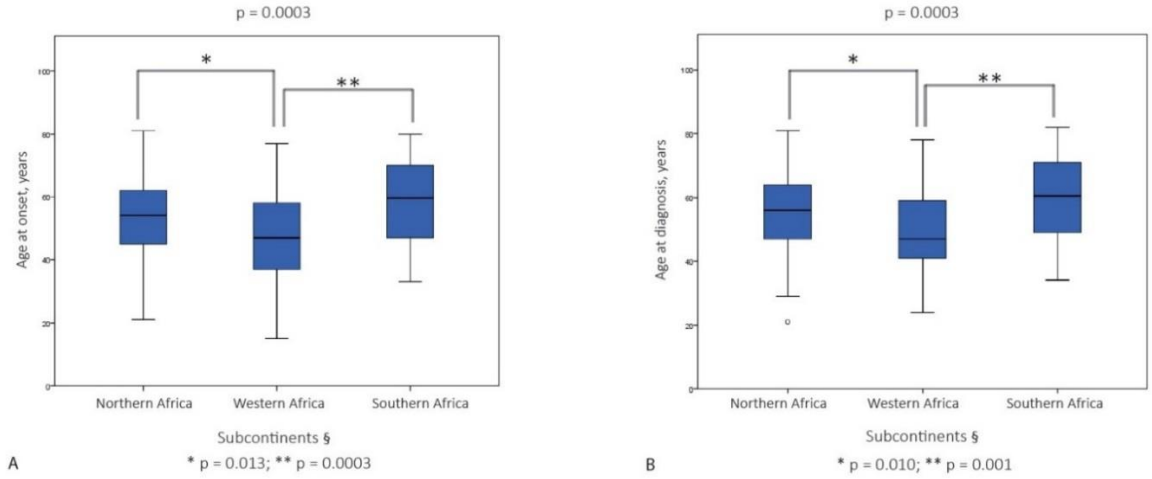


Figure 9 : Age of patients with ALS by subcontinent: The TROPALS study
Age at onset, years (A), age at diagnosis, years (B); §.Post hoc analysis: One-Way ANOVA, Scheffe post hoc: Age first symptom (NA vs WA, p=0.013; NA vs SA, p=0.114; WA vs SA, p=0.0003); Age of diagnosis (NA vs WA, p= 0.010; NA vs SA, p=0.175; WA vs SA, p=0.001).

Approximately four fifths of patients (85.3%) had support from caregivers, mostly in NA (86.8%) and WA (94.4%) (p = 0.006). Most of the patients lived with partners (married or cohabiting 83.2%). The sociodemographic characteristics at time of diagnosis are shown in table 6.

Proxies for ethnicity were only available in Southern Africa. A heterogeneous mixture of ethnic profiles was found. Considering the 30 ALS cases in SA, 16 were of European ancestry, 12 mixed (European and African ancestry) and two of African ancestry.

Table 6 : Sociodemographic characteristics of patients with ALS by subcontinents: The TROPALS study

	Overall (n=185)	Northern Africa (NA) (n=114)	Western Africa (WA) (n=41)	Southern Africa (SA) (n=30)	*p* value
Gender, n (%)					
Male	138 (74.6)	82 (71.9)	32 (78.0)	24 (80.0)	0.563 [a]
Female	47 (25.4)	32 (28.1)	9 (22.0)	6 (20.0)	
Sex Ratio M/F	2.9	2.6	3.5	4.0	
Age at onset (years)					
Median (IQR)	53.0 (44.5 – 64.0)	54.0 (45.0 – 62.0)	47.0 (36.0 – 58.0)	59.5 (47.0 – 70.7)	0.0003 [b]
Age <25 years, n (%)	4 (2.2)	1 (0.9)	3 (7.3)	0 (0)	
Age <30 years, n (%)	8 (4.3)	2 (1.8)	6 (14.6)	0 (0)	
Age at diagnosis (years)					
Median (IQR)	55.0 (46.0 - 66.5)	56.0 (47.0 – 64.5)	47.0 (38.5 – 59.0)	60.5 (48.5 – 71.8)	0.0003 [b]
Age <25 years, n (%)	4 (2.2)	1 (0.9)	3 (7.3)	0 (0)	
Age <30 years, n (%)	8 (4.3)	2 (1.8)	6 (14.6)	0 (0)	
Education level, n (%) †					
Illiteracy	51 (28.4)	30 (26.5)	21 (56.8)	0 (0)	< 0.0001 [a]
Elementary school	58 (32.2)	41 (36.3)	4 (10.8)	13 (43.3)	
High school	49 (27.2)	31 (27.4)	7 (18.9)	11 (36.7)	
University	22 (12.2)	11 (9.7)	5 (13.5)	6 (20.0)	
Marital status, n (%) †					
Married/cohabiting	153 (83.2)	101 (88.6)	30 (73.2)	22 (75.9)	0.040 [a]
Not married	31 (16.8)	13 (11.4)	11 (26.8)	7 (24.1)	
Caregivers, n (%) †					
Yes	151 (85.3)	99 (86.8)	34 (94.4)	18 (66.7)	0.006 [a]
No	26 (14.7)	15 (13.2)	2 (5.6)	9 (33.3)	

a. X^2 test; b. Analysis of variance (ANOVA)
† Missing data: Education level (n=5), marital status (n=1), caregivers (n=8)

III.2.2.2. Personal and family medical history: The TROPALS study

The most common medical antecedents of patients with ALS were hypertension (29.2%), diabetes (7.6%) and musculoskeletal disorders (7.0%). Antecedent trauma was reported in approximately 3%. Depression and anxiety were identified in 2.7% of cases. Personal medical history of all included patients is shown in table 7.

Table 7 : Personal medical history of patients with ALS at time of diagnosis: The TROPALS study

Personal medical history	Overall (n=185)
Cardiovascular diseases, n (%)	
Hypertension	54 (29.2)
Coronary artery disease	7 (3.8)
Heart failure	6 (3.2)
Arrhythmias	5 (2.7)
Stroke	2 (1.1)
Neurological disorders, n (%)	
CNS infections	6 (3.2)
Meningitis	4 (2.2)
Parkinson	2 (1.1)
Dementia	1 (0.5)
Epilepsy	1 (0.5)
Meningoencephalitis	1 (0.5)
Psychiatric disorders, n (%)	
Depression	5 (2.7)
Anxiety	5 (2.7)
Psychosis	1 (0.5)
Behavior impairment	1 (0.5)
Hallucinations	1 (0.5)
Antecedent trauma, n (%)	
Traumatic brain injury	6 (3.2)
Spinal trauma	1 (0.5)
Other medical conditions, n (%)	
Diabetes	14 (7.6)
Musculoskeletal Disorders	13 (7.0)
Infections	8 (4.3)
Cancer	6 (3.2)

One hundred sixty-one patients had knowledge of their family medical history. Familial ALS was reported in 5.7% with no significant differences among the subcontinents (p = 0.463). Familial history of other neurodegenerative disorders was described such as dementia and Parkinson's disease in 9.7% and 4.5%, respectively. Consanguinity was reported more frequently in NA (25.8%) and WA (20.7%) compared to SA (0%). Familial medical history of ALS patients is shown in table 8.

Table 8 : Familial medical history of patients with ALS by subcontinent: The TROPALS study

ALS cases who had knowledge of family medical history	Overall (n=161)	Northern Africa (NA) (n=98)	Western Africa (WA) (n=33)	Southern Africa (SA) (n=30)	p value
fALS, n (%) †	9 (5.7)	4 (4.1)	2 (6.3)	3 (10.0)	0.471 [a]
Dementia, n (%) †	15 (9.7)	15 (15.8)	0 (0.0)	0 (0.0)	0.006 [a, §]
Parkinson, n (%) †	7 (4.5)	6 (6.3)	1 (3.2)	0 (0.0)	0.322 [a]
Consanguinity, n (%) †	31 (21.1)	25 (25.8)	6 (20.7)	0 (0.0)	0.032 [a, §]

a. X^2 test.
§.Post hoc analysis: cognitive impairment family history (NA vs WA, p=0.090; NA vs SA, p=0.081); consanguinity family history (NA vs WA, p=0.999; NA vs SA, p=0.035; WA vs SA, p=0.105).
† Missing data: fALS (n=2), dementia (n=7), consanguinity (n=14)
fALS, familial Amyotrophic Lateral Sclerosis

III.2.2.3. Clinical characteristics: The TROPALS study

Overall, bulbar onset was exhibited in 22.7% of cases. There were no significant differences on the site at onset (spinal or bulbar) among the subcontinents (p = 0.098). Of the 143 patients with spinal onset, 45.1% exhibited upper limb onset, 23.2% lower limb onset and 31.7% combined upper and lower limb onset with significant variability between the subcontinents (p = 0.001). The proportion patients according to site at onset are shown in table 9.

Table 9 : Site at onset of patients with ALS by subcontinent: The TROPALS study

		Overall (n=185)	Northern Africa (NA) (n=114)	Western Africa (WA) (n=41)	Southern Africa (SA) (n=30)	*p* value
Onset site, n (%)	Bulbar	42 (22.7)	26 (22.8)	13 (31.7)	3 (10.0)	0.098 [a]
	Spinal	143 (77.3)	88 (77.2)	28 (68.3)	27 (90.0)	
	Spinal form †					
	Pure upper limb	64 (45.1)	39 (44.3)	13 (48.1)	12 (44.4)	0. 001 [a]
	Pure lower limb	33 (23.2)	13 (14.8)	7 (25.9)	13 (48.1)	
	Lower and upper	45 (31.7)	36 (40.9)	7 (25.9)	2 (7.4)	

a. X^2 test
† Missing data; spinal form (n=1)

The median diagnostic delay was 12.0 months (IQR 6.0 – 23.0 months). There was no statistically significant difference between the subcontinents (p = 0.380, figure 10).

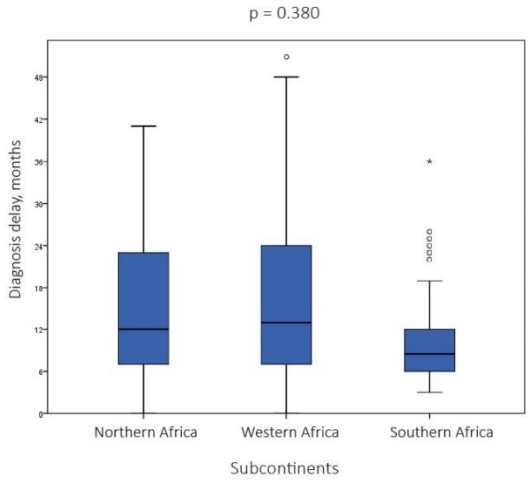


Figure 10 : Diagnosis delay by subcontinent: The TROPALS study

§ Kruskal Wallis test.

At time of diagnosis, patients were categorized as definite (29.7%), probable (35.1%), probable with laboratory support (29.2%), and possible (6.0%) ALS according to Airlie House criteria. Statistically significant differences were found between the subcontinents ($p < 0.0001$). Post-hoc analysis showed that WA patients were more likely to be diagnosed with definite disease compared to NA ($p < 0.001$) and SA ($p = 0.009$) (table 10).

Table 10 : Airlie House criteria of patients with ALS by subcontinent: The TROPALS study

	Overall (n=185)	**Northern Africa (NA) (n=114)**	**Western Africa (WA) (n=41)**	**Southern Africa (SA) (n=30)**	***p* value**
Airlie House Criteria					
Definite	55 (29.7%)	25 (21.9%)	24 (58.5%)	6 (20%)	<0.0001 [a §]
Probable	65 (35.1%)	42 (36.8%)	14 (34.1%)	9 (30%)	
Probable with laboratory support	54 (29.2%)	40 (35.1%)	3 (7.3%)	11 (36.7%)	
Possible	11 (5.9%)	7 (6.1%)	0 (0%)	4 (13.3%)	

a. X^2 test
[§] Post-hoc test:
Definite (NA vs WA, p<0.001; NA vs SA, p=0.999; WA vs SA, p=0.009)
Probable (NA vs WA, p=0.999; NA vs SA, p=0.999; WA vs SA, p=0.999)
Probable with laboratory support (NA vs WA, p=0.005; NA vs SA, p=0.999; WA vs SA, p=0.017)
Possible (NA vs WA, p=0.835; NA vs SA, p=0.999; WA vs SA, p=0.129)

Motor deficit was the most common symptom in ALS patients at time of diagnosis. More than half of cases reported muscle cramps (55.6%), asthenia or fatigue (53.6%) and dysarthria (51.6%). There was a wide variability of symptoms at diagnosis between subcontinents (table 11).

Table 11 : Symptoms of patients with ALS at time of diagnosis by subcontinent: The TROPALS study

Symptoms at diagnosis	**Overall (n=185)**	**Northern Africa (NA) (n=114)**	**Western Africa (WA) (n=41)**	**Southern Africa (SA) (n=30)**	***p* value**
Motor deficit, n (%)	162 (87.6)	97 (85.1)	36 (87.8)	29 (96.7)	0.231 [a]
Muscle cramps, n (%) †	99 (55.6)	68 (60.7)	23 (62.2)	8 (27.6)	0.004 [a]
Asthenia/Fatigue, n (%) †	98 (53.6)	75 (65.8)	23 (57.5)	0 (0.0)	<0.0001 [a]
Dysarthria, n (%) †	95 (51.6)	53 (46.9)	30 (73.2)	12 (40)	0.006 [a]
Dysphagia, n (%) †	88 (47.8)	55 (48.7)	27 (65.9)	6 (20)	0.004 [a]
Spasticity, n (%) †	80 (43.7)	29 (25.9)	34 (82.9)	17 (56.7)	<0.0001 [a]
Anxiety/Depression, n (%) †	69 (38.8)	56 (49.1)	11 (31.4)	2 (6.9)	0.0001 [a]
Dyspnea, n (%)	51 (27.6)	24 (21.1)	10 (24.4)	17 (56.7)	0.0004 [a]
Pain, n (%) †	48 (26.8)	27 (24.5)	20 (51.3)	1 (3.3)	0.0001 [a]
Sialorrhea, n (%) †	47 (25.4)	30 (26.8)	15 (37.5)	2 (6.7)	0.013 [a]
Sleep disorders, n (%) †	36 (20.3)	24 (21.4)	8 (22.9)	4 (13.3)	0.569 [a]
Pseudobulbar affect, n (%) †	11 (6.0)	8 (7.0)	2 (5.1)	1 (3.3)	0.727 [a]
Bronchial hypersecretion, n (%) †	8 (4.3)	6 (5.3)	2 (4.9)	0 (0.0)	0.440 [a]
Laryngospasm, n (%) †	3 (1.6)	3 (2.7)	0 (0.0)	0 (0.0)	0.242 [a]

a. X^2 test
† Missing data (in alphabetical order): Anxiety/Depression (n=7), Asthenia/Fatigue (n=2), Bronchial hyper secretion (n=1), Dysarthria (n=1), Dysphagia (n=1), Laryngospasm (n=3), Muscle cramps (n=7), Pain (n=6), Pseudobulbar affect (n=2), Sialorrhea (n=3), Sleep disorders (n=8), Spasticity (n=2).

The neurological examination revealed muscular atrophy in 90.8% of cases with a predominance of upper limb atrophy. Fasciculations were a frequent clinical finding in 95.1%, mostly in the upper limb. Reflex test data was available in 181 (97.8%) of cases. The description of deep tendon reflexes explored at diagnosis are presented in table 12.

Extra-motor involvement was presented in 59 patients. Among these patients, sensory involvement was observed in 54.7% (paresthesia or dysesthesia). Cognitive impairment was found in 38.8%, specifically in speech, memory and executive function. We also found 28% with dysautonomic impairments, 22.6% with vesical-sphincter disorders, 10.2% with extrapyramidal involvement and 6.3% with oculomotor involvement.

Table 12 : Reflex testing in patients with ALS: The TROPALS study

Deep tendon reflexes	Overall (n=181)	Deep tendon reflexes	Overall (n=181)
Biceps left, n (%) †		**Biceps right, n (%)** †	
Brisk	109 (61.2)	Brisk	116 (65.5)
Diffuse	29 (16.3)	Diffuse	24 (13.6)
Normal	26 (14.6)	Normal	26 (14.7)
Absent	14 (7.9)	Absent	11 (6.2)
Triceps left, n (%) †		**Triceps right, n (%)** †	
Brisk	114 (64.0)	Brisk	120 (67.4)
Diffuse	17 (9.6)	Diffuse	15 (8.4)
Normal	33 (18.5)	Normal	32 (18.0)
Absent	14 (7.9)	Absent	11 (6.2)
Brachioradialis left, n (%) †		**Brachioradialis right, n (%)** †	
Brisk	100 (57.1)	Brisk	104 (59.4)
Diffuse	27 (15.4)	Diffuse	25 (14.3)
Normal	33 (18.9)	Normal	33 (18.9)
Absent	15 (8.6)	Absent	13 (7.4)
Patellar left, n (%) †		**Patellar right, n (%)** †	
Brisk	121 (68.0)	Brisk	120 (67.4)
Diffuse	31 (17.4)	Diffuse	31 (17.4)
Normal	17 (9.6)	Normal	16 (9.0)
Absent	9 (5.1)	Absent	11 (6.2)
Achilles left, n (%) †		**Achilles right, n (%)** †	
Brisk	97 (54.8)	Brisk	99 (55.9)
Diffuse	16 (9.0)	Diffuse	18 (10.2)
Normal	46 (26.0)	Normal	39 (22.0)
Absent	18 (10.2)	Absent	21 (11.9)
Babinski left, n (%) †		**Babinski right, n (%)** †	
Positive	51 (28.3)	Positive	59 (33.3)
Negative	86 (47.8)	Negative	81 (45.8)
Indifferent	43 (23.9)	Indifferent	37 (20.9)
Hoffman left, n (%) †		**Hoffman right, n (%)** †	
Present	101 (57.1)	Present	100 (56.8)
Absent	76 (42.9)	Absent	76 (43.2)

† Missing data: Biceps left (n=3); Biceps right (n=4); Triceps left (n=3); Triceps right (n=3); Brachioradialis left (n=6); Brachioradialis right (n=6); Patellar left (n=3); Patellar right (n=3); Achilles left (n=4); Achilles right (n=4); Babinski left (n=1); Babinski right (n=4); Hoffman left (n=4); Hoffman right (n=5).

The median ALSFRS-R was 38.0 (IQR 29.0 – 42.0) at time of diagnosis. WA patients had a lower ALSFRS-R score (median = 27.6) compared to NA (median = 40.0) and SA (median = 39.0) patients (p = 0.0001). The ALSFRS-R slope was estimated at 0.8 (IQR 0.4 – 1.7), which estimates the progression of disability between symptom onset and diagnosis. In the same line, WA patients had a significantly higher ALSFRS-R slope (median = 1.6) compared to NA (median = 0.7) and SA (median = 0.7) patients (p = 0.001). These results imply that WA patients presented severe disability status at diagnosis. The ALSFRS-R score and slope by subcontinents are shown in table 13.

Table 13 : ALS Functional Rating Scale Revised and slope in patients with ALS at time of diagnosis by subcontinent: The TROPALS study

	Overall (n=185)	**Northern Africa (NA) (n=114)**	**Western Africa (WA) (n=41)**	**Southern Africa (SA) (n=30)**	***p* value**
ALSFRS-R (/48), median (IQR)	38.0 (29.0 –42.0)	40.0 (35.0 – 43.2)	27.6 (20.5 – 36.0)	39.0 (34.5 – 44.0)	<0.0001 [a, §]
ALSFRS-R slope (unit/month), median (IQR)	0.8 (0.4 – 1.7)	0.7 (0.4 – 1.3)	1.6 (0.7 – 2.5)	0.7 (0.5 – 1.9)	0.001 [a, §]

a. Kruskal Wallis
§ Post-hoc test:
ALSFRS-R (NA vs WA, p<0.001; NA vs SA, p=0.999; WA vs SA, p<0.001)
ALSFRS-R Slope (NA vs WA, p<0.001; NA vs SA, p=0.999; WA vs SA, p=0.109)

III.2.2.4. Complementary exams: The TROPALS study

In total, 167 patients with ALS underwent neurophysiological examination, specifically electroneuromyography (ENMG). ENMG was mostly done in NA (99.1%) and SA (90.0%) compared to WA (76.9%) (p = 0.0001).

Brain magnetic resonance imaging (MRI) scan was performed in 74 patients and spinal MRI in 116 patients. Cranial and spine computed tomography (CT) scan were performed in 18 and 16 patients, respectively.

III.2.2.5. Conventional and traditional treatment: The TROPALS study

One hundred thirty-four patients received conventional medical treatment, consisting mainly of symptomatic treatments or physiotherapy (64.9%). Overall, one quarter of patients received disease-modifying therapy (riluzole). Patients with ALS received riluzole mostly in NA (33.0%)

and WA (25.0%) compared to SA (3.3%). Traditional medicine was sought by 20.0% of cases, mainly in WA. Among these patients, approximately 60.0% used plants or substances made from plants as treatment. Conventional and traditional medicine are described in table 14.

Table 14 : Conventional and traditional treatment in patients with ALS: The TROPALS study

	Overall (n=185)	**Northern Africa (NA) (n=114)**	**Western Africa (WA) (n=41)**	**Southern Africa (SA) (n=30)**	***p* value**
Conventional medicine treatment					
Therapy with riluzole, n (%) †	47 (26.3)	36 (33.0)	10 (25.0)	1 (3.3)	0.005 [a]
Traditional medicine treatment					
Traditional medicine, n (%) †	34 (20.0)	20 (19.2)	14 (37.8)	0 (0.0)	0.001 [a]

a. X^2 test
† Missing data: riluzole (n=6); traditional medicine (n= 15)

III.2.2.6. Survival and prognostic factors: The TROPALS study

Overall, 128 patients were included in the survival analysis considering 138.7 person-years of follow-up (PYFU). The sociodemographic, family medical histories, clinical features and treatment of ALS patients included in the survival analysis are shown in table 15. Fifty-seven patients were excluded from the survival analysis because they lacked follow-up data of at least 1 month after diagnosis. Patients excluded were younger (median age 50 vs 56 years, $p = 0.046$) and less likely to have a partner (70.2% vs 89.0%, $p = 0.002$).

Table 15 : Sociodemographic data, family medical histories, clinical characteristics, and treatments of ALS patients included in the survival analysis. The TROPALS study.

	Overall (n=128)	Northern Africa (NA) (n=79)	Western Africa (WA) (n=25)	Southern Africa (SA) (n=24)	p value
1a. Sociodemographic characteristics					
Gender, n (%)					
Male	98 (76.6)	59 (74.7)	18 (72.0)	21 (87.5)	0.360 [a]
Female	30 (23.4)	20 (25.3)	7 (28.0)	3 (12.5)	
Sex Ratio M/F	3.3	2.9	2.6	7.0	
Age at onset (years)					
Median (IQR)	55.0 (46.0 – 63.7)	56.0 (48.0 – 62.0)	48.0 (39.0 – 61.5)	58.5 (47.0 – 72.2)	0.078 [b]
Age ≤30 years	2 (1.6)	0 (0.0)	2 (8.0)	0 (0.0)	
Age at diagnosis (years)					
Median (IQR)	56.0 (47.0 – 64.7)	58.0 (49.0 – 63.0)	50.0 (41.5 – 62.0)	59.0 (47.5 – 73.2)	0.079 [b]
Education level, n (%) †					
Illiteracy	36 (28.4)	22 (28.2)	14 (56.0)	0 (0.0)	0.0001 [a]
Elementary school	37 (29.1)	25 (32.1)	1 (4.0)	11 (45.8)	
High school	37 (29.1)	25 (32.1)	5 (20.0)	7 (29.2)	
University	17 (13.4)	6 (7.6)	5 (20.0)	6 (25.0)	
Marital status, n (%) †					
Married/cohabiting	113 (89.0)	75 (94.9)	20 (80.0)	18 (78.3)	0.022 [a]
Not married/widow	14 (11.0)	4 (5.1)	5 (20.0)	5 (21.7)	
1b. Family medical history					
Family medical history awareness					
fALS, n (%) ¥†	4 (3.7)	2 (3.1)	0 (0.0)	2 (8.3)	0.351 [a]
Dementia, n (%) ¥†	14 (13.1)	14 (21.5)	0 (0.0)	0 (0.0)	0.006 [a]
Consanguinity, n (%) ¥†	21 (19.6)	15 (23.1)	6 (33.3)	0 (0.0)	0.032 [a]
1c. Clinical characteristics					
Onset site, n (%)					
Spinal	101 (78.9)	62 (78.5)	17 (68.0)	22 (91.7)	0.126 [a]
Bulbar	27 (21.1)	17 (21.5)	8 (32.0)	2 (8.3)	
Diagnostic delay (months)					
Median (IQR)	10.5 (6.0 – 20.5)	10.0 (6.0 -22.0)	11.0 (3.0 – 22.5)	10.0 (6.2 – 17.2)	0.854 [c]
Airlie House Criteria, n (%)					
Definite	37 (28.9)	17 (21.5)	15 (60.0)	5 (20.8)	0.003 [a]
Probable	44 (34.4)	29 (36.7)	8 (32.0)	7 (29.2)	
Probable with laboratory support	37 (28.9)	27 (34.2)	2 (8.0)	8 (33.3)	
Possible	10 (7.8)	6 (7.6)	0 (0.0)	4 (16.7)	

Table 15. Sociodemographic data, family medical histories, clinical characteristics, and treatments of ALS patients included in the survival analysis (continued). The TROPALS study.

	Overall (n=128)	Northern Africa (NA) (n=79)	Western Africa (WA) (n=25)	Southern Africa (SA) (n=24)	p value
ALSFRS-R (/48)					
Median (IQR)	38.5 (29.2 – 42.0)	40.0 (36.0 – 44.0)	24 (20.5 – 31.5)	38.5 (31.5 – 42.7)	<0.0001 c £
ALSFRS-R slope (unit/month)					
Median (IQR)	0.7 (0.4 – 1.7)	0.6 (0.3 – 1.3)	2.0 (0.7 – 8.5)	0.6 (0.4 – 1.9)	0.001 c £
Extra-motor involvement, n (%)	43 (33.6)	24 (30.4)	11 (44.0)	8 (33.3)	0.454 a
1d. Treatment					
Therapy with riluzole, n (%) †	37 (29.4)	29 (37.7)	7 (28.0)	1 (4.2)	0.007 a

a. X^2 test; b. ANOVA (Welch); c. Kruskal Wallis
£. Kruskal Wallis Test, post hoc test: ALSFRS-R (NA vs WA, p<0.0001; NA vs SA, p=0.986; WA vs SA, p=0.001); ALSFRS R Slope (NA vs WA, p<0.001; NA vs SA, p=0.999; WA vs SA, p=0.047), Bonferroni correction for multiple tests was used.
¥ Percentages represent the proportion of ALS cases that had knowledge of family medical history (n=107).
† Missing data: educational level (n=1), marital status (n=1), fALS (n=2); dementia (n=3); consanguinity (n=10), riluzole (n=2).

The median survival time was 14.0 months (95% CI 10.7 to 17.2 months) since diagnosis (figure 11) and 35.0 months (95% CI 29.1 to 40.8 months) since disease onset (figure 12).

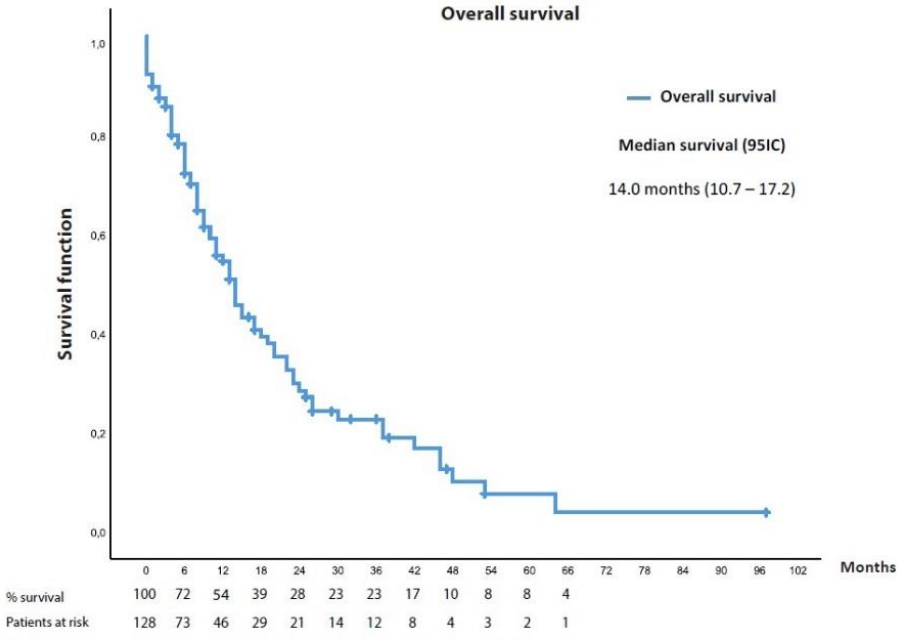


Figure 11 : Overall survival from diagnosis: The TROPALS study

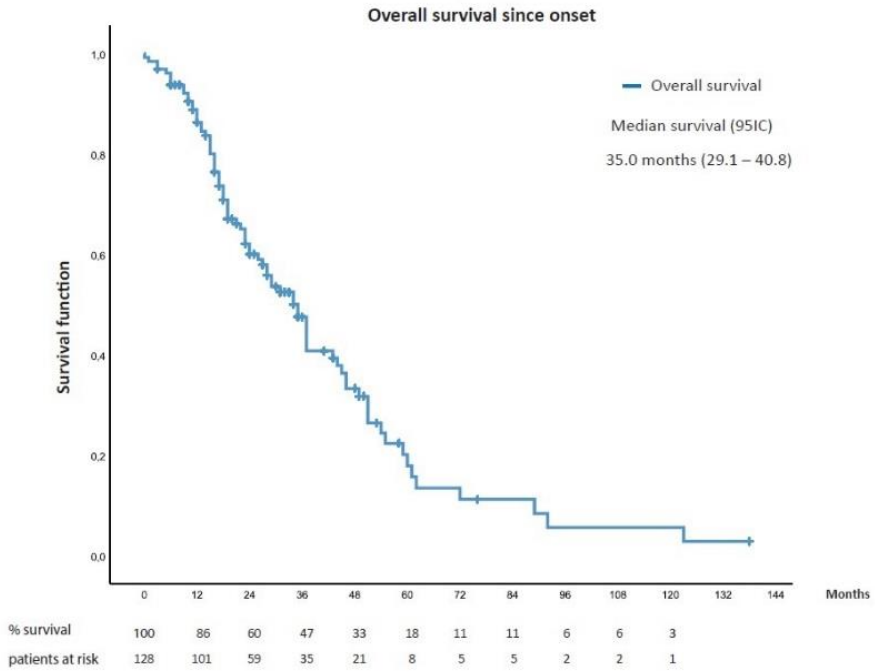


Figure 12 : Overall survival from onset: The TROPALS study

Cox proportional hazards modelling was performed to identify factors associated with survival. The sociodemographic, clinical characteristics and disease-modifying treatment were considered in the univariate model. The subcontinents, type of onset, Airlie House criteria, ALSFRS-R score at diagnosis, cognitive impairment status and riluzole treatment were included in the full multivariate model. A backwards selection method was used to obtain the final multivariate model. The analysis showed that subcontinent and riluzole were independently associated with survival ($p < 0.0001$ and $p = 0.002$, respectively).

Baseline characteristics of ALS patients and their association with survival from the time of diagnosis are shown in table 16.

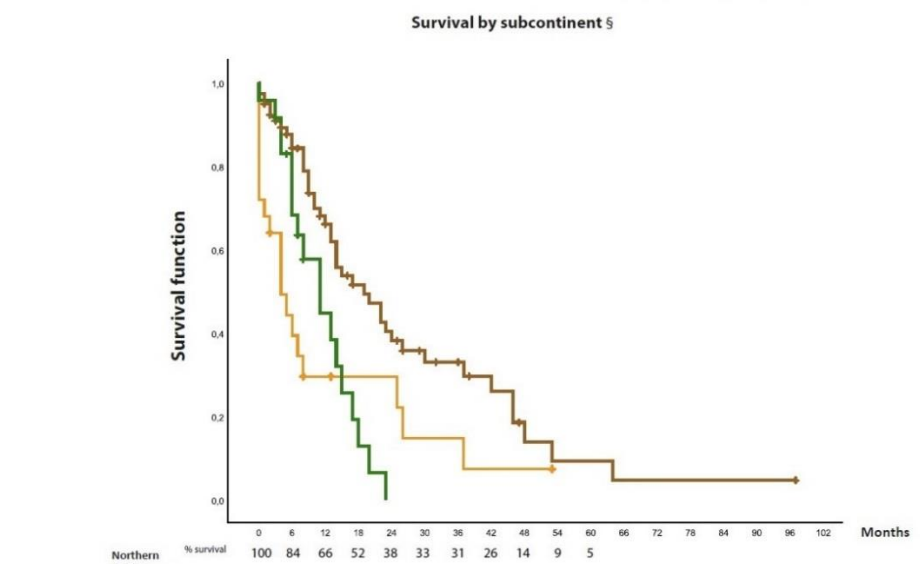
Table 16: Baseline characteristics of patients with ALS and their associations with survival from the time of diagnosis, in univariate and multivariate analyses. The TROPALS study.

	Description (n=128)	Univariate model (n=128)			Full multivariate model (n=126)			Final multivariate model (n=126)		
	Median (IQR) or n (%)	cHR	95 CI	*p* value	aHR	95 CI	*p* value	aHR	95 CI	*p* value
Subcontinent §										
Northern Africa	79 (61.7)	1.00		0.0002	1.00		0.043	1.00		<0.0001
Western Africa	25 (19.5)	4.80	2.20 – 10.48		2.94	1.17 – 7.35		4.83	2.19 – 10.65	
Southern Africa	24 (18.8)	0.94	0.32 – 2.76		0.85	0.28 – 2.59		0.81	0.27 – 2.42	
Gender										
Male	98 (76.6)	1.00		0.459						
Female	30 (23.4)	1.22	0.72 – 2.04							
Age at diagnosis *	56.0 (47.0 – 64.7)	1.06	0.97 – 1.16	0.209						
Marital Status †										
Not married/widow	14 (11.0)	1.00		0.262						
Married/cohabiting	113 (89.0)	0.70	0.38 – 1.30							
Diagnosis delay ¥	10.5 (6.0 – 20.5)	1.29	0.77 – 2.19	0.328						
Onset site										
Spinal	101 (78.9)	1.00		0.059	1.00		0.219			
Bulbar	27 (21.1)	1.71	0.98 – 3.00		1.54	0.77 – 3.06				
Airlie House criteria §										
Definite	37 (28.9)	1.00		0.018	1.00		0.268			
Probable	44 (34.4)	0.36	0.16 – 0.81		0.52	0.21 – 1.29				
Probable with lab support	37 (28.9)	0.45	0.19 – 1.09		0.85	0.28 – 2.56				
Possible	10 (7.8)	0.02	0.001 – 0.77		0.08	0.003 – 2.20				
ALSFRS-R at diagnosis ¶	38.5 (29.2 – 42.0)	0.85	0.75 – 0.97	0.014	0.91	0.75 – 1.11	0.381			
ALSFRS-R slope	0.7 (0.4 – 1.7)	0.99	0.99 – 1.00	0.432						
Atypical signs										
No	85 (66.4)	1.00		0.694						
Yes	43 (33.6)	0.91	0.57 – 1.46							
Cognitive impairment										
No	112 (87.5)	1.00		0.112	1.00		0.224			
Yes	16 (12.5)	1.62	0.89 – 2.95		1.57	0.75 – 3.26				
Riluzole †										
Therapy without riluzole	89 (70.6)	1.00		0.0003	1.00		0.023	1.00		0.002
Therapy with riluzole	37 (29.4)	0.36	0.20 – 0.62		0.49	0.26 – 0.91		0.41	0.22 – 0.73	

§ Covariates with non-proportional hazards (interaction with time p value): Subcontinent (p=0.001); Airlie House criteria (p=0.028); Subcontinents and Airlie House criteria were considered as time-dependent variables in the models (HR are reported at t = 0).
* HR for baseline time calculated for 5 years increment
¥ HR for 6 months increment
¶ HR for baseline time calculated for 5 units increment.
† Missing data: Marital status (n=1), riluzole (n=2).
aHR, adjusted Hazard Ratio; ALSFRS-R, ALS Functional Rating Scale Revised; cHR, crude Hazard Ratio;

The median survival time from diagnosis was longer in NA (19.0 months, 95% CI 10.8 – 27.2 months) than in WA (4.0 months, 95% CI 0.8 – 7.1 months) and SA (11.0 months, 95% CI 5.6 – 16.4 months) (Breslow test $p<0.0001$). Compared with NA, WA patients experienced a higher

instantaneous risk of dying at baseline (adjusted HR (aHR) (T0) = 4.83, $p < 0.0001$), which progressively decreased over time (6 months aHR (T6) = 3.43, $p = < 0.0001$; 12 months aHR (T12) = 2.43, $p = 0.004$; 18 months aHR (T18) = 1.73, $p = 0.181$). On the other hand, there was no significant difference in the instantaneous risk of death at baseline between NA and SA patients (aHR (T0) = 0.81, $p = 0.712$); however, the difference increased over time, becoming significant at both 12 and 18 months (6 months aHR (T6) = 1.49, $p = 0.261$; 12 months aHR (T12) = 2.75, $p = 0.002$; 18 months aHR (T18) = 5.06, $p = 0.0009$) (Figure 13).



Subcontinent §	Median survival (95IC)	aHR T0 *	p value	aHR T6 *	p value	aHR T12 *	p value	aHR T18 *	p value
Northern Africa	19.0 months (10.8 – 27.2)	1.00		1.00		1.00		1.00	
Western Africa	4.0 months (0.8 – 7.1)	4.83	<0.0001	3.43	<0.0001	2.43	0.004	1.73	0.181
Southern Africa	11.0 months (5.6 – 16.4)	0.81	0.712	1.49	0.261	2.75	0.002	5.06	0.0009

Breslow test p < 0.0001

Figure 13 : Survival from diagnosis by subcontinents: The TROPALS study

Therapy with riluzole was significantly associated with longer survival (aHR = 0.41, 95% CI 0.22 – 0.73, *p* = 0.002). Kaplan Meier survival estimates stratified by riluzole treatment since diagnosis are shown in figure 14.

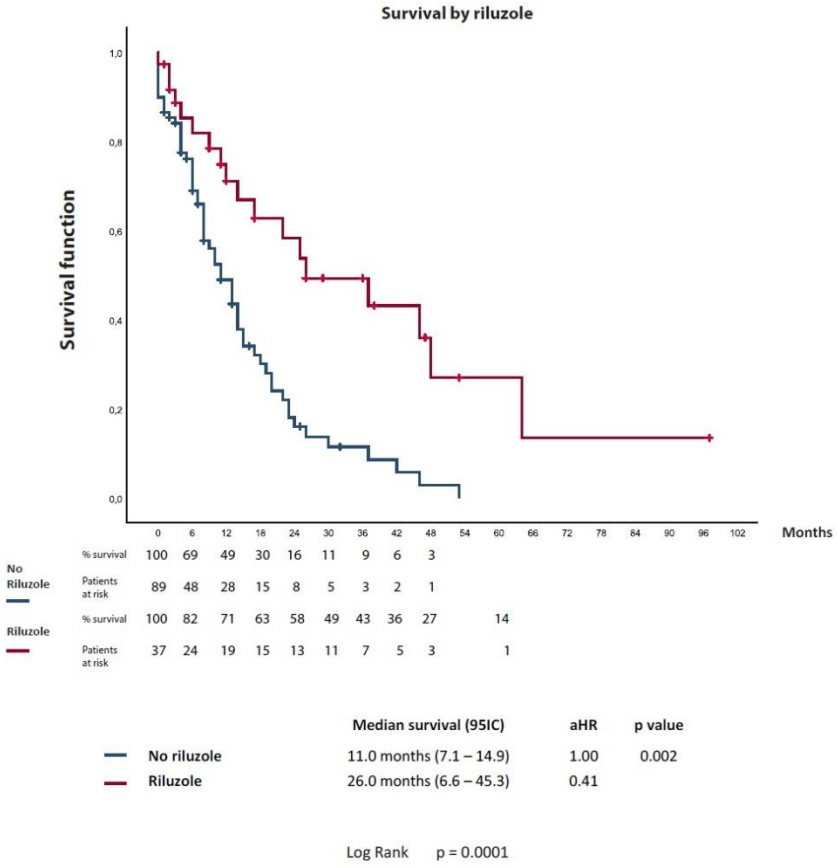


Figure 14 : Survival from diagnosis by riluzole treatment: The TROPALS study

In the same line, we performed a survival analysis since disease onset. The results were congruent with the analysis since diagnosis. A longer median survival was found in NA (37.0 months, 95% CI 25.8 – 48.1 months) compared to WA (17.0 months, 95% CI 10.7 – 23.3 months) and SA (23.0 months, 95% CI 17.8 – 28.2 months) (Breslow test *p* = 0.0002).

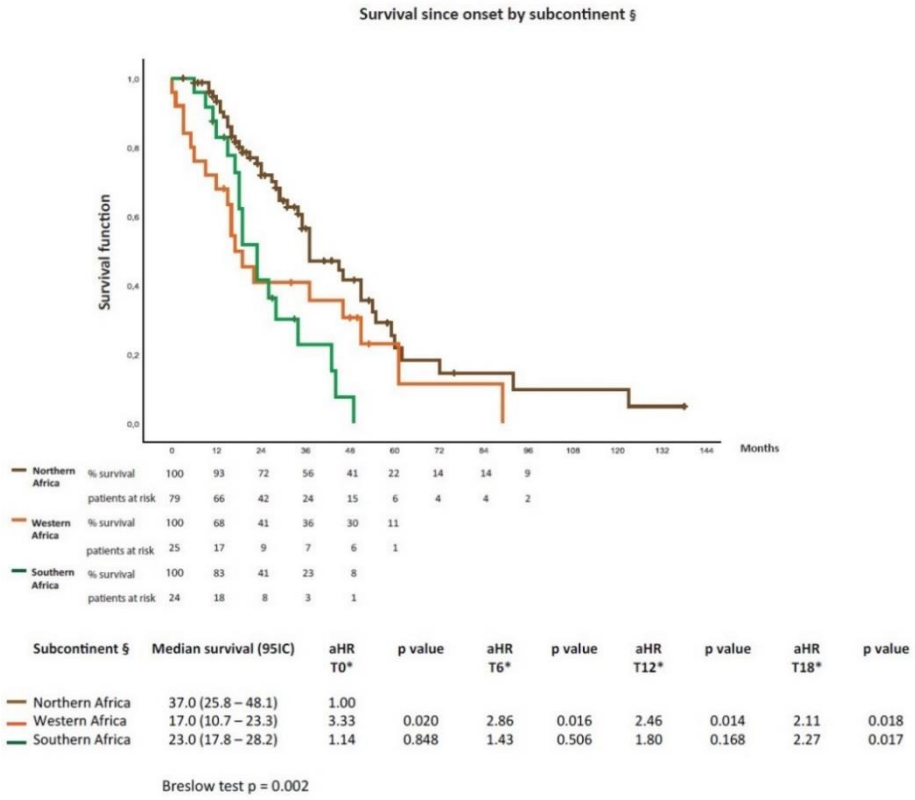
The final multivariate model found that the subcontinent and riluzole were also significantly associated to survival since disease onset (*p* = 0.057 and *p* = 0.018, respectively). Moreover, bulbar onset was associated with shorter survival (aHR = 2.78, 95% CI 1.48 – 5.23, *p* = 0.001) (table 17).

Table 17: Baseline characteristics of patients with ALS and their associations with survival from the time of onset, in univariate and multivariate analyses. The TROPALS study

	Description (n=128)	Univariate model (n=128)			Full multivariate model (n=125)			Final multivariate model (n=125)		
	Median (IQR) or n (%)	**cHR**	**95 CI**	***p* value**	**aHR**	**95 CI**	***p* value**	**aHR**	**95 CI**	***p* value**
Subcontinent §										
Northern Africa	79 (61.7)	1.00		0.017	1.00		0.079	1.00		0.057
Western Africa	25 (19.5)	4.11	1.52 – 11.08		2.95	1.07 – 8.16		3.33	1.21 – 9.14	
Southern Africa	24 (18.8)	1.28	0.37 – 4.43		0.94	0.25 – 3.59		1.14	0.31 – 4.21	
Gender										
Male	98 (76.6)	1.00		0.239						
Female	30 (23.4)	1.37	0.81 – 2.31							
Age at diagnosis *	56.0 (47.0 – 64.7)	1.04	0.95 – 1.13	0.444						
Marital Status †										
Not married/widow	14 (11.0)	1.00		0.061	1.00		0.058			
Married/cohabiting	113 (89.0)	0.55	0.29 – 1.03		0.52	0.26 – 1.02				
Onset site										
Spinal	101 (78.9)	1.00		0.008	1.00		<0.001	1.00		0.001
Bulbar	27 (21.1)	2.15	1.22 – 3.78		3.07	1.63 – 5.81		2.78	1.48 – 5.23	
Airlie House criteria										
Definite	37 (28.9)	1.00		0.380						
Probable	44 (34.4)	0.82	0.49 – 1.38							
Probable with lab support	37 (28.9)	1.13	0.61 – 2.10							
Possible	10 (7.8)	0.35	0.08 – 1.49							
ALSFRS-R at diagnosis ¶	38.5 (29.2 – 42.0)	0.93	0.82 – 1.05	0.229						
ALSFRS-R slope	0.7 (0.4 – 1.7)	1.00	0.99 – 1.00	0.721						
Atypical signs										
No	85 (66.4)	1.00		0.434						
Yes	43 (33.6)	0.83	0.52 – 1.33							
Cognitive impairment										
No	112 (87.5)	1.00		0.236						
Yes	16 (12.5)	1.44	0.79 – 2.61							
Riluzole †										
Therapy without riluzole	89 (70.6)	1.00		0.006	1.00		0.009	1.00		0.018
Therapy with riluzole	37 (29.4)	0.48	0.28 – 0.81		0.46	0.26 – 0.83		0.50	0.29 – 0.89	

§ Covariate with non-proportional hazards (interaction with time p value): Subcontinent (p=0.022); Subcontinents was considered as time-dependent variables in the models (HR are reported at t = 0).
* HR for baseline time calculated for 5 years increment
¶ HR for baseline time calculated for 5 units increment.
† Missing data: Marital status (n=1), riluzole (n=2).
aHR, adjusted Hazard Ratio; ALSFRS-R, ALS Functional Rating Scale Revised; cHR, crude Hazard Ratio.

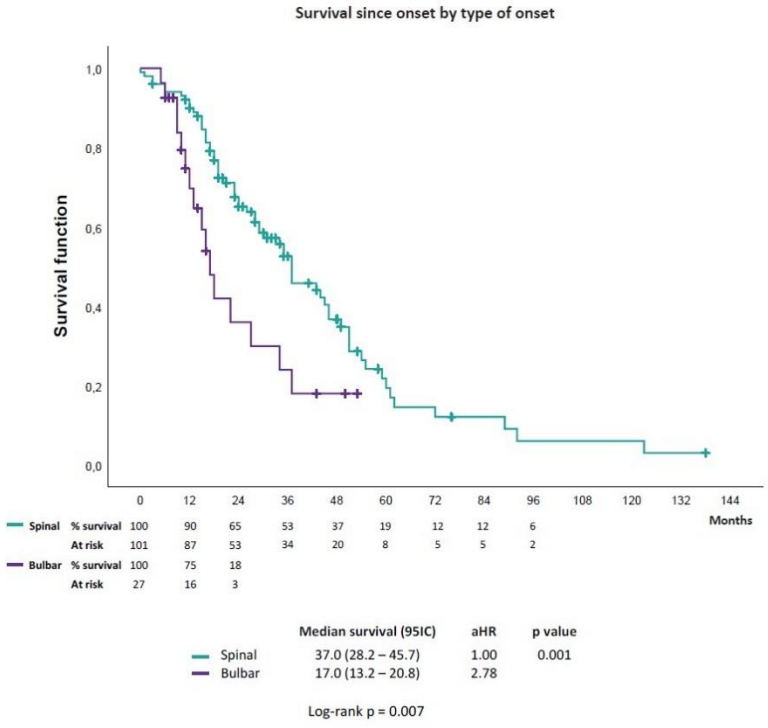
Kaplan-Meier curves since onset are shown below stratified by subcontinent (figure 15), onset site (figure 16) and riluzole treatment (figure 17).



Subcontinent §	Median survival (95IC)	aHR T0*	p value	aHR T6*	p value	aHR T12*	p value	aHR T18*	p value
Northern Africa	37.0 (25.8 – 48.1)	1.00							
Western Africa	17.0 (10.7 – 23.3)	3.33	0.020	2.86	0.016	2.46	0.014	2.11	0.018
Southern Africa	23.0 (17.8 – 28.2)	1.14	0.848	1.43	0.506	1.80	0.168	2.27	0.017

Breslow test p = 0.002

Figure 15 : Survival since onset by subcontinents: The TROPALS study



	Median survival (95IC)	aHR	p value
Spinal	37.0 (28.2 – 45.7)	1.00	0.001
Bulbar	17.0 (13.2 – 20.8)	2.78	

Log-rank p = 0.007

Figure 16 : Survival since onset by site of onset: The TROPALS study

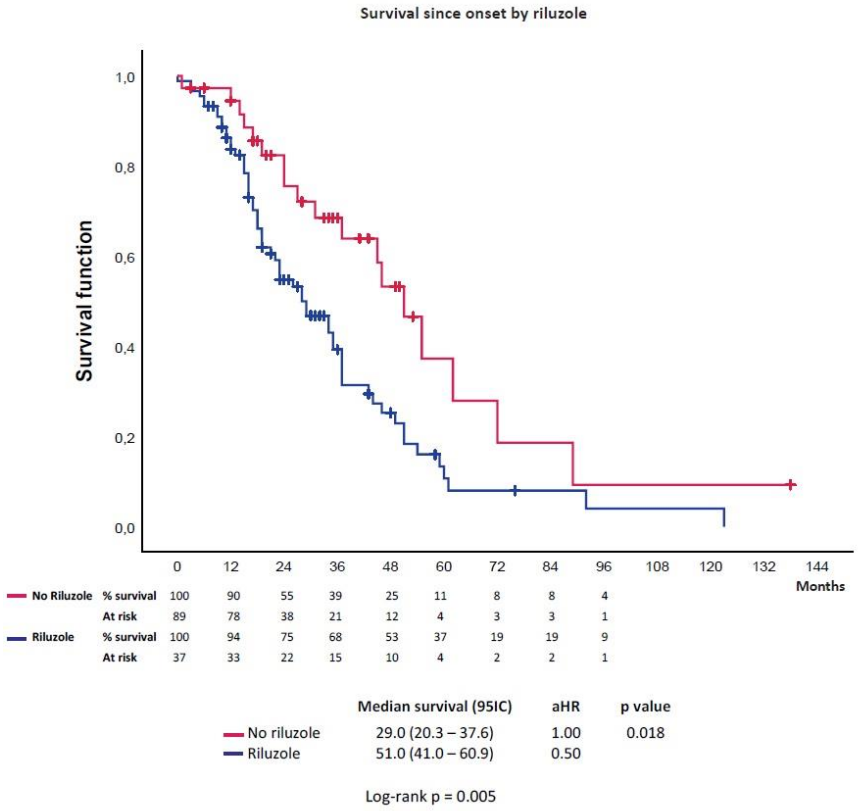


Figure 17 : Survival since onset by riluzole treatment: The TROPALS study

III.2.3. Discussion: The TROPALS study

The TROPALS study represents the first strong collaboration involving multiple hospital centers across Africa in order to assess sociodemographic characteristics, clinical features and prognostic factors on ALS using standardized and homogenous methodology. The principal results are discussed in the next section to provide a general perspective of these findings.

III.2.3.1. Sex ratio: The TROPALS study

The male predominance observed in the TROPALS study is consistent with previous reports in Africa. In Western studies, there is only a slightly higher proportion of male cases with a SR close to 1.3 (Logroscino et al., 2008; Marin et al., 2016b). In the particular case of African patients, it is still to be determined whether ALS occurrence is genuinely lower in African women (e.g. due to environmental or occupational factors) or rather reflects limited access to health care or misdiagnosis in female cases.

III.2.3.2. Age at onset: The TROPALS study

Previous studies in Africans have reported an age at onset ranging from 40 to 50 years and a high proportion of juvenile cases (13.5%-50% of cases) (Marin et al., 2012). In contrast, age at onset in patients with ALS from Europe and North America ranged from 60 to 65 years (Marin et al., 2016b). In the TROPALS study, we found a median age at onset of 53.0 years that was close to previous reports in Africa and almost a decade younger compared with Western studies. Additionally, a lower proportion of juvenile cases was found compared to previous studies. This could be related to differences in terms of life expectancy and different age structure of the population. In addition, we cannot exclude the possibility of a systematic inclusion of younger cases due to the selection bias related to hospital-based approach. Western studies have shown that hospital-based cohorts are on average younger than the ALS cases from population-based studies (Lee et al., 1995; Logroscino et al., 2018a).

Interestingly, a recent study using data from four European ALS registers found that the age difference varied only moderately (ranging from 1.1 years to 2.4 years) between patients with ALS attending to referral centers and the entire ALS population from the registers (Logroscino et al., 2018a).

III.2.3.3. Familial medical history: The TROPALS study

Few studies provided information on family medical history of ALS cases in Africa. Most of them described the absence (Collomb et al., 1968; Imam and Ogunniyi, 2004; Ndiaye et al., 1986; Sene Diouf et al., 2004; Wall and Gelfand, 1972) or a low proportion of familial ALS around 2.0% (Ben Hamida and Hentati, 1984; Osuntokun et al., 1974). On the other hand, one study described that proportion of fALS was 14.3% in Sudan (Abdulla et al., 1997). According to the TROPALS study, we found that the proportion of fALS among African patients included was 5.7%, which is consistent with Western reports (4.7 % (95 % CI 3.9 – 5.7)) (Marin et al., 2016b). It should be noted, however, that there were wide differences of fALS proportions between subcontinents.

III.2.3.4. Diagnostic delay: The TROPALS study

Contrary to the previous reports concerning diagnostic delay in Africa such as Libya (42 months) (Radhakrishnan et al., 1986) and Senegal (24 months) (Collomb et al., 1968), diagnostic delay in the TROPALS study was close to that observed in Western studies (Europe, median = 12 months; North America, median = 17 months) (Marin et al., 2016b). This diagnosis delay could suggest a selection of ALS cases considering the challenging context for diagnosis of ALS in Africa. In this continent, there are limited resources for diagnosis and management of neurology illnesses. Several reports pointed out the scarce number of neurologists, the lack of hospital beds for neurologic disorders and the lack of neurological services (e.g. electroencephalogram and electromyography) (Aarli et al., 2007; World Health Organization and the World Federation of Neurology, 2017). In addition, access to healthcare is limited, mainly in rural areas, and social insurances are not available in several African

countries (Diop A, 2014). Therefore, patients attending hospital centers might be, for example, those who could afford health care.

III.2.3.5. Onset site: The TROPALS study

In the TROPALS study, the proportion of bulbar onset was 22.7%, which is in accord with previous studies reported in Africa (around 20%) (Abdulla et al., 1997; Imam and Ogunniyi, 2004). Bulbar onset was lower compared to European studies (around 30%) (Marin et al., 2016b). This result may be attributable to selection bias and/or a young patient age. It has been shown that older patients exhibited more frequently a bulbar onset (Dandaba et al., 2017; Logroscino et al., 2015).

III.2.3.6. Diagnosis criteria and progression of disability: The TROPALS study

El Escorial criteria has rarely been used in Africa. That is because most of the studies were performed before these criteria were established and difficulties regarding the availability of ENMG (Marin et al., 2018a). However, a recent study in Tanzania that included 84 ALS cases, only reported El Escorial criteria in half of the cases (Dekker et al., 2018).

In European studies, at the time of diagnosis, patients presented a definite form of ALS among 15% to 25% (Huisman et al., 2011; Logroscino et al., 2005; Marin et al., 2014) and the median ALSFRS-R score ranges from 35 to 40/48 (Creemers et al., 2015; Marin et al., 2014). A similar pattern was observed in NA and SA. However, it appeared that WA patients were diagnosed at a more advanced stage (58.5% with definite ALS) accompanied by greater functional impairment (median ALSFRS-R score 27.6/48). This was not explained by a longer time to diagnosis (13 months, IQR 6.5 - 24.0 months). Such differences may be associated with variation in the clinical neurological practices, examination protocols, and criteria used among centers.

III.2.3.7. Cognitive impairment: The TROPALS study

In Western studies, cognitive impairment was described ranging from 30% to 50% of patients with ALS (Montuschi et al., 2015; Ringholz et al., 2005; Rippon et al., 2006). In the TROPALS study, 19 patients (10.3%) presented cognitive impairment overall, which is a lower proportion compared to the Western populations. However, we have to consider that cognitive functions were assessed through standard clinical examination on three aspects (speech, memory and executive function). Cognitive assessment battery, as the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (Abrahams and Bak, 2013), was not used because it was available after the initiation of the TROPALS study. In addition, the ECAS was designed for Western populations and has not been validated in the African context. Further studies are needed to assess cognitive functions in ALS African patients.

III.2.3.8. Survival and prognosis: The TROPALS study

Median survival of patients in the TROPALS study (35.0 months since onset and 14.0 months since diagnosis) were closed to median survival reported in Europe and North America (25.0 to 35.0 months since onset and 13 to 25 months since diagnosis) (Marin et al., 2016b). This is contrary to previous suggestions that African patients experienced a better prognosis (Abdulla et al., 1997; Osuntokun et al., 1974; Radhakrishnan et al., 1986). The fact that African cases were younger and exhibited lower proportion of bulbar onset would lead us to expect far better survival. Insufficient access to highly specialized ALS care might explain this observation.

Riluzole was an independent factor associated with a longer survival in the TROPALS study. We provided observational evidence that riluzole benefited African patients with ALS. This result is consistent with the evidence from randomized controlled trials in Western populations (Miller et al., 2012). Unfortunately, riluzole is not widely available or is extremely expensive in African countries. Subcontinent was another factor associated with survival. A longer survival was observed in NA (median survival = 19.0 months) compared to WA (median survival = 4.0 months) and SA (median survival = 11.0 months). This can be related to differences by

subcontinents in terms of clinical characteristics (e.g. more advanced stage and greater functional impartment at time of diagnosis in WA patients). Heterogeneity in terms of medical care, non-availability of disease-modifying therapy and the absence of specific ALS referral centers may also explain the survival differences. Bulbar onset was identified as risk factor for shorter survival since onset. This finding is similar to those in Western studies indicating that bulbar function plays a major role in patients survival (Chiò et al., 2009). Other factors in the literature associated to prognosis could not be included in the analysis due to lack of data such as respiratory status measured via forced vital capacity, nutrition, and need for non-invasive ventilation.

III.2.3.9. Strengths and limitations: The TROPALS study

There are several strengths and limitations to consider in the TROPALS study. Despite the efforts, it was not possible to include additional African hospitals, therefore, the data may not reflect Africa-wide situation. On the other hand, multicenter collaboration allowed the inclusion of an unprecedented sample size in African studies. Patients with ALS were identified in hospital centers that tent to lead to selection bias. Population-based ALS studies are currently impractical in most parts of Africa. Hence, large multicenter hospital-based studies are useful as initial approaches towards understanding ALS on this continent. Standard methodology was applied with neurological and research teams in each center that performed case ascertainment, data collection and follow-up. Although we established a protocol, some inter-center variations in clinical examinations may remain. Ethnicity information was not available for the entire cohort, which would have allowed us to describe and compare several characteristics among ethnic groups.

III.2.4. Conclusion: The TROPALS study

The TROPALS study was a pioneering initiative intended to improve our understanding of ALS in Africa. This has proved the importance of collaboration among epidemiologist, clinicians and researchers in order to provide reliable data in regions poorly represented in the literature. Its contribution consists with a comprehensive description of sociodemographic and clinical characteristics, treatments, prognoses and survival times of patients with ALS in Africa.

This study has shown that more patients with ALS in Africa were male, younger and exhibited a lower proportion of bulbar onset compared to patients with ALS from Western studies. Survival was similar to that of Western studies; however, it was far shorter than what would be expected for young patients with ALS. Subcontinent and riluzole were independently associated with survival.

Population-based studies are necessary to provide a clear picture on incidence, mortality, genetics and management of ALS in Africa. Further research across African countries and African populations is essential to clarify some keys points to the variability of ALS.

III.3. Article 2 - Clinical features and prognosis of ALS in Africa

Journal:

Journal of Neurology, Neurosurgery, and Psychiatry

IF: 7.144 (2017)

British Medical Association

Title:

Clinical features and prognosis of amyotrophic lateral sclerosis in Africa: the TROPALS study

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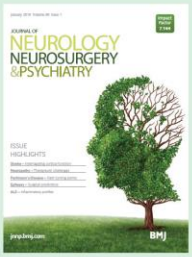

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RESEARCH PAPER

Clinical features and prognosis of amyotrophic lateral sclerosis in Africa: the TROPALS study

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ABSTRACT

Objective We describe and compare the sociodemographic and clinical features, treatments, and prognoses and survival times of patients with amyotrophic lateral sclerosis (ALS) in Africa.

Methodology We conducted a multicentre, hospital-based cohort study in Africa. Patients with ALS diagnosed in the neurology departments of participating hospitals from 2005 to 2017 were included. Subgroup analysis was performed by subcontinent. Survival analyses were conducted using the Cox proportional hazards model.

Results Nine centres from eight African countries participated. A total of 185 patients with ALS were included: 114 from Northern Africa, 41 from Western Africa and 30 from Southern Africa. A male predominance (male to female ratio 2.9) was evident. The median age at onset was 53.0 years (IQR 44.5–64.0 years). The onset was bulbar in 22.7%. Only 47 patients (26.3%) received riluzole, mainly in Northern and Western Africa. The median survival from the time of diagnosis was 14.0 months (95% CI 10.7 to 17.2 months). The median survival was longer in Northern Africa (19.0 months, 95% CI 10.8 to 27.2 months) than in Western (4.0 months, 95% CI 0.8 to 7.1 months) and Southern (11.0 months, 95% CI 5.6 to 16.4 months) Africa (Breslow test, p<0.0001). Both subcontinental location and riluzole treatment independently affected survival.

Conclusion More African patients with ALS were male and younger and exhibited a lower proportion of bulbar onset compared with patients with ALS from Western nations. Survival was consistent with that in Western registers but far shorter than what would be expected for young patients with ALS. The research improves our understanding of the disease in Africa.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rare, fatal neurodegenerative disease of unknown aetiology characterised by rapidly progressive paralysis and respiratory failure. In the 19th century, Jean-Martin Charcot performed clinical observations and meticulous laboratory work detailing the pathophysiology of ALS.[1] ALS had not been reported in Africans until 1955.[2] Even today, ALS data from Africa are limited. The few studies are mostly case series that vary in methodology, sample size and data collected. A recent systematic review on ALS in Africa identified certain specific characteristics compared with Western series: a higher male to female ratio, a juvenile form of the disease and younger age at onset.[3] However, it remains difficult to draw firm conclusions on the clinical features, prognostic factors and survival of Africans.

In recent years, the increased interest in ALS variability among populations has suggested that genetic factors (ancestry), together with environmental and lifestyle factors, play significant roles in disease occurrence and phenotype.[3–5] Studies among less-studied populations could identify novel factors affecting disease susceptibility and resistance.[6] In this context, we describe and compare the sociodemographic and clinical features, treatments, and prognoses and survival times of patients with ALS in Africa.

METHODS

Study design and participants

We performed a multicentre, hospital-based cohort study in Africa. The Inserm UMR 1094 Tropical Neuroepidemiology unit in Limoges, France, invited hospitals across Africa to join the TROPALS Collaboration (Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques: http://www.tropals.unilim.fr/). All participating centres enrolled all of their cases. Each centre featured neurology and research teams coordinating the data collection.

Patients with ALS diagnosed in the neurology departments of the participating hospitals were included from 2005 to 2017. Incident and prevalent cases were included using exhaustive and continuous approach. In particular, the South African centre joined the TROPALS Collaboration later (2015), recruiting only incident cases over a 1-year period. An expert ALS neurologist (PC) from the ALS referral centre of Limoges teaching hospital confirmed all diagnoses by reviewing all medical records and paraclinical tests when available (eg,

electromyoneurography (EMNG)). Patients were categorised at the time of diagnosis (via centralised certification according to the Airlie House criteria) as having definite, probable, probable laboratory-supported or possible ALS based on the presence of upper and/or lower motor neuron signs in four defined central nervous system regions.[7] A neurologist in each centre performed a standard clinical examination to assess cognitive functions on three aspects (speech, memory and executive function) and extramotor involvement including extrapyramidal, cerebellar, sensory, autonomic, urinary and oculomotor involvement. When possible, 3-month follow-up clinical consultations were performed at all centres. If more than 6 months elapsed without patient contact, the researcher in charge contacted the patient or the family to assess the vital status of the patient.

Data collection

Baseline sociodemographic and clinical data were collected at the time of ALS diagnosis of the incident cases, and medical records were used to collect the baseline data of the prevalent cases. We recorded the date of the first symptom, the type of onset, symptoms, signs of involvement of the upper and lower motor neurons and the regional distributions of the signs, any cognitive impairments, any extramotor involvement (extrapyramidal, cerebellar, sensory, autonomic, urinary or oculomotor), and the ALS Functional Rating Scale Revised (ALSFRS-R) score. The ALSFRS-R slope is the ratio of the difference between the ALSFRS-R score obtained at diagnosis and a presumed normal score (48 points) just before symptom onset to the diagnostic delay (in months). The extent of access to treatment was also recorded.

Data management

The Centre of Biostatistics and Methodology of Research (CEBIMER) of the Limoges teaching hospital created a secure database using the Ennov clinical software. The CEBIMER is a member of EUCLID and achieved an French Clinical Research Infrastructure Network platform status in 2014. The software complies with the 21 Code of Federal Regulations Part 11 of the US Food and Drug Administration. Data were coded anonymously based on numerical sequences and were safely stored.

Statistical analysis

All findings were reported using the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology[8] and the Standards of Reporting of Neurological Disorders.[9]

Descriptive and analytical statistical analyses were conducted using IBM SPSS Statistics V.22 and SAS V.9.3 software. Quantitative variables were described as medians with IQRs. The Shapiro-Wilk test was used to explore the normal distributions of continuous variables. Qualitative variables were shown as frequencies with percentages. The subcontinental regions were defined according to the United Nations Statistics Division.[10] Means were compared by analysis of variance (ANOVA) or Kruskal-Wallis test, depending on the conditions of application. Percentages were compared using the Pearson's χ^2 test. For post-hoc analysis, χ^2 post-hoc test or one-way ANOVA followed by the Scheffe or Kruskal-Wallis post-hoc test was employed, depending on the conditions of application. The Bonferroni correction for multiple tests was applied in post-hoc tests. All missing data were reported.

The survival and prognostic analyses included patients for whom at least 1 month of follow- up data were available and those who died in the first month. All analyses were conducted from the date of diagnosis or onset until the date of death or censoring. Survival was analysed using the Kaplan-Meier method and the Breslow and log-rank tests. Cox proportional hazards modelling was performed to identify factors associated with survival. The interaction-with-time method was used to assess proportional hazard assumptions. Variables with non-proportional hazards were considered as time-dependent variables. Variables with p values <0.20 in univariate analysis were selected for entry into a multivariate model. The full model was simplified via a backward selection procedure considering potential confounding at each step.[11] HRs with 95% CIs were estimated. A p value <0.05 was considered statistically significant.

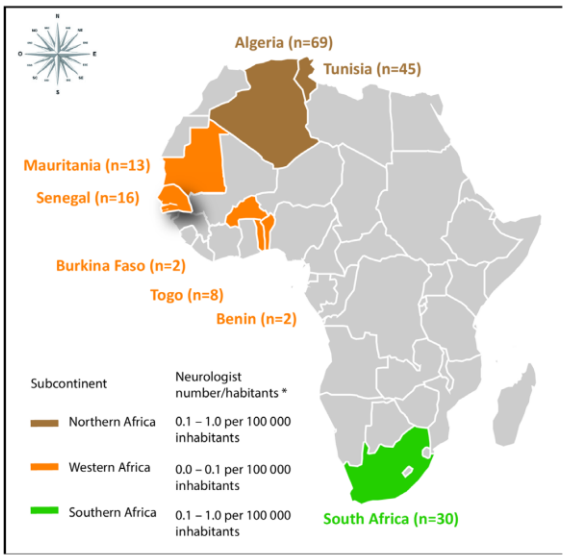

Figure 1 The African countries and numbers of patients with amyotrophic lateral sclerosis included in the TROPALS study (Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques). *WHO. Atlas: country resources for neurological disorders, 2004.

RESULTS

Participating centres and patients

Nine centres in eight African countries participated. We included 185 patients with ALS: 114 from Northern Africa (NA) (Algeria (n=69), Tunisia (n=45)), 41 from Western Africa (WA) (Benin (n=2), Burkina Faso (n=2), Mauritania (n=13), Senegal (n=16), Togo (n=8)) and 30 from Southern Africa (SA) (South Africa (n=30)) (figure 1).

Sociodemographic characteristics

Overall, the median age at onset was 53.0 years (IQR 44.5–64.0 years) (table 1A). WA patients were significantly younger at onset (47.0 years) than NA (55.0 years) and SA (59.5 years) patients (p=0.0003) (figure 2). Eight patients (4.3%) were juvenile cases with onset prior to age 30 years. Given the overall median diagnostic delay of 12.0 months (IQR 6.0–23.0 months), the median age at diagnosis was 55.0 years (IQR 46.0–66.5 years), with significant differences among the subcontinents (p=0.0003).

A male predominance was evident; the overall male to female sex ratio (SR) was 2.9. A higher proportion of illiteracy was found in WA (56.8%) cases compared with NA (26.5%, p=0.006) and SA (0%, p<0.001) cases (table 1, post-hoc analysis). Approximately 75% of cases lived with partners (married/cohabiting). The

Table 1 Sociodemographic, family medical history, clinical and treatment characteristics of all included patients with ALS by subcontinent: the TROPALS study (Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques)

	Overall (n=185)	Northern Africa (NA) (n=114)	Western Africa (WA) (n=41)	Southern Africa (SA) (n=30)	P values
(A) Sociodemographic characteristics					
Gender, n (%)					
Male	138 (74.6)	82 (71.9)	32 (78.0)	24 (80.0)	0.563*
Female	47 (25.4)	32 (28.1)	9 (22.0)	6 (20.0)	
Sex ratio, male to female	2.9	2.6	3.5	4.0	
Age at onset (years)					
Median (IQR)	53.0 (44.5–64.0)	54.0 (45.0–62.0)	47.0 (36.0–58.0)	59.5 (47.0–70.7)	0.0003†‡
Age ≤30 years, n (%)§	8 (4.3)	2 (1.8)	6 (14.6)	0 (0.0)	
Age at diagnosis (years)					
Median (IQR)	55.0 (46.0–66.5)	56.0 (47.0–64.5)	47.0 (38.5–59.0)	60.5 (48.5–71.8)	0.0003†‡
Education level, n (%)¶					
Illiteracy	51 (28.4)	30 (26.5)	21 (56.8)	0 (0.0)	<0.0001*‡
Elementary school	58 (32.2)	41 (36.4)	4 (10.8)	13 (43.3)	
High school	49 (27.2)	31 (27.4)	7 (18.9)	11 (36.7)	
University	22 (12.2)	11 (9.7)	5 (13.5)	6 (20.0)	
Marital status, n (%)¶					
Married/cohabiting	153 (83.2)	101 (88.6)	30 (73.2)	22 (75.9)	0.040*·‡
Not married/widow	31 (16.8)	13 (11.4)	11 (26.8)	7 (24.1)	
(B) Family medical history					
Family medical history awareness					
fALS, n (%)**¶	9 (5.7)	4 (4.1)	2 (6.3)	3 (10.0)	0.471*
Cognitive impairment, n (%)**¶	15 (9.7)	15 (15.8)	0 (0.0)	0 (0.0)	0.006*‡
Consanguinity, n (%)**¶	31 (21.1)	25 (25.8)	6 (20.7)	0 (0.0)	0.032*‡
(C) Clinical characteristics					
Onset site, n (%)					
Spinal	143 (77.3)	88 (77.2)	28 (68.3)	27 (90.0)	0.098*
Bulbar	42 (22.7)	26 (22.8)	13 (31.7)	3 (10.0)	
Diagnostic delay (months)					
Median (IQR)	12.0 (6.0–23.0)	12.0 (6.7–23.0)	13.0 (6.5–24.0)	8.5 (6.0–13.7)	0.380††
Airlie House criteria, n (%)					
Definite	55 (29.7)	25 (21.9)	24 (58.5)	6 (20.0)	<0.0001*‡
Probable	65 (35.1)	42 (36.9)	14 (34.2)	9 (30.0)	
Probable with laboratory support	54 (29.2)	40 (35.1)	3 (7.3)	11 (36.7)	
Possible	11 (6.0)	7 (6.1)	0 (0.0)	4 (13.3)	
ALSFRS-R (/48)					
Median (IQR)	38.0 (29.0–42.0)	40.0 (35.0–43.2)	27.6 (20.5–36.0)	39.0 (34.5–44.0)	<0.0001††‡
ALSFRS-R slope (unit/month), median (IQR)	0.8 (0.4–1.7)	0.7 (0.4–1.3)	1.6 (0.7–2.5)	0.7 (0.5–1.9)	0.001††‡
Extramotor involvement, n (%)¶	59 (32.1)	34 (29.8)	15 (37.5)	10 (33.3)	0.661*
(D) Treatment					
Therapy with riluzole, n (%)¶	47 (26.3)	36 (33.0)	10 (25.0)	1 (3.3)	0.005*

*X^2 test.
†ANOVA.
‡Post-hoc analysis: one-way ANOVA, Scheffe post-hoc: age of diagnosis (NA vs WA, p= 0.010; NA vs SA, p=0.175; WA vs SA, p=0.001); age at first symptom (NA vs WA, p=0.013; NA vs SA, p=0.114; WA vs SA, p=0.0003). X^2 post-hoc test. Educational level: illiteracy (NA vs WA, p=0.006; NA vs SA, p=0.012; WA vs SA, p<0.001); elementary school (NA vs WA, p=0.027; NA vs SA, p=0.999; WA vs SA, p=0.018); high school (NA vs WA, p=0.999; NA vs SA, p=0.999; WA vs SA, p=0.825); university (NA vs WA, p=0.999; NA vs SA, p=0.980; WA vs SA, p=0.999). Marital status (NA vs WA, p=0.077; NA vs SA, p=0.310; WA vs SA, p=0.999). Airlie House criteria: definite (NA vs WA, p<0.001; NA vs SA, p=0.999; WA vs SA, p=0.009); probable (NA vs WA, p=0.999; NA vs SA, p=0.999; WA vs SA, p=0.999); probable with laboratory support (NA vs WA, p=0.005; NA vs SA, p=0.999; WA vs SA, p=0.017); possible (NA vs WA, p=0.835; NA vs SA, p=0.999; WA vs SA, p=0.129). Cognitive impairment family history (NA vs WA, p=0.090; NA vs SA, p=0.081). Consanguinity family history (NA vs WA, p=0.999; NA vs SA, p=0.035; WA vs SA, p=0.105). Kruskal-Wallis post-hoc test: ALSFRS-R (NA vs WA, p<0.001; NA vs SA, p=0.999; WA vs SA, p<0.001); ALSFRS-R slope (NA vs WA, p<0.001; NA vs SA, p=0.999; WA vs SA, p=0.109). Bonferroni correction for multiple tests has been applied.
§Age ≤25 years (n=4).
¶Missing data: education level (n=5), marital status (n=1), fALS (n=2), cognitive impairment family history (n=7), consanguinity family history (n=14), extramotor involvement (n=1) and riluzole (n=6).
**Percentages represent the proportion of ALS cases whohad knowledge of family medical history (n=161).
††Kruskal-Wallis.
AFSFRS-R, ALS Functional Rating Scale Revised; ALS, amyotrophic lateralsclerosis; ANOVA , analysis of variance; TROPALS, Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques;fALS, familial amyotrophic lateral sclerosis.

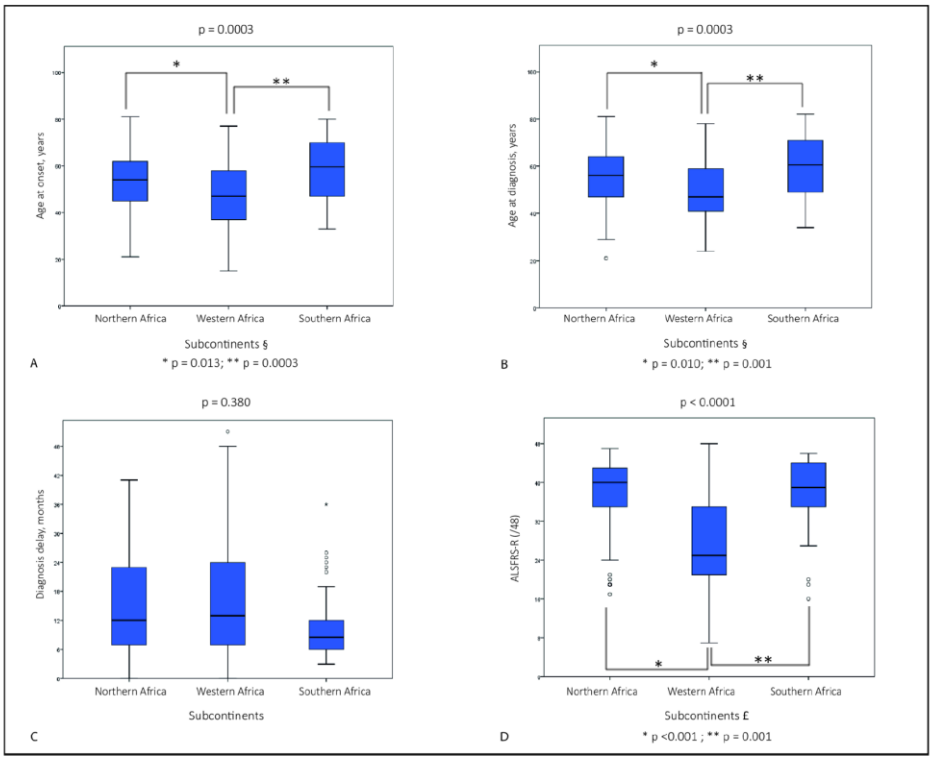

Figure 2 Characteristics of patients with ALS by subcontinent; the TROPALS study (Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques). Age at onset, years (A), age at diagnosis, years (B), diagnosis delay, months (C) and ALSFRS-R, /48 (D). The Shapiro-Wilk test was used to determine normality of the distribution. For post-hoc analysis: §one-way analysis of variance Tukey test; £ Kruskal-Wallis post-hoc test. The asterisks represents the significant differences between the subcontinents. Outliers above 50 months were removed in (C). ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale Revised; TROPALS, Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques.

principal sociodemographic characteristics at the time of diagnosis (overall and by subcontinent) are shown in table 1A.

Proxies for ethnicity were only available in SA. A heterogeneous mixture of ethnic profiles was found: 16 were of European ancestry, 12 mixed and 2 of African ancestry.

Family medical history

Patients were aware of their family medical histories in 87.3% of cases. Nine (5.7%) reported familial ALS antecedents. A family history of cognitive impairment was reported in 15.8% of NA cases (vs 0% in WA and SA, p=0.006), and consanguinity was more frequent in NA (25.8%) and WA (20.7%) compared with SA (0%) cases (p=0.032, table 1B).

Clinical characteristics

Overall, disease onset was bulbar in 42 (22.7%) patients; although a difference in the proportion of bulbar form was apparent among subcontinents, it was not significant (NA 22.8%, WA 31.7% and SA 10.0%; p=0.098) (table 1C). Of the 143 patients who presented spinal onset, 45.1% exhibited upper limb onset, 23.2% lower limb onset and 31.7% combined upper and lower limb onset. Significant variability was evident among the subcontinents (p=0.001; figure 3).

Cases were categorised as definite (29.7%), probable (35.1%), probable with laboratory support (29.2%) and possible (6.0%) ALS according to the Airlie House criteria. WA patients were more likely to be diagnosed with definite disease compared with NA (p<0.001) and SA (p=0.009) (table 1, post-hoc analysis). In total, 167 (92.8%) patients with ALS underwent neurophysiological examination (EMNG) (NA 99.1%, WA 76.9% and SA 90%).

At the time of diagnosis, motor deficit (87.6%) was the most common symptom. Over half of all cases reported muscle cramps (55.6%), asthenia (53.6%) and dysarthria (51.6%).

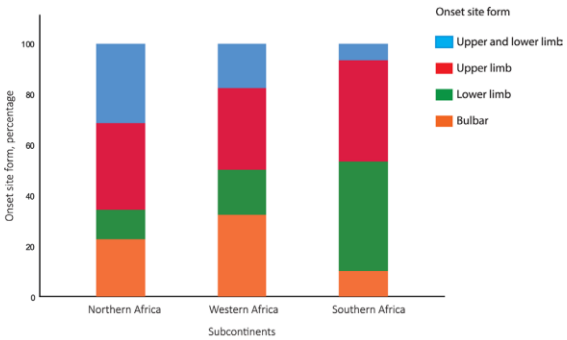

Figure 3 Onset sites by subcontinent: the TROPALS study (Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques).

On neurological examination, muscle atrophy (90.8%) and fasciculation (95.1%) were common. Fifty-nine cases (32.1%) presented with extramotor involvement, mostly sensory involvement (54.7%) (paresthesia or dysesthesia), 38.8% with cognitive impairments (in speech, memory or executive function), 28% with dysautonomic impairments, 22.6% with vesical-sphincter disorders, 10.2% with extrapyramidal involvement and 6.3% with oculomotor signs.

The median ALSFRS-R score at the time of diagnosis was 38.0 (IQR 29.0–42.0) overall. The median ALSFRS-R score was significantly lower in WA compared with NA and SA ($p<0.0001$), and the ALSFRS-R slope was significantly greater in WA compared with the other subcontinents ($p=0.001$).

Treatment

Overall, 134 patients received 'occidental'-type treatment, mostly physiotherapy and/or symptomatic management (64.9%). Only 47 patients (26.3%) received riluzole, mostly in NA (33.0%) and WA (25.0%) compared with SA (3.3%) (table 1D).

Survival and prognostic factors

Fifty-seven patients were excluded from the survival analysis because they lacked follow-up data of at least 1 month after diagnosis. Conversely, 128 patients were available for analysis (138.7 person-years of follow-up). Of these patients, 80 died, and the mortality rate was 58 per 100 person-years. Patients excluded from the survival analysis were younger (median age 50 vs 56 years, $p=0.046$) and less likely to live with a partner (70.2 vs 89.0%, $p=0.002$). The sociodemographic, clinical features and treatments of the patients included in the survival analysis are shown in online supplementary table e-1.

The median survival time from diagnosis was 14.0 months (95% CI 10.7 to 17.2 months; figure 4), and the median survival time from disease onset was 35.0 months (95% CI 29.1 to 40.8 months; online supplementary figure e-1).

The median survival time from diagnosis was longer in NA (19.0 months, 95% CI 10.8 to 27.2 months) than in WA (4.0 months, 95% CI 0.8 to 7.1 months) and SA (11.0 months, 95% CI 5.6 to 16.4 months) (Breslow test $p<0.0001$). The subcontinents, type of onset, Airlie House criteria, ALSFRS-R score, cognitive impairment status and riluzole treatment status were included in the full multivariate model (table 2). The final model was obtained after backward selection, and only subcontinent and riluzole treatment were independently associated with survival ($p<0.0001$ and $p=0.002$, respectively) (table 2). Kaplan-Meier survival estimates stratified by subcontinent and riluzole therapy are shown in figure 4. Compared with NA, WA patients experienced a higher instantaneous risk of dying at baseline (adjusted HR (aHR) (T0)=4.83, $p<0.0001$), which progressively decreased over time (figure 4B). On the other hand, there was no significant difference in the instantaneous risk of death at baseline between NA and SA patients (aHR (T0)=0.81, $p=0.712$); however, the difference increased over time, becoming significant at both 12 and 18 months (figure 4B).

The results of the survival analysis from disease onset were congruent. The median survival time since onset was longer in NA (37.0 months, 95% CI 25.8 to 48.1 months) than in WA (17.0 months, 95% CI 10.7 to 23.3 months) and SA (23.0 months, 95% CI 17.8 to 28.2 months) (Breslow test $p=0.0002$) (online supplementary figure e-1). Subcontinent and riluzole were also significantly associated with survival in the final multivariate model, which also identified bulbar onset as associated with a shorter survival (aHR 2.78, 95% CI 1.48 to 5.23, $p=0.001$) (online supplementary table e-2).

DISCUSSION

Here, we report the first multicentre, hospital-based cohort study investigating ALS in African countries using a standardised questionnaire and homogeneous methodology. This is also the first prognostic assessment of African patients with ALS.

Sociodemographic characteristics

Historical case series of patients with ALS from Africa reported ages of onset ranging from 40 to 50 years[3 12 13] and the presence of a juvenile form (13.5%–50% of cases).[14] We found that the median age at onset was 53.0 years, although eight cases (4.3%) experienced disease onset before 30 years of age (four before 25 years of age). The overall age of onset was far younger than those of occidental series, in which the age at onset ranged from 60 to 65 years.[15] The age differences between African and Western patients with ALS reflect differences in population age structures, which in turn are associated with differences in life expectancy and birth rates.[16] Interestingly, age at disease onset was also significantly lower in African–Americans than in subjects of European ancestry (55 vs 61 years, $p=0.011$) in a hospital-based cohort of patients with ALS evaluated in the USA.[17] Systematic inclusion of the youngest African patients with ALS cannot be discarded. It is known from studies in Western countries that due to selection bias, hospital-based cohorts are on average younger than the overall ALS population.[18] The differences among subcontinents suggest regional variations in demographic structures[19] and referral practices.

As in the previous African reports, the male to female SR approached 3.[20 21] Interestingly, Western studies published before 1990 consistently reported an SR around 2,[22] which decreased to a modest male predominance (SR=1.3) in recent studies.[15] This apparent trend of SR was explained by differences in study design (retrospective vs prospective in the most recent studies) and in case ascertainment (referral-based vs population-based studies in the most recent studies).[5] It remains to be determined whether the ALS incidence in Africa genuinely is lower in women, for example due to reduced exposure to occupational or environmental risk factors,[3] or whether the difference in the SR rather reflects misdiagnosis or limited access to care for female cases.

Family medical history

Previous studies in Africa have described the absence[23 24] or low proportion of familial ALS (1.2% in Tunisia[14] and 2% in Nigeria[21]). We found that the proportion of familial cases was similar to that in Western populations (4.7%, 95% CI 3.9% to 5.7%).[15]

Clinical characteristics

It was previously reported that the proportion of bulbar-onset ALS was lower in Africa (20%)[12 13] than in Europe (~30%).[15 25] US researchers reported slightly lower bulbar-onset levels in patients of African origin than those of European origin.[17 26] We found that the bulbar onset proportion was 22.7% overall, ranging from 10% to 32% among the subcontinents. These results may be attributable to selection bias and/or a young patient age. Previous studies found that ALS differed in terms of clinical presentation by age, in that older patients exhibited more frequent bulbar onset.[27 28] Interestingly, population-based studies from Europe also identified differences in the

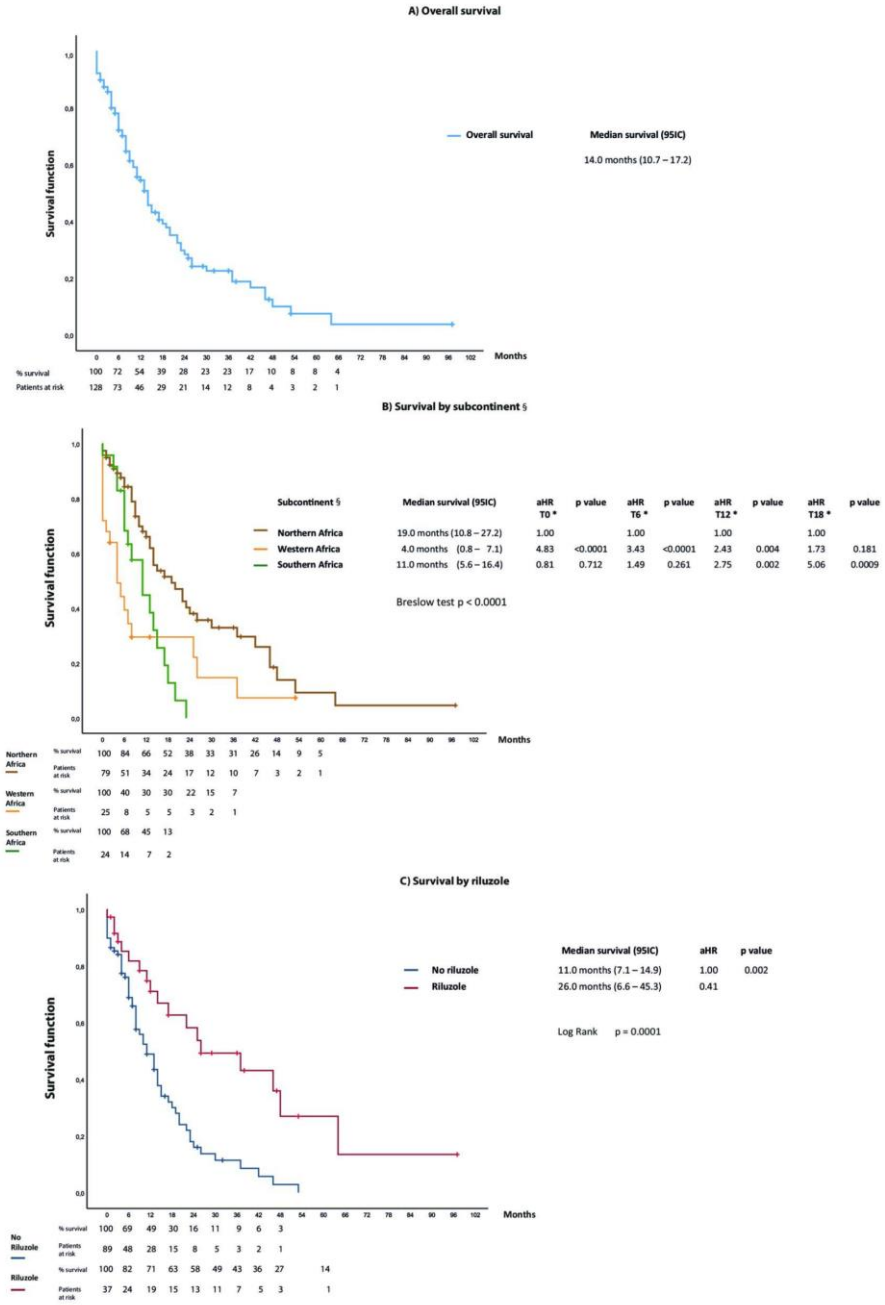

Figure 4 Kaplan-Meier survival curves for patients with amyotrophic lateral sclerosis since diagnosis: the TROPALS study (Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques). Kaplan-Meier curves: (A) overall survival, (B) by subcontinent and (C) by riluzole use. aHR, adjusted HR, 95% CI. §Proportional hazard assumption was not satisfied for subcontinent. *Subcontinent aHRs were calculated as time-dependent variable from baseline time (T0), 6 months from baseline (T6), 12 months from baseline (T12) and 18 months from baseline/diagnosis (T18).

proportion of bulbar onset between Northern Europe (45.4%) and Western and Southern Europe (34.9% and 34.2%, respectively).[15] To date, such differences remain underexplored. The heterogeneous distributions of the spinal onset forms of the disease can be explained by phenotypic population variability. One case–control study performed in the UK reported that Africans were at a fourfold higher risk of presenting with the 'flail arm' variant of motor neuron disease compared with subjects of European ancestry.[29] A recent hospital-based report in Eastern Africa found 84 ALS cases over two periods (1984–1992 and

Table 2 Baseline characteristics of patients with ALS and their associations with survival from the time of diagnosis, in univariate and multivariate analyses: the TROPALS study (Etude Epidémiologique de la Sclérose Latérale Amyotrophique sous les Tropiques)

	Description (n=128)	Univariate model (n=128)			Full multivariate model (n=126)			Final multivariate model (n=126)		
	Median (IQR) or n (%)	cHR	95% CI	P values	aHR	95% CI	P values	aHR	95% CI	P values
Subcontinent*										
Northern Africa	79 (61.7)	1.00		0.0002	1.00		0.043	1.00		<0.0001
Western Africa	25 (19.5)	4.80	2.20 to 10.48		2.94	1.17 to 7.35		4.84	2.19 to 10.65	
Southern Africa	24 (18.8)	0.94	0.32 to 2.76		0.85	0.28 to 2.59		0.81	0.27 to 2.42	
Gender										
Male	98 (76.6)	1.00		0.459						
Female	30 (23.4)	1.22	0.72 to 2.04							
Age at diagnosis†	56.0 (47.0–64.7)	1.06	0.97 to 1.16	0.209						
Marital status‡										
Not married/widow	14 (11.0)	1.00		0.262						
Married/cohabiting	113 (89.0)	0.70	0.38 to 1.30							
Diagnosis delay§	10.5 (6.0–20.5)	1.29	0.77 to 2.19	0.328						
Onset site										
Spinal	101 (78.9)	1.00		0.059	1.00		0.219			
Bulbar	27 (21.1)	1.71	0.98 to 3.00		1.54	0.77 to 3.06				
Airlie House criteria*										
Definite	37 (28.9)	1.00		0.018	1.00		0.268			
Probable	44 (34.4)	0.36	0.16 to 0.81		0.52	0.21 to 1.29				
Probable with laboratory support	37 (28.9)	0.45	0.19 to 1.09		0.85	0.28 to 2.56				
Possible	10 (7.8)	0.02	0.001 to 0.77		0.08	0.003 to 2.20				
ALSFRS-R at diagnosis¶	38.5 (29.2–42.0)	0.85	0.75 to 0.97	0.014	0.91	0.75 to 1.11	0.381			
ALSFRS-R slope	0.7 (0.4–1.7)	0.99	0.99 to 1.00	0.432						
Atypical signs										
No	85 (66.4)	1.00		0.694						
Yes	43 (33.6)	0.91	0.57 to 1.46							
Cognitive impairment										
No	112 (87.5)	1.00		0.112	1.00		0.224			
Yes	16 (12.5)	1.62	0.89 to 2.95		1.57	0.75 to 3.26				
Riluzole‡										
Therapy without riluzole	89 (70.6)	1.00		0.0003	1.00		0.023	1.00		0.002
Therapy with riluzole	37 (29.4)	0.36	0.20 to 0.62		0.49	0.26 to 0.91		0.41	0.22 to 0.73	

*Covariates with non-proportional hazards (interaction with time p value): subcontinent (p=0.001); Airlie House criteria (p=0.028); subcontinents and Airlie House criteria were considered as time-dependent variables in the models (HRs are reported at t=0).
†HR for baseline time calculated for 5-year increment.
‡Missing data: marital status (n=1) and riluzole (n=2).
§HR for 6-month increment.
¶HR for baseline time calculated for 5-unit increment.
aHR, adjusted HR; ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale Revised; cHR, crude HR.

2007–2015). The El Escorial classification was possible only in 42 patients and electromyography was not available, which make it difficult to describe well-defined phenotypes.[30] Increasing evidence suggests that the clinical and aetiological heterogeneity of ALS is far greater than assumed previously.[15 31]

In Western series, at the time of diagnosis, the definite form of ALS ranges from 15% to 25% of patients,[25 32 33] and the median ALSFRS-R score ranges from 35 to 40/48.[25 34] African patients from NA and SA exhibited similar patterns. However, it appeared that WA patients were diagnosed at a more advanced stage (58.5% with definite ALS) accompanied by greater functional impairment (median ALSFRS-R score 27.6/48). This was not explained by a longer time to diagnosis (12 months overall, in contrast to the long diagnostic delays reported in previous African studies[3]). Such differences may be associated with variation in ALS clinical characteristics according to subcontinent differences in the clinical neurological examination protocols and criteria used among centres.

Prognosis

Contrary to previous suggestions that African patients with ALS experience a better prognosis compared with Western patients,[12 20 21] the median survival times did not differ from those in Western nations. Marin *et al*[15], who reviewed population-based studies, found that the median survival time of patients with ALS in Europe and North America ranged from 25 to 35 months (since onset) and from 13 to 25 months (since diagnosis).The median overall survival times of African patients (35 months from disease onset and 15 months from diagnosis) may be in agreement with Western data. Nevertheless, the age difference between patients from Europe/North America and

Africa (~10 years) and the finding that younger age is consistently a favourable prognostic factor in Western series[35] would lead us to expect far better survival for a cohort of younger African patients. Insufficient access to highly specialised ALS care might explain this observation.

In contrast to previous findings, older age was not associated with shorter survival. The finding that the median age was relatively young (few patients were older than 65 years) might explain this observation.

We found that riluzole benefited African patients with ALS (aHR 0.41, 95% CI 0.22 to 0.73). Our results are consistent with those of a meta-analysis that reported a pooled relative risk at 12 months of 0.78 (95% CI 0.65 to 0.92) for riluzole compared with placebo.[36] Unfortunately, riluzole is not widely available or is extremely expensive in African countries, especially in certain regions. For example, riluzole costs about the same as the average monthly household income in SA and is not funded by the state or private health insurance.

In terms of prognosis, the situation was shown to differ greatly by subcontinents (longer survival in NA as compared with WA and SA). This can be related to differences by subcontinents in terms of clinical characteristics. Heterogeneity in terms of medical care and the absence of specific ALS referral centres may also explain the survival differences.

Limitations and strengths

Our research has several limitations that should be considered. First, cases were identified in hospitals. We are aware that hospital-based studies feature selection bias. Patients included here might be, for example, those who could afford the social and financial costs of hospital care. Also, demographic or phenotypical characteristics might have influenced the referral pattern to the participating hospitals. The fact that diagnostic delay is close to that reported from Western countries, despite the challenging context for diagnosis of ALS in Africa, might indicate a selection. Hence, our results cannot be considered representative of ALS in the general population. A recent study illustrated in the European context the selection bias of ALS cohorts drawn solely from referral or hospital databases.[37] In Western countries, patients referred to hospitals or tertiary centres are younger, with better prognoses, and with clinical presentations that differ from the classical phenotype (less frequent bulbar involvement and more familial ALS antecedents) compared with general ALS populations.[22 37] Population-based ALS studies (the gold standard methodology) are currently impractical in most parts of Africa. Therefore, large multicentre referral studies are useful as initial approaches towards understanding ALS on this continent. Second, with the exception of SA, where only incident cases were included, other centres included both incident and prevalent cases. Prevalent cohorts are of course subject to survival selection and are different from incident cohorts; fewer patients exhibit bulbar onset, and the patients are on average younger.[18] Third, ethnicity of the patients was available for SA only. Fourth, we lacked data on other prognostic factors (respiratory status at the time of diagnosis, measured via assessment of forced vital capacity; enteral nutrition; and any need for non-invasive ventilation). Fifth, although we established a protocol, some intercentre variations in clinical examinations may remain. For example, Beghi *et al*[38] showed that the El Escorial criteria without previous training is generally poor in agreement between centres. In an effort to control this issue, an expert neurologist examined all medical records and validated ALS diagnosis and criteria. Sixth, a standard cognitive assessment battery as the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was not used because it was created after TROPALS study initiation. In addition, the ECAS was designed for Western populations and has not been validated in the African context. Lastly, despite much effort, it was not possible to include additional African hospitals. Thus, the data may not reflect Africa-wide situation.

Nevertheless, our study had certain intrinsic strengths. The first is that multicentre collaboration allowed the inclusion of 185 African ALS cases, which is an unprecedented sample size in African studies. Second, standard methodology was applied by all centres. Data were collected in a standardised manner; the coordinating centre worked with the hospitals to correct aberrant or gather missing data. Third, neurological and research teams in each centre performed case ascertainment, data collection and follow-up. Fourth, we employed the Airlie House diagnostic criteria (rarely used in previous African works[3]) and the ALSFRS-R. Finally, all clinical charts were reviewed by a neurologist expert in the ALS field, who confirmed the diagnoses and categorised patients using the Airlie House criteria.

Prospects

The number of elderly Africans is expected to increase rapidly; increases of over 60% are projected from 2015 to 2030.[39] Thus, the burden of age-related conditions such as neurodegenerative diseases will progressively increase.[40] A recent study to project the epidemiological trend of ALS showed that the global number of individuals with ALS will grow significantly between 2015 and 2040 at around 69%. According to the projection in this study, the largest increase will be seen in Africa.[41] The World Federation of Neurology recently launched a programme to train African neurologists and develop neurological services across the continent.[42] These initiatives could form a solid base for improvements in healthcare and development of research programme on neurodegenerative disorders in Africa.

Population-based studies in Africa are needed. Population-based studies performed in the USA or in Europe have been shown to be instrumental for accurate clinical and epidemiological description of ALS in these contexts (eg, that ALS is an age-dependent disease and not only of young adults). The same population-based approach should be encouraged to improve knowledge of ALS in Africa. To date, only one population-based study investigated the incidence of ALS in Africa (Libya); after standardisation on the US population, the incidence was 2.03/100 000 person-years of follow-up.[20] A systematic review of neurodegenerative diseases in sub-Saharan Africa[40] found only two community-based studies on ALS, in which the ALS prevalence was 5/100 000 in Ethiopia[43] and 15/100 000 in Nigeria.[44]

Improving our understanding of ALS among different populations will also clarify the genetic and environmental determinants of the disease and the risks of disease development. Molecular and genetic research must take a more comprehensive approach towards ALS in African populations. A review of motor neuron diseases in sub-Saharan Africa strongly suggested that population-specific causes of motor neuron diseases are present among Africans, and that they differ between African and non-African populations.[6] Clinical features and prognostic factors in various geographical regions and populations must be identified to facilitate management of disease heterogeneity in clinical practice and improve the methodologies of therapeutic trials. Survivorship pattern across different ethnic groups needs to be addressed with high-quality studies to improve our understanding of disease variability. Lastly, further studies have to

investigate the implications of genetic (eg, populations' ancestries) along with environmental and lifestyle factors in the ALS occurrence.

CONCLUSION

Our research adds to our understanding of the demographic, clinical and prognostic features of ALS in Africa. Riluzole treatment was independently associated with longer survival, which is consistent with studies in Western populations.[36] International collaboration is essential to provide new data and clarify key aspects on ALS, especially from certain global regions that are currently poorly represented in the literature. Population-based studies are necessary to clarify the incidence of ALS in Africa and the genetic, clinical and prognostic variations thereof.

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Chapter IV. Amyotrophic lateral sclerosis in Latin America

IV.1. Framework of ALS in Latin America

Latin America is underrepresented in the ALS literature. This geographic region has seized the attention of researchers in recent decades due to the apparent lower occurrence of ALS. One of the first publication already stated this query with a study performed in Mexico City (Olivares et al., 1972). The current evidence seems to continue supporting these claims, which has drawn international attention to the need for more original research in the region. However, there is limited data on ALS from Latin America as indicated by the Global Burden Disease study 2016 (Logroscino et al., 2018b).

IV.1.1. Epidemiology of ALS in Latin America

To the best of our knowledge, 12 epidemiological researches have been performed in Latin America. Almost all of the studies used a retrospective observational approach. Brazil is the country with the highest number of epidemiological surveys (n = 4). There is at least one study in the following countries: Argentina, Chile, Costa Rica, Cuba, Ecuador, Guadeloupe (overseas region of France in the Caribbean), Mexico and Uruguay.

IV.1.1.1. Incidence and prevalence of ALS in Latin America

A national population-based study from Uruguay has been the only research in Latin America that used a prospective design with multiple sources of case ascertainment (neurologists, other medical specialties, general physicians, neurophysiology laboratories, hospital medical records and death certificates) (Vázquez et al., 2008). During a 2-year period, researchers identified 89 new diagnosed ALS cases giving an incidence of 1.42 per 100,000 person-years (95% CI, 1.13 to 1.72), which was estimated through capture recapture method (Hook and Regal, 1995). The age-adjusted incidence to the 1990 US population, for the 45–74 age group, was 3.6 (95% CI, 2.7 to 4.5) person-years.

A national survey was also performed in Brazil. The study requested the participation of the neurologists across the country (Dietrich-Neto et al., 2000). The incidence of ALS ranged from 0.3 to 0.5 per 100,000 person-years. Private neurologists identified most of the patients. However, less than 10% of the neurologists in the country participated in the survey.

Another two studies in Latin America identified cases through medical records from hospitals and neurologists. The first one was a retrospective study carried out in Mexico City that found only 16 ALS cases between 1962 and 1969. The crude incidence was 0.40 per 100,000 (Olivares et al., 1972). The second was another retrospective study in Guadeloupe (overseas region of France in the Caribbean) that identified 63 cases of ALS between 1996 and 2011 (Lannuzel et al., 2015). The crude ALS incidence was 0.93 (0.71 to 1.19) per 100,000 person-year. The standardized incidence was 1.13 (0.84 to 1.42) based on the European population in 2000. A higher incidence was observed (3.73 per 100,000 person-year) in a small island Marie-Galante in the Guadeloupe archipelago. The authors have mentioned genetic and environmental factors as potential explanations.

Three studies based their epidemiological estimates on cases identified only from hospitals medical records. In Costa Rica, a retrospective study estimated an incidence of 0.97 (95% CI 0.8 a 1.2) per 100.000 person-year through neurology departments of different national hospitals (Rodríguez- Paniagua et al., 2007). In Argentina, a retrospective study performed in Buenos Aires found an incidence of 3.17 (95% CI 2.24 – 4.48) per 100.000 person-year using medical records from prepaid Health Maintenance Organizations (Bettini et al., 2013). In Ecuador, a retrospective study in two hospitals in Quito reported an incidence ranging from 0.2 to 0.6 per 100.000 person-year (Bucheli et al., 2014).

ALS incidence studies in Latin America and the Caribbean are shown in table 18.

Table 18: Incidence of ALS per 100,000 person-year in Latin America and the Caribbean by study period according to subcontinents

Subcontinent	Country	Authors	Study period	Study design	Case ascertainment sources	Crude incidence (95% CI)	Standardized incidence (95% CI)
Caribbean	Guadeloupe*	(Lannuzel et al., 2015)	1996 - 2011	R	Hosp + Neuro	0.93 (0.71 – 1.19)	1.13 (0.84 – 1.42)
Central America	Costa Rica	(Rodríguez-Paniagua et al., 2007)	1998 - 2001	R	Hosp	0.97 (0.8 - 1.2)	
South America	Ecuador	(Bucheli et al., 2014)	2000 - 2012	R	Hosp	r: 0.2 – 0.6	0.29 (0.35 – 0.24)
	Argentina	(Bettini et al., 2013)	2003 - 2010	R	Hosp + HI	3.17 (2.24 – 4.48)	2.23 (1.45 – 3.01)
	Uruguay	(Vázquez et al., 2008)	2002 - 2003	P	Hosp,+ Neuro + Spe + HI + PCP + DC	1.42 (1.13–1.72) ǂ	3.6 (2.7–4.5)
	Brazil	(Dietrich-Neto et al., 2000)	1998	R	Neuro	r: 0.3 - 0.5	
	Mexico	(Olivares et al., 1972)	1962 - 1969	R	Hosp + Neuro	0.40	

* Guadeloupe is an overseas region of France, ǂ, estimated by capture recapture method
Study design: CR, Cross-sectional; P; Prospective; R, retrospective
Case ascertainment sources: Asso, patients' association; DC, death certificates; HI, Health insurance data; Hosp, hospital discharge data; Neuro, neurologist; PCP, primary care physicians; Spe, other specialist.
r, range

Prevalence was reported in some studies ranging from 0.8 in Mexico (Olivares et al., 1972) to 8.9 in Argentina (Bettini et al., 2013). In Brazil, a specific population-based study assessed ALS prevalence in the metropolitan area of Porto Alegre using multiple sources of case ascertainment (Hospital - clinics - neurologists – patient associations). The prevalence was 5.0 cases per 100,000 (95% CI, 3.9 to 6.2) (Linden-Junior et al., 2013).

IV.1.1.2. Mortality of ALS in Latin America

In Latin America, mortality studies have been based on death certificates. ALS cases were identified and retrieved from mortality registers using the International Classification of Diseases (ICD) coding. The crude mortality ranged from 0.28 in Mexico (Olivares et al., 1972) to 0.76 in Brazil (Matos et al., 2011). The standardized mortality ranged from 0.44 in Brazil (Matos et al., 2011) to 0.83 in Cuba (Zaldivar et al., 2009).

ALS mortality rates in Latin America are presented in table 19.

Table 19: Mortality of ALS per 100,000 person-years in Latin America and the Caribbean by study period according to subcontinents

Subcontinent	Country	Authors	Study period	Study design	Case ascertainment sources	Crude mortality (95% CI)	Standardized mortality (95% CI)
South America	Brazil	(Moura et al., 2016)	2004 - 2013	R	DC	r: 0.36 - 0.58	r: 0.61 - 0.89
	Chile	(Valenzuela et al., 2015)	1994 - 2010	R	DC	1.13	
	Brazil	(Matos et al., 2011)	2002 - 2006	R	DC	r: 0.44 - 0.76	r: 0.44 - 0.78
	Cuba	(Zaldivar et al., 2009)	2001 - 2006	R	DC	0.67 (0.6–0.72)	0.83 (0.72– 0.8)
	Mexico	(Olivares et al., 1972)	1962 - 1969	R	DC	0.28	

DC, death certificates; r, range; R, retrospective.

IV.1.1.3. ALS occurrence between geographic areas and ethnic groups in Latin America

A higher incidence of ALS was reported in studies from Uruguay and Argentina compared to other Latin American nations. These differences could be related to the study design and exhaustiveness of case ascertainment. For instance, the national study in Uruguay used a prospective design with multiple sources of case ascertainment, which could lead to an accurate estimation of incidence.

Another potential explanation for the variability of ALS within Latin America is the influence of socioeconomic factors. Nevertheless, ALS incidence and mortality varied between countries within the same economic category according the World Bank classification. During the study period, countries with higher incidence, such as Argentina and Uruguay, and countries with lower incidence, such as Costa Rica and Brazil, all were categorized as upper-middle-income countries. This suggests that maybe other factors are involved in ALS heterogeneity.

It is necessary to take into account that populations from Uruguay and Argentina are characterized by an important European background (Seldin et al., 2007). In those countries, ALS occurrence seems to be close to the reports from European studies. Conversely, standardized incidence and mortality rates were lower in Ecuador, Guadeloupe, Brazil and

Cuba (ranging from 0.2 to 1.13). Those nations have a multiethnic population shaped throughout its history of continuous admixture among European, Native Amerindian, and African populations (Homburger et al., 2015).

Furthermore, results from studies assessing differences between ethnic groups within Latin America found that a higher proportion of ALS cases were identified as whites. In Costa Rica, a hospital-based study included 102 patients with ALS; all of them were identified as white individuals (Rodríguez- Paniagua et al., 2007). In Chile, higher mortality rates were reported in the Austral area, which is constituted by a large population of European origin (Valenzuela et al., 2015). In Brazil, a national mortality study described a higher risk for white population with an OR of 2.29 (95% CI 2.78–3.07) (Moura et al., 2016). In Cuba, adjusted mortality rate was higher in whites (0.93; CI 0.83–1.03) compared to admixed populations (0.55; CI 0.4–0.72) (Zaldivar et al., 2009).

IV.1.1.4. Methodological concerns of epidemiological studies in Latin America

The lower incidence and mortality in Latin America studies support the hypothesis that admixed populations exhibit a lower susceptibility to develop ALS. As has already been mentioned, these findings could also be explained by the retrospective design or exhaustiveness of case ascertainment. This could also be due to differences in terms of access to health, socio-economic factors, study period and inequality among different ethnic groups. These methodological issues need to be considered for explaining the results.

Specific methodological concerns have been observed in certain studies from Latin America. For instance, some studies only considered probable or definite ALS according to El Escorial excluding suspected, possible cases (Bettini et al., 2013; Dietrich-Neto et al., 2000; Vázquez et al., 2008). This could underestimate the incidence of the disease. Moreover, it is difficult to compare epidemiological indicators in Latin America due to the lack of standardized data and the use of different reference population for standardization. Further studies are required to draw a clearer picture on ALS epidemiology in Latin America.

IV.1.2. Clinical characteristics of ALS in Latin America

The clinical characteristics of ALS patients have been described in few studies in Latin America. Brazil is the country with most publications in this topic (n = 6), followed by Argentina (n = 2), Ecuador (n = 1), Uruguay (n = 1), Costa Rica (n = 1) and Guadeloupe (an overseas region of France in the Caribbean, n = 1). The majority of the studies were performed using a retrospective hospital-based design. The number of cases ranged from 29 to 443 with a median sample size of 109 cases (IQR 65 - 217). El Escorial criteria has been widely used. The demographic and clinical characteristics of ALS cases in Latin America are shown in table 20.

A male predominance was observed with a male/female SR between one and two. The mean age at onset was reported in the fifth decade of life according to most studies. Reports from Brazil and Argentina described a later age at onset (around the sixth and seventh decades) (Bettini et al., 2011; Linden-Junior et al., 2013). Conversely, a study in Brazil described a particular young age at onset (42 years) in 78 cases (21.1% of the all included cases) (de Castro-Costa et al., 1999). The percentage of familial ALS ranged from 2.6% to 6.4% (de Castro-Costa et al., 1999; Dietrich-Neto et al., 2000; Lannuzel et al., 2015; Vázquez et al., 2008; Werneck et al., 2007), with only one study reporting no fALS cases (Bettini et al., 2013).

The proportion of cases with bulbar onset was broadly variable ranging from 10% to 40% (Bettini et al., 2013, 2013; de Castro-Costa et al., 1999; Dietrich-Neto et al., 2000; Lannuzel et al., 2015; Lima and Nucci, 2011; Loureiro et al., 2012; Rodríguez- Paniagua et al., 2007; Vázquez et al., 2008; Werneck et al., 2007). The median diagnosis delay was around 11 to 12 months (Dietrich-Neto et al., 2000; Lannuzel et al., 2015; Vázquez et al., 2008). Although all the studies used El Escorial criteria to establish diagnosis, few described the proportion of patients in each diagnosis category (e.g. definite, probable, probable with laboratory support, possible) (Bucheli et al., 2014; de Castro-Costa et al., 1999; Werneck et al., 2007). Some studies only included patients with probable or definite ALS (Bettini et al., 2013; Bucheli et al.,

2014; Dietrich-Neto et al., 2000; Lima and Nucci, 2011; Loureiro et al., 2012; Vázquez et al., 2008).

The mean survival time since onset was between 34 months to 42 months (Dietrich-Neto et al., 2000; Lannuzel et al., 2015; Vázquez et al., 2008). The median survival since onset was 49 months (95% CI 42.4 to 55.5) (Loureiro et al., 2012). The main limitation in these studies was the high number loss of follow-up. For instance, one study identified 443 patients reporting survival only from 23 patients (Dietrich-Neto et al., 2000).

Table 20: Studies reporting demographic and clinical charactersitics of patients with ALS in Latin America and the Caribbean by study period according to subcontients

Subcontinent	Country	Authors	Study period	Study design	Sources of case ascertainment	Number of ALS cases	Male/Female sex ratio	Mean age onset (years)	Familial forms	Diagnosis	Diagnosis delay (month)	Mean survival since onset (months)
Caribbean	Guadeloupe*	(Lannuzel et al., 2015)	1996 - 2011	Retrospective	Hosp + Neuro	63	1.4	58.4	6.4%	El Escorial	12 ∫	34 §1
Central America	Costa Rica	(Rodríguez-Paniagua et al., 2007)	1998 - 2001	Retrospective	Hosp	102	1.7	Dg: 53.1m; 54.4 f		El Escorial		
South America	Ecuador	(Bucheli et al., 2014)	2000 - 2012	Retrospective	Hosp	116	1.3	54.3 ∫		El Escorial	15.9	
	Argentina	(Bettini et al., 2013)	2003 - 2010	Retrospective	Hosp + HI	32	0.9	72	0.0%	El Escorial	9.2	
	Brazil	(Linden-Junior et al., 2013)	2010	Cross-sectional	Hosp + Neuro + Asso	70	1.1	64.5		El Escorial		
	Argentina	(Bettini et al., 2011)	2001 - 2008	Retrospective	Hosp	187 †	1.6s	Dg: 55		El Escorial		
	Brazil	(Lima and Nucci, 2011)	2006 - 2007	Prospective	Hosp	29	1.9	Dg: 49.2		El Escorial		
	Brazil	(Loureiro et al., 2012)	2000 – 2007	Retrospective	Hosp	227 †	1.7s	53.6		El Escorial		49 ∫
	Brazil	(Werneck et al., 2007)	1977 - 2004	Retrospective	Hosp + PC	251	1.6	Dg: 54.4	2.8%	El Escorial	20.7 Hosp 14.5 PC	
	Uruguay	(Vázquez et al., 2008)	2002 - 2003	Prospective	Hosp,+ Neuro + Spe + HI + PCP + DC	143	2.0	58.7	4.2%	El Escorial	10.9 ∫	
	Brazil	(de Castro-Costa et al., 1999)	1980 - 1999	Retrospective	Hosp	78	1.8 NC	21.1% jc	2.6%	El Escorial		
	Brazil	(Dietrich-Neto et al., 2000)	1998	Retrospective	Neuro	443	1.4	52.0	5.9%	El Escorial	11 ∫	42 §2

Asso, patients' association; DC, death certificates; Dg: age at diagnosis; f, female; Hosp, hospital; HI, Health insurance; jc, juvenile cases; m, male; NC, calculated; Neuro, neurologist; PC; private clinic; PCP, primary care physicians; s, sporadic ALS; Spe, other specialist.
*, an overseas region of France in the Caribbean; ∫, median; §1 Mean survival from 38 patients; §2 Mean survival from 23 patients; † only sporadic ALS cases included

IV.2. Amyotrophic lateral sclerosis mortality study in Ecuador

In order to contribute to the scientific literature regarding ALS in Latin America, our research team carried out a population-based study to describe and compare mortality rates among ethnic groups in Ecuador, a multiethnic country.

Ecuador is an upper-middle income country located in South America with a total population of 14,483,499 inhabitants according to the National Institute of Statistics and Censuses in Ecuador (INEC) 2010. The country is composed of four regions: the Pacific coast, the Andean region (the highlands), the Amazon region and the Galápagos Islands.

Ecuador is a multiethnic country consisting of a predominant admixed population named Mestizos (79.3%), which combines a mixed origin between European (mostly Spanish) and Indigenous or Native Amerindian. Several ethnic populations are identified in the country as Indigenous (7.0%), Africans or Afro-Ecuadorian (7.2%), whites or Caucasians (6.1%), and other populations (Asians and Arabs) (0.4%) according to the National Census 2010. Ethnicity is self-reported based on cultural and traditions aspects. Ecuador is a very interesting country from a population genetics point of view. The admixed events have been associated with the settlement of different populations in the territory including Native Amerindians or Indigenous, European settlers, and African slaves (Homburger et al., 2015). A recent study to assess the genetic diversity and ancestry in Ecuador found that admixed population (Mestizos) had on average 65.8% of Indigenous ancestry, 30.1% of European ancestry, and 4% of African ancestry (Santangelo et al., 2017).

IV.2.1. Methodological design: ALS mortality study in Ecuador

The national mortality register established by the National Institute of Statistics and Censuses was searched to determine ALS deaths from 1990 to 2016. The International Statistical Classification of Diseases (ICD) codes were used to identify patients with ALS. ICD code is the standard tool for epidemiology, health management, and clinical purposes recommended

by the World Health Organization (WHO). The Ninth Revision (ICD- 9) code 335.2 was used for 1990 through 1996 and the Tenth Revision (ICD-10) code G12.2 was used for 1997 through 2016. The ICD-9 code 335.2 considers ALS, progressive muscle atrophy (PMA), progressive bulbar palsy (PBP), pseudobulbar palsy, primary lateral sclerosis (PLS), and other motor neuron diseases. The ICD-10 code G12.2 includes ALS, motor neuron disease unspecified, familial motor neuron disease, PBP, PLS, progressive spinal muscle atrophy, and other motor neuron diseases. These codes were used following the "ICD consist" criteria provided by the epidemiological practice guideline for ALS mortality studies (Marin et al., 2011a). The causes of death are coded in the death certificates according to the ICD classification. Given that, the ICD codes have changed over time (ICD-7, ICD-8, ICD-9 and ICD-10), it is suggested to use consistent ICD codes. The codes used need to represent the same diseases on the different ICD classifications. A recommended approach for ALS/MND is to use the following codes: 356.0 and 356.1 for ICD-7, 348.0, 348.1 and 348.2 for ICD-8, 335.2 for ICD-9, and G12.2 for ICD-10 (Chiò et al., 1993; Marin et al., 2011a).

The national mortality register gathers underlying and contributory cases of death. The principal cause of death is coded from death certificates (Appendix 2) using the World Health Organization's rules and guidelines for mortality coding in the International Statistical Classification of Diseases and Related Health Problems Instruction Manual (World Health Organization, 2010).

The sociodemographic characteristics of ALS cases were collected including sex, age at time of death and medical death certification. We excluded ALS cases younger than 15 years to avoid likely misclassified cases.

Ethnicity was gathered, when available. Ethnic data were collected using the INEC's definition and classification (B. Villacís and D. Carrillo, 2011). Ethnic groups were classified as Mestizos, Indigenous, Afro-descendants, whites and other groups. Definitions are described below:

i) Mestizo: A person descending from both Indigenous and white roots.

ii) Indigenous: A person descending from populations that inhabited the country or the geographical region before the time of conquest or colonization.

iii) Afro-descendant: A person having origins of African descent in America.

iv) White: A person having origins of European or Caucasian race.

v) Other groups: If the person is not in the aforementioned groups. Asians and Arabs are included in this category.

The population at risk was obtained from the Annual Demographic Yearbook published by the United Nations Statistics Division (The United Nations Statistics Division, n.d.) and the data of the National Censuses provided by the INEC (Instituto Nacional de Estadística y Censos, n.d.). The mid-year population was considered per each year to calculate the mortality rates.

The following guidelines were used to perform this study:

i) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Vandenbroucke et al., 2007).

ii) Standards of Reporting of Neurological Disorders (STROND) (Bennett et al., 2015).

iii) Epidemiological practice criteria for ALS mortality studies (Marin et al., 2011a).

R software version 3.5.0 and SAS enterprise guide version 5.1 (SAS Institute, Cary, NC) were used to conduct the analyses. Quantitative variables were described as medians with interquartile ranges (IQRs). Qualitative variables were shown as frequencies with percentages. Percentages were compared using the Pearson's X^2 test and means by Kruskal-Wallis test, depending on the conditions of application.

Frequency counts of ALS deaths were categorized in 5-year age increments. Crude mortality rates per 100,000 PYFU were calculated and a Poisson distribution was assumed for calculation of 95% confidence interval (95% CI). Direct age- and sex-standardization was

performed based on the 2010 Ecuador population (Instituto Nacional de Estadística y Censos, n.d.) and the 2010 US population (US Census Bureau, 2010).

Mortality rates among ethnic populations were reported from 2009 to 2016. Ethnic population projections were estimated for each year to determine the population at risk. Projections were based on ethnic group weight according to the 2010 Ecuador census (Instituto Nacional de Estadística y Censos, n.d.).

For the statistical analysis, ethnic groups were categorized into admixed (Mestizo), white (Caucasians), black (Africans), and other populations (Indigenous, Asians and Arabs). Rate ratio statistics were performed to compare age- and sex-standardized rates based on the 2010 US population among ethnic groups (SAS/STAT(R) 14.1 User's Guide, n.d.). A p value <0.05 was considered statistically significant.

IV.2.2. Results: ALS mortality study in Ecuador

IV.2.2.1. ALS mortality in Ecuador

A total of 570 ALS deaths were identified in the national mortality register from 1990 to 2016. A physician certified all ALS deaths and a treating physician certified 67.4% of those deaths. A predominance of male cases was observed with a sex ratio of 1.18 overall. An inversion of the SR was observed above 75 years (SR = 1.41 under the age of 65 years, SR = 1.11 between 65 and 75 years and SR = 0.74 above 75 years). The median age of death was 61.5 years (IQR 52.0 – 71.0 years). ALS mortality showed an age-related profile with a peak between 55 and 70 years (Figure 18).

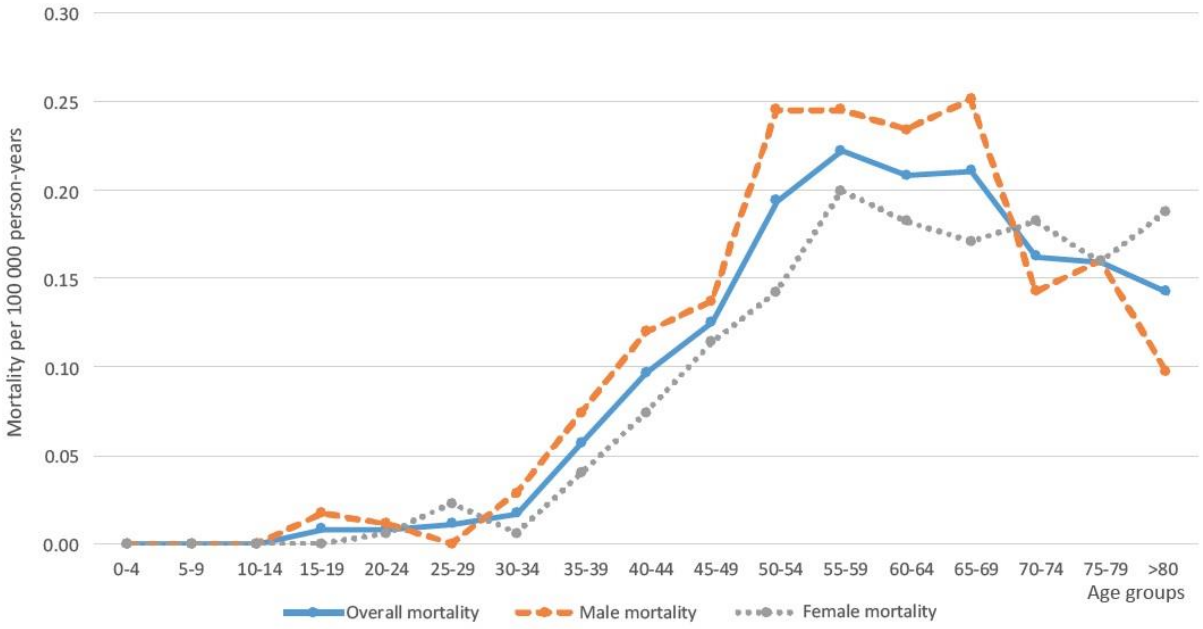

Figure 18 : The crude ALS mortality per 100,000 person-years by age groups in Ecuador from 1990 to 2016: ALS mortality study in Ecuador

The number of ALS cases and population at risk in Ecuador by age and sex from 1990 to 2016 are shown in Appendix 3.

IV.2.2.2. Crude and standardized mortality rates in Ecuador

The overall crude mortality was 0.16 (CI 0.15–0.18) per 100,000 PYFU. The age- and sex-standardized mortality rate per 100,000 PYFU was 0.18 (CI 0.17–0.19) for the 2010 Ecuador population and 0.33 (CI 0.30–0.36) for the 2010 US population. The standardized mortality based on 2010 US population was 0.34 (CI 0.29 - 0.38) in male and 0.32 (CI 0.28 - 0.36) in female. Crude and adjusted mortality rates are shown in table 21.

Table 21 : Crude and adjusted mortality rates per 100,000 population in Ecuador from 1990 to 2016: ALS mortality study in Ecuador

Overall crude mortality (95% CI)	**Male crude mortality (95% CI)**	**Female crude mortality (95% CI)**
0.16 (0.15 - 0.18)	0.18 (0.16 - 0.20)	0.15 (0.13 - 0.17)
Age-sex adjusted mortality Ecuador 2010 (95% CI)	**Male adjusted mortality Ecuador 2010 (95% CI)**	**Female adjusted mortality Ecuador 2010 (95% CI)**
0.18 (0.17 - 0.19)	0.20 (0.18 - 0.22)	0.17 (0.15 - 0.19)
Age-sex adjusted mortality US 2010 (95% CI)	**Male adjusted mortality US 2010 (95% CI)**	**Female adjusted mortality US 2010 (95% CI)**
0.33 (0.30- 0.36)	0.34 (0.29 - 0.38)	0.32 (0.28 - 0.36)

IV.2.2.3. Mortality rates among ethnic groups

The ethnicity of the cases was available from 2009 to 2016. Three hundred seven ALS deaths were identified with ethnic profile information in this period: 272 were admixed, 20 were white, 7 were black and 8 were other ethnic populations (only two cases were identified as Indigenous). The number of ALS cases and population at risk (INEC census 2010 in Ecuador) by ethnic groups, sex and age are shown in Appendix 4.

There was a disparity in the sex ratio between the ethnic groups. A clear predominance of male cases was observed in blacks, while male/female SR was similar in admixed and other

ethnic groups (SR close to 1). Conversely, a higher proportion of female cases was observed in whites.

The crude mortality was 0.27 (CI 0.24 - 0.30) in admixed, 0.26 (CI 0.15 - 0.38) in white, 0.11 (CI 0.03 - 0.19) in black, and 0.09 (CI 0.03 - 0.15) in other ethnics. The age- and sex-standardized mortality rate per 100,000 based on 2010 US population was 0.49 (CI 0.43–0.55) in admixed, 0.37 (CI 0.20–0.53) in white, 0.26 (CI 0.05–0.47) in black, and 0.19 (CI 0.05–0.34) in other ethnics. Crude and standardized mortality rates between ethnic populations are shown in table 22.

Table 22 : Crude and adjusted mortality rates per 100,000 population by ethnic groups in Ecuador from 2009 to 2016: ALS mortality study in Ecuador

Ethnic group	Overall crude mortality (95% CI)	Male crude mortality (95% CI)	Female crude mortality (95% CI)	Age-Sex adjusted mortality Ecuador 2010 (95% CI)	Male adjusted mortality Ecuador 2010 (95% CI)	Female adjusted mortality Ecuador 2010 (95% CI)	Age-Sex adjusted mortality US 2010 (95% CI)	Male adjusted mortality US 2010 (95% CI)	Female adjusted mortality US 2010 (95% CI)
Admixed	0.27 (0.24 - 0.30)	0.28 (0.23 - 0.32)	0.27 (0.22 - 0.31)	0.27 (0.23 - 0.30)	0.27 (0.22 - 0.31)	0.26 (0.22 - 0.31)	0.49 (0.43 - 0.55)	0.46 (0.38 - 0.54)	0.51 (0.42 - 0.61)
White	0.26 (0.15 - 0.38)	0.22 (0.07 - 0.37)	0.31 (0.14 - 0.49)	0.20 (0.11 - 0.29)	0.18 (0.05 - 0.30)	0.23 (0.09 - 0.36)	0.37 (0.20 - 0.53)	0.28 (0.09 - 0.48)	0.45 (0.19 - 0.71)
Black	0.11 (0.03 - 0.19)	0.18 (0.04 - 0.33)	0.03 (0.00 - 0.09)	0.14 (0.03 - 0.25)	0.25 (0.04 - 0.46)	0.04 (0.00 - 0.11)	0.26 (0.05 - 0.47)	0.47 (0.06 - 0.88)	0.05 (0.00 - 0.15)
Others	0.09 (0.03 - 0.15)	0.09 (0.001 - 0.18)	0.09 (0.002 - 0.17)	0.10 (0.03 - 0.18)	0.12 (0.00 - 0.24)	0.08 (0.002 - 0.17)	0.19 (0.05 - 0.34)	0.22 (0.00 - 0.46)	0.16 (0.003 - 0.33)

The rate ratio statistics showed no statistical differences between admixed and white ethnic groups (p = 0.231), admixed and black ethnic groups (p = 0.125), and white and black ethnic groups (p = 0.447). Differences reached statistical significance between admixed and other ethnics (p = 0.015) (table 23).

Table 23 : Comparing directly standardized rates among ethnic groups with a rate ratio statistics in Ecuador: ALS mortality study in Ecuador

Ethnic group	**Mortality rate (95% CI) / 100,000**	***p* value**
Admixed	0.49 (0.43 - 0.55)	0.231
White	0.37 (0.20 - 0.53)	
Admixed	0.49 (0.43 - 0.55)	0.125
Black	0.26 (0.05 - 0.47)	
Admixed	0.49 (0.43 - 0.55)	0.015
Others	0.19 (0.05 - 0.34)	
White	0.37 (0.20 - 0.53)	0.447
Black	0.26 (0.05 - 0.47)	
White	0.37 (0.20 - 0.53)	0.143
Others	0.19 (0.05 - 0.34)	
Black	0.26 (0.05 - 0.47)	0.611
Others	0.19 (0.05 - 0.34)	

IV.2.3. Discussion: ALS mortality study in Ecuador

This epidemiological study is an original contribution to the scientific literature of ALS in Latin America. A lower mortality rate was found in this predominant admixed population from Latin America compared to European and North America populations. This findings support a lower ALS occurrence in admixed populations, which is consistent with previous reports from other Latin American countries and Hispanic populations in the USA. There were no statistically significant differences in mortality rates between admixed, white and black ethnic groups. Differences reached statistical significance between admixed and other ethnic groups (Indigenous, Asians and Arabs).

IV.2.3.1. Sex ratio: ALS mortality study in Ecuador

A slightly higher predominance of male cases was observed with an overall SR of 1.18, which is similar to the ratio described in population-based studies from Europe and North America (SR = 1.3) (Marin et al., 2016b). These results are also consistent with other mortality studies in Latin America that reported a SR around 1.1 to 1.3 (Moura et al., 2016; Valenzuela et al., 2015; Zaldivar et al., 2009).

In the mortality study in Ecuador, the male predominance remained steady until 75 years with a further increase in female cases resulting in SR inversion above 75 years. This could reflect differences in population age structures, differences in accessibility to the health system, or reduced ascertainment of male cases in the elderly age groups. SR was also different between the ethnic groups with a predominance of male cases in blacks and female predominance in whites. It is difficult to draw conclusions on this matter related to the few number of cases in these ethnic groups. Further studies are needed to address this issue.

IV.2.3.2. Age-related pattern: ALS mortality study in Ecuador

We found an age-related pattern in ALS with a progressive increase leading to a peak (around 55 and 70 years) followed by a sudden decrease. This age-specific phenomenon is consistent

with the results of a recent meta-analysis considering population-based studies, which described a peak of ALS incidence between the 60s or 70s with a sharp decrease afterwards (Marin et al., 2018b).

This pattern could suggests that a specific age group is at higher risk to develop ALS. However, this could also be explained by an underestimation of cases in elderly population. Underestimation in this age group could be related to several reasons, among which we can mention the following: i) Elderly patients are less likely to access to specialized health care such as neurology consultation (Forbes et al., 2004). ii) Since age is a well-known prognosis factor, we could assume that older patients with ALS will probably present a shorter survival. This fact implies less time to establish the diagnosis. iii) Patients at risk of developing ALS at an advanced age could die from other causes before the diagnosis (Gunnarsson et al., 1990). Another alternative could be that elderly people who survive beyond the age of 80 are protected against motor neuron damage (Riggs, 1996). Concerning mortality studies, an underestimation in this age group may be linked to the accuracy of death certificates in the elderly population. A study showed that older age and shorter survival since onset were correlated to reduced death certificate accuracy (Ragonese et al., 2004). Further studies are needed to asses ALS in elderly population to clarify all these issues.

IV.2.3.3. ALS mortality in Latin America and admixed populations

Our study found lower ALS mortality rates in Ecuador than in Europe or North America. The results are consistent with other mortality studies in Latin America countries: Brazil, Cuba, and Mexico (Matos et al., 2011; Moura et al., 2016; Olivares et al., 1972; Zaldivar et al., 2009). Furthermore, these findings are similar to the mortality rates described in Hispanic populations from the USA (McCluskey L, 2004; Noonan et al., 2005; Roberts et al., 2016). This suggests a lower occurrence of ALS in admixed populations compared to Europe and North America populations. Nevertheless, socioeconomic factor and access to health services could explain these observations.

This study found no statistical differences on ALS mortality rates among admixed, white and black ethnic groups, while there was a statistically significant difference between admixed and other ethnics. Our results are in contrast with studies from Cuba (Zaldivar et al., 2009) and Brazil (Moura et al., 2016). The findings could also be affected by differences on health care access and socioeconomic status. Interestingly, only two ALS cases were reported among the Indigenous group, which is a very limited number of cases in an ethnic group representing 7.0% of Ecuador population considering a relative suitable period of time (8 years). In the Latin American context, Indigenous populations still have inadequate access to health services. Several barriers have been described, such as the isolation of Indigenous communities, geographic distance of health care facilities, limited economic resources, language, and cultural aspects, as Indigenous could prefer traditional medicine rather than conventional medicine (Montenegro and Stephens, 2006). Specific studies on ALS among Indigenous people are needed to clarify this point.

IV.2.3.4. Validity of the use of death certificates: ALS mortality study in Ecuador

Concerns have been expressed regarding the validity of using death certificates to estimate ALS occurrence. This appears to be related to the fact that several studies found variable ranges of accuracy in ALS cases certification (Chiò et al., 1992; Ragonese et al., 2004; Stickler et al., 2012). On the other hand, studies from England and China have reported that mortality rates were consistent with incidence rates for the same countries and periods of time (Dean et al., 1994; Fong et al., 1996), when standard epidemiological criteria were used. These studies applied most of the practice epidemiological criteria for ALS mortality studies (Marin et al., 2011a) that we followed including: i) definition of the population at risk, ii) mortality data should be based on ‘underlying’ and ‘contributory’ causes, iii) examination of ALS rate time trends, iv) examining ALS variations between ethnic groups.

IV.2.3.5. Strengths and limitations: ALS mortality study in Ecuador

The main strengths of this work rely on the population-based data considering 27-year period for the overall results and 8-year period for the ethnicity rates. This time frame was long enough to collect sufficient numbers of events for the analyses. We considered age and sex structure of the population per year during the study period from official data. Moreover, physicians certified all ALS deaths in the national mortality register.

Some limitations need to be discussed. It could be questioned whether cultural identity is a reliable method to classify ethnicity, which is the official method in Ecuador Census according to the INEC. A genetic study in Ecuador found that people identified as Mestizo (admixed), which is the predominant population in the country, showed higher average genetic diversities with Indigenous and European ancestries (Santangelo et al., 2017). Hence, ethnic identity could be considered a reliable proxy of ancestral origin. It is difficult to determine the influence of health care access or socioeconomic status in our results. Further studies need to consider the impact of these factors.

IV.2.4. Conclusion: ALS mortality study in Ecuador

The mortality rates reported in this population-based study in Ecuador support the current evidence that admixed populations from Latin America display lower occurrence of ALS compared with European and North American populations. Nevertheless, our study found no significant differences between admixed, white and black ethnic groups. Statistical significant differences were only found between admixed and other ethnics.

Genetic epidemiology studies across different populations are needed to reveal the influence of genetic factors, especially ancestral genetic origin, admixture, and mutations. Further studies are needed in Latin America. Studies using a prospective population-based design with multiple sources of case ascertainment should be especially encouraged.

IV.3. Article 3 - ALS mortality rates among ethnic groups in a predominant admixed population

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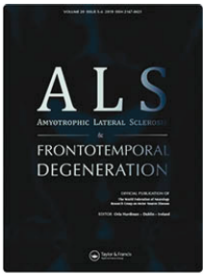

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Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2019; 20: 404–412

ORIGINAL ARTICLE

Amyotrophic lateral sclerosis mortality rates among ethnic groups in a predominant admixed population in Latin America: a population-based study in Ecuador

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Abstract

Current evidence suggests heterogeneity of amyotrophic lateral sclerosis (ALS) among geographic areas and populations. Lower mortality rates have been reported in admixed populations compared to European origin populations. We aimed to describe and compare ALS mortality rates among ethnic groups using a population-based approach in a multiethnic country. Annual mortality cause registers were searched to determine ALS deaths from the National Institute of Statistics and Censuses in Ecuador (INEC) from 1990 to 2016. Mid-year population was considered for each year. The time trend was assessed using a negative binomial regression. Rate ratio statistics were performed to compare the age and sex standardized rates based on the 2010 US population among ethnic groups. Overall, 570 ALS deaths were identified. ALS mortality showed an age-related profile with a peak between 55 and 70 years. After age–sex standardization on the 2010 US population, mortality rate was 0.33 (CI 0.30–0.36) per 100,000. The time trend showed an increase of ALS mortality ($p < 0.001$). There was no statistical difference in age–sex standardized mortality rates per 100,000 when admixed was compared to white ($p = 0.231$) and black ($p = 0.125$). Differences reached statistical significance between admixed and other ethnics ($p = 0.015$). Our population-based study supports the hypothesis that ALS occurrence is lower in predominant admixed populations from Latin America compared to European and Northern American populations. Further studies are needed to clarify the role of ancestral origin in ALS susceptibility.

Keywords: *Amyotrophic lateral sclerosis, mortality, ethnicity, risk, admixed population, population-based study*

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder involving the upper and lower motor neurons that leads to progressive paralysis of voluntary muscles until death. The median survival time from diagnosis is around 15–20 months (1).

It could be assumed that all patients diagnosed with the condition will eventually be identified via the death certificate given the invariably fatal outcome of the disease (2). As a result, mortality rates have been used as proxies of ALS incidence rates. A study showed that mortality rates were highly consistent with incidence rates estimated in the same area once standard epidemiological practice criteria were satisfied (3).

Current evidence indicates heterogeneity of ALS incidence and mortality among geographic areas (4) and populations (5). This heterogeneity suggests that the differences might be due to ethnicities and ancestries (6). Several studies in the US reported lower mortality rates in Hispanic

Supplemental data for this article can be accessed here.

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populations compared to white and black populations (7,8). A mortality study in Cuba determined a lower adjusted mortality rate per 100,000 person-years of follow-up (PYFU) in admixed populations 0.55 compared to whites 0.93 and blacks 0.87 (9). Only one hospital-based study investigated ALS in Ecuador, a multiethnic Latin American country with a predominant admixed population. The researchers found a crude incidence ranging from 0.2 to 0.6 per 100,000 (10) which is consistent with results seen in other admixed populations (9,11). However, ethnicity of the cohort was available only for a reduced number of subjects.

Lower mortality rates in the admixed populations could be explained by lower risk of developing ALS, supporting the notion that ancestral origin may play a role in disease pathogenesis. In this context, we aimed to describe and compare ALS mortality rates among ethnic groups in Ecuador using a population-based approach. Moreover, we described temporal trends of ALS mortality in the country.

Materials and methods

Study area and population

Ecuador is an upper-middle income country located in Latin America (12), characterized by four distinctive regions: the Pacific coast, the Andean region, the Amazon region, and the Galápagos Islands. A total population of 14,483,499 inhabitants was stated according to the 2010 census conducted by the National Institute of Statistics and Censuses in Ecuador (INEC). Ecuador is a multiethnic country consisting of a predominant admixed population named Mestizos (79.3%), which combines a mixed origin between European (mostly Spanish) and Indigenous. Several ethnic populations are identified in the country as Indigenous (7.0%), Africans (7.2%), whites or Caucasians (6.1%), and other (Asians and Arabs) populations (0.4%) according to the INEC (13).

Case ascertainment

The INEC in Ecuador annual mortality cause registers were searched in order to determine ALS deaths from 1990 to 2016. Death cause was based on underlying and contributory causes using the International Classification of Diseases (ICD) coding. The Ninth Revision (ICD- 9) code 335.2 was used for 1990 through 1996 and the Tenth Revision (ICD-10) code G12.2 was used for 1997 through 2016. The principal cause of death is coded from death certificates using the World Health Organization's rules and guidelines for mortality coding in the International Statistical Classification of Diseases and Related Health Problems Instruction Manual (14). We excluded ALS cases younger than 15 years to avoid likely misclassified cases.

Data collection

Data were collected according to epidemiological practice criteria for ALS mortality studies (3). Socio-demographic information was obtained included sex and age at the time of death. The self-reported ethnicity was also collected. Ethnic groups were reported according to the INEC census (15).

Estimates of population at risk were obtained from the Annual Demographic Yearbook published by the United Nations Statistics Division (16) and the data of the national censuses provided by the INEC (13). The mid-year population was considered per each year to calculate the mortality rates.

Statistical analysis

The Standards of Reporting of Neurological Disorders (STROND) guideline (17) and the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) (18) were followed to perform and report this work.

R software version 3.5.0 and SAS enterprise guide version 5.1 (SAS Institute, Cary, NC) were used to conduct the analyses. Quantitative variables were described as medians with interquartile ranges (IQRs). Qualitative variables were shown as frequencies with percentages. Frequency counts of ALS deaths were categorized in 5-year age increments.

Crude mortality rates per 100,000 PYFU were calculated and a Poisson distribution was assumed for calculation of 95% confidence interval (95% CI). Direct age–sex standardization was performed based on the 2010 Ecuador population (13) and the 2010 US population (19).

Three time periods were considered based on the ICD coding system and the availability of ethnic population information: (i) 1990–1996; (ii) 1997–2008; and (iii) 2009–2016. A negative binomial regression adjusted by age was used to test the time trend considering the population older than 15 years.

Mortality rates among ethnic populations were reported for the 2009–2016 period. Ethnic population projections were estimated for each year to determine the population at risk. Projections were based on ethnic group weight according to the 2010 Ecuador census (20).

For the statistical analysis, ethnic groups were categorized into admixed (Mestizo), white (Caucasians), black (Africans), and other (Indigenous, Asians and Arabs) populations. Rate ratio statistics (21) were performed to compare the age and sex standardized rates based on the 2010 US population among ethnic groups.

A p value <0.05 was considered statistically significant.

Results

ALS mortality

Overall, 570 ALS deaths were identified from 1990 to 2016. A physician certified all ALS deaths and 384 (67.4%) of those cases were certified by the treating physician. A male predominance was observed with a male/female sex ratio (SR) of 1.18. SR was 1.41 under the age of 65 years, 1.11 between 65 and 75 years and 0.74 above 75 years. The median age of death was 61.5 years (IQR 52.0 – 71.0 years). ALS mortality showed an age-related profile with a peak between 55 and 70 years (Figure 1).

The overall crude mortality per 100,000 PYFU was 0.16 (CI 0.15–0.18), 0.18 (CI 0.16–0.20) for male, and 0.15 (CI 0.13–0.17) for female. Age–sex standardized mortality rate per 100,000 PYFU was 0.18 (CI 0.17–0.19) for the 2010 Ecuador population and 0.33 (CI 0.30–0.36) for the 2010 US population. Crude and standardized mortality rates are shown in Table 1a.

The number of ALS cases and population at risk by age and sex are shown in Supplementary Table e1.

Time trend

ALS mortality seemed to increase over time (Figure 2). The crude mortality rates per 100,000 were 0.09 (CI 0.07–0.11) from 1990 to 1996, 0.11 (CI 0.09–0.13) from 1997 to 2008, and 0.27 (CI 0.24–0.29) from 2009 to 2016 (Table 1b). The results seemed to be congruent after standardization to the 2010 US population (Table 1b).

Negative binomial regression showed a significant p value for the time trend ($p<0.001$) and age ($p<0.001$). The model adjusted by age found statistically significant differences between the first period (1900–1996) compared to the second period (1997–2008), $p<0.0001$ and the third period (2009–2016), $p<0.0001$.

The ICD version, ethnic data, and ALS cases characteristics in the considered time periods are shown in Table 2.

ALS mortality rates among ethnic groups

Three hundred seven ALS cases were identified with ethnic profile information in the period 2009–2016: 272 were admixed, 20 were white, 7 were black, and 8 were other ethnic populations (only two were identified as Indigenous). The number of cases and population at risk by ethnic group, sex, and age at death are shown in Supplementary Table e2.

The age–sex standardized mortality rate per 100,000 based on 2010 US population was 0.49 (CI 0.43–0.55) in admixed, 0.37 (CI 0.20–0.53) in white, 0.26 (CI 0.05–0.47) in black, and 0.19 (CI 0.05–0.34) in other ethnics. Crude and standardized mortality rates between ethnic populations are shown in Table 3. No statistical difference was found between admixed and white ethnic groups ($p=0.231$), admixed and black ethnic groups ($p=0.125$), and white and black ethnic groups ($p=0.447$). Differences reached statistical significance between admixed and other ethnics group ($p=0.015$) (Table 3).

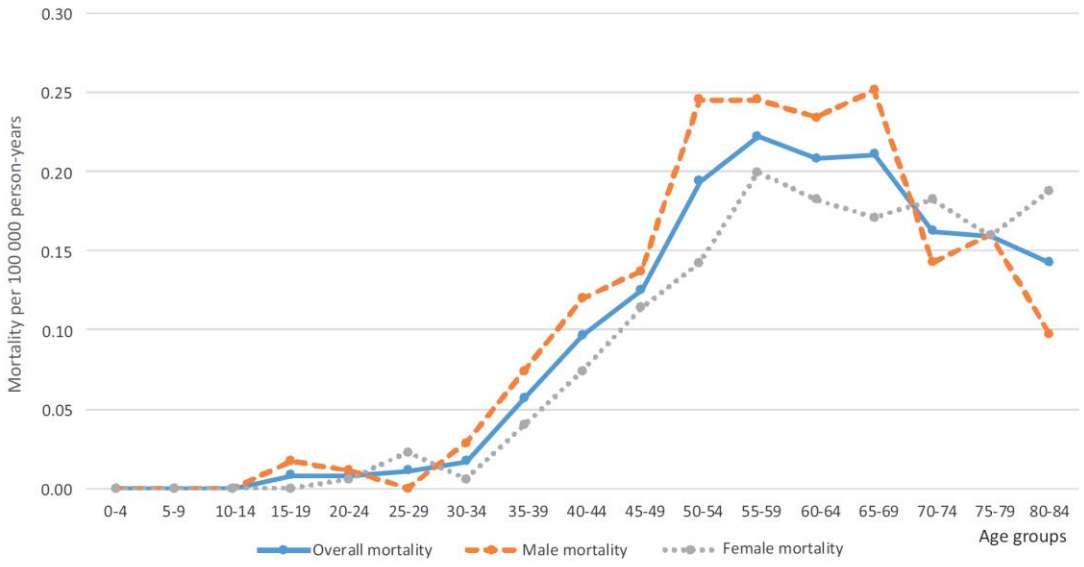

Figure 1. Crude ALS mortality per 100,000 person-years by age groups in Ecuador 1990–2016.

Table 1. Crude and adjusted mortality rates per 100,000 population in Ecuador 1990–2016 .

	Overall crude mortality (95% CI)	Male crude mortality (95% CI)	Female crude mortality (95% CI)	Age–sex adjusted mortality Ecuador 2010 (95% CI)	Male adjusted mortality Ecuador 2010 (95% CI)	Female adjusted mortality Ecuador 2010 (95% CI)	Age–sex adjusted mortality US 2010 (95% CI)	Male adjusted mortality US 2010 (95% CI)	Female adjusted mortality US 2010 (95% CI)
1a. Overall									
1990–2016	0.16 (0.15–0.18)	0.18 (0.16–0.20)	0.15 (0.13–0.17)	0.18 (0.17–0.19)	0.20 (0.18–0.22)	0.17 (0.15–0.19)	0.33 (0.30–0.36)	0.34 (0.29–0.38)	0.32 (0.28–0.36)
1b. Time periods									
1990–1996	0.09 (0.07–0.11)	0.11 (0.08–0.14)	0.07 (0.05–0.10)	0.13 (0.09–0.15)	0.15 (0.11–0.19)	0.10 (0.06–0.14)	0.23 (0.17–0.29)	0.26 (0.18–0.34)	0.20 (0.12–0.28)
1997–2008	0.11 (0.09–0.13)	0.14 (0.11–0.16)	0.09 (0.07–0.11)	0.13 (0.11–0.15)	0.15 (0.12–0.18)	0.10 (0.08–0.13)	0.22 (0.19–0.26)	0.26 (0.21–0.31)	0.19 (0.14–0.23)
2009–2016	0.27 (0.24–0.29)	0.27 (0.23–0.31)	0.26 (0.22–0.31)	0.26 (0.23–0.29)	0.26 (0.22–0.30)	0.26 (0.22–0.30)	0.48 (0.42–0.53)	0.45 (0.38–0.52)	0.50 (0.42–0.58)

Discussion

This population-based study supports the hypothesis that ALS occurrence is lower in predominant admixed populations from Latin America compared to European and Northern American populations. The results are consistent with previous ALS reports in Latin America and Hispanic populations in the United States. No statistical differences on age–sex standardized mortality were found among admixed, white and black ethnic groups, while the difference was statistically significant between admixed and other ethnics.

Sex ratio in ALS mortality

The overall SR described a slightly predominance of male cases which is similar to the ratio reported in Europe and North America (22). The male predominance remained steady until 75 years, while an increase in female cases was found above 75 years. This could reflect differences in population age structures, differences in accessibility to the health system, or reduced ascertainment of male cases in the elderly age groups.

Age-related pattern in ALS mortality

ALS mortality followed an age-related pattern; increasing gradually and leading to a peak followed by a sudden decrease. As previously discussed, this pattern could imply for example that a specific age group is at higher risk to develop ALS. The age-specific phenomenon is consistent with the results reported in a recent meta-analysis based on population-based studies of newly-diagnosed ALS cases (23). On the other hand, some researchers are still debating that this phenomenon may be the result of under-ascertainment of cases in elderly population (24).

Time trend in ALS mortality

Our study showed that ALS mortality rates are rising. The results were consistent with several reports in Norway, Denmark, New Zealand, United States, and Chile (25–29). A hospital-based study in Ecuador showed that the prevalence of degenerative diseases increased from 5.7% in 1990–1994 to 10.2% in 2005–2009 (30). A study projected a worldwide increase of ALS cases from 222,801 in 2015 to 376,674 in 2040 mainly related to the aging population (31). Another reason for the increase could be a better case ascertainment or an escalation of environmental risk factors.

Variability of ALS between geographic areas and populations

Evidence based on population-based studies has shown that ALS incidence is homogenous among

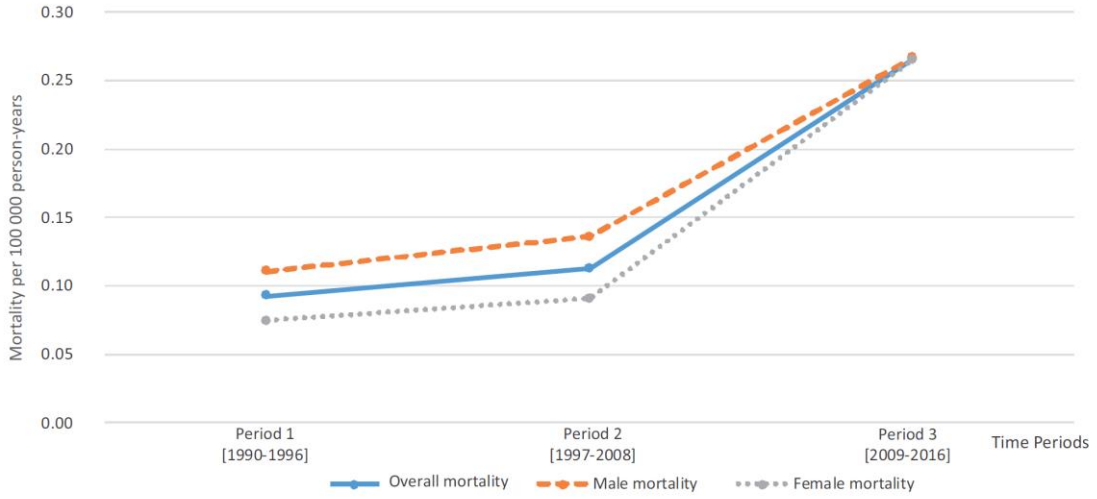

Figure 2. Time trend of ALS mortality per 100,000 person-years in Ecuador.

Table 2. International classification of diseases version, ethnic data, and ALS cases characteristics by period of time.

	Overall 1990–2016 ($n = 570$)	Period of time 1990–1996 ($n = 70$)	1997–2008 ($n = 173$)	2009–2016 ($n = 327$)
2a. Information available				
ICD	ICD-9 / ICD-10	ICD-9	ICD-10	ICD-10
Ethnic data	N/A - Available	N/A	N/A	Available
2b. ALS cases characteristics				
Gender, *n* (%)				
Male	309 (54.2)	42 (60.0)	104 (60.1)	163 (49.8)
Female	261 (45.8)	28 (40.0)	69 (39.9)	164 (50.2)
Sex ratio M/F	1.18	1.5	1.5	0.99
Age of death (years)				
median (IQR)	61.5 (52.0–71.0)	62.0 (52.7–72.0)	58.0 (49.0–68.0)	63.0 (53.0–73.0)

European origin populations from Europe, North America, and New Zealand with an estimation of 1.81 (1.66–1.97)/100,000 PYFU. Epidemiological studies performed in Latin America have consistently reported a lower ALS mortality. Studies described a crude mortality rate of 0.3 per 100,000 in Mexico and Chile (11,32). Mortality rates also remain lower after standardization. The overall standardized mortality rate was 0.44 in Brazil (33) and 0.83 in Cuba (9) per 100,000 PYFU.

Only one population-based mortality study has been performed in the admixed population of Cuba to assess ALS among ethnic groups (9). The adjusted mortality rate per 100,000 was considerably lower in the admixed population (0.55 (95%CI 0.4–0.72)) compared to white population (0.93 (95%CI 0.83–1.03)), and black population (0.87 (95%CI 0.62–1.17)). These results in Cuba are similar to those described in Hispanic populations in the United States (7,34). Mortality studies consistently reported that ALS mortality was lower among Hispanic population (0.9 per 100,000) and African American population (1.1 per 100,000) (7) compared to white population (close to 2/100,000) (3). Incidence studies have also shown similar results among ethnic groups. A study performed in three states in the US (Florida, New Jersey, and Texas) and eight metropolitan areas described a lower age standardized incidence per 100,000 of ALS in Hispanics (0.84, CI 0.75–0.92) compared to non-Hispanics (1.36, CI 1.31–1.41) (35). A study in San Francisco Bay Area (SFBA) and Los Angeles County (LA) also showed lower rates of age standardized incidence per 100,000 in Hispanics compared to non-Hispanics (SFBA: 1.57 (CI 1.0–2.3) Hispanics *vs.* 1.89 (CI 1.7–2.2) non-Hispanics; LA: 0.66 (CI 0.5–0.9) Hispanics *vs.* 1.01 (CI 0.9–1.2) non-Hispanics) (36). However, these variations could also be related to differences in the access to health care or the socioeconomic status among ethnic groups. A recent mortality study in US used an adjusted model for socioeconomic status, type of health insurance, and birthplace to estimate the ALS mortality risk in different ethnic groups. Higher rates of ALS

Table 3. Crude and adjusted mortality rates per 100,000 population by ethnic groups in Ecuador 2009–2016.

Ethnic group	Overall crude mortality (95% CI)	Male crude mortality (95% CI)	Female crude mortality (95% CI)	Age–sex adjusted mortality Ecuador 2010 (95% CI)	Male adjusted mortality Ecuador 2010 (95% CI)	Female adjusted mortality Ecuador 2010 (95% CI)	Age–sex adjusted mortality US 2010* (95% CI)	Male adjusted mortality US 2010 (95% CI)	Female adjusted mortality US 2010 (95% CI)
Admixed	0.27 (0.24–0.30)	0.28 (0.23–0.32)	0.27 (0.22–0.31)	0.27 (0.23–0.30)	0.27 (0.22–0.31)	0.26 (0.22–0.31)	0.49* (0.43–0.55)	0.46 (0.38–0.54)	0.51 (0.42–0.61)
White	0.26 (0.15–0.38)	0.22 (0.07–0.37)	0.31 (0.14–0.49)	0.20 (0.11–0.29)	0.18 (0.05–0.30)	0.23 (0.09–0.36)	0.37* (0.20–0.53)	0.28 (0.09–0.48)	0.45 (0.19–0.71)
Black	0.11 (0.03–0.19)	0.18 (0.04–0.33)	0.03 (0.00–0.09)	0.14 (0.03–0.25)	0.25 (0.04–0.46)	0.04 (0.00–0.11)	0.26* (0.05–0.47)	0.47 (0.06–0.88)	0.05 (0.00–0.15)
Others	0.09 (0.03–0.15)	0.09 (0.001–0.18)	0.09 (0.002–0.17)	0.10 (0.03–0.18)	0.12 (0.00–0.24)	0.08 (0.002–0.17)	0.19* (0.05–0.34)	0.22 (0.00–0.46)	0.16 (0.003–0.33)

*Comparing directly standardized rates among ethnic groups with a rate ratio statistics: admixed *vs.* white ($p = 0.231$); admixed *vs.* black ($p = 0.125$); admixed *vs.* others ($p = 0.015$); white *vs.* black ($p = 0.447$); white *vs.* others ($p = 0.143$); black *vs.* others ($p = 0.611$).

were still reported among whites compared to other populations (Hispanic, HR 0.64 (0.46–0.88); non-Hispanic black, HR 0.61 (0.48–0.78); other races, non-Hispanic, HR 0.52 (0.31– 0.86)) (37).

The lower incidence and mortality in admixed population could suggest that genetics, especially ancestral origin, is a main factor on ALS. Zaldivar et al. proposed that European populations share a variety of at-risk genes, which may increase ALS susceptibility. Admixed populations have a wider variety and different combinations of at-risk genes, which leads to a lower risk of developing the disease (9). Conversely, the variation on epidemiological indicators could also be explained by reduced case ascertainment due to lower access to health care, limited number of neurologists, and underreporting of ALS in death certificates.

Ecuador is a very interesting country from a population genetics point of view. The admixed events have been associated with the settlement of different populations in the territory including pre-Columbian Indigenous, European settlers, and African slaves (38). A recent study to assess the genetic diversity and ancestry in Ecuador found that admixed population (Mestizos) had on average 65.8% of Indigenous ancestry, 30.1% of European ancestry, and 4% of African ancestry (39). Our study found no statistical differences on ALS mortality rates among admixed, white and black ethnic groups, while there was a statistically significant difference between admixed and other ethnics. The results could be similarly affected by differences on health care access and socioeconomic status. Interestingly, only two ALS cases were reported among the Indigenous group. In the Latin American context, Indigenous populations still have inadequate access to health services. Several barriers have been described, such as the isolation of Indigenous communities, geographic distance of health care facilities, limited economic resources, language, and cultural aspects, as Indigenous could prefer traditional medicine rather than conventional medicine (40). Specific studies on ALS among Indigenous people are needed to clarify this point.

Epidemiological studies on ancestral origin are limited by heterogeneity of terminology and population's categorization. Researchers in the US categorize populations using "races" (white, black/African American, and Asian) and ethnicities (Hispanic and non-Hispanic), while some studies in UK used the origin (e.g. European or African origin). Another closely related issue is the variety of definitions to identify ethnicities. In the US, Hispanic ethnicity was defined as a person of South or Central America culture or origin according to the National Institutes of Health (NIH). In Ecuador, ethnicity was self-reported based on cultural and traditional aspects, which is the official

method used in the Ecuadorian census. In contrast, in Cuba, ethnicity was self-reported according to the skin color which is the official method used in the Cuban census. The definition of ethnicity is therefore widely different across Latin American countries. Ethnic self-identification is subjective and based on cultural aspects rather than ancestral origin. Instead, molecular signature of ancestral origin using genetic markers could provide an objective and reliable way of assessing genetic biogeographic ancestry. Biogeographic ancestry is a person's origin associated with the geographic location of presumed ancestors inferred by comparison with contemporary populations living in these locations (41). A genetic approach will clarify the role of ancestral origin on the risk of developing ALS.

Genetic epidemiology is another important matter on ALS. A meta-analysis showed a wide range of frequencies of ALS mutations between geographic areas and populations (42). European populations showed more frequently C9orf72 mutations, while SOD1 and FUS mutations were more frequent in Asian populations. To better understand the genetic architecture of ALS, further research is necessary in regions of the world that are poorly represented in the literature.

Validity of the use of death certificates

Certain researchers have expressed concerns about the validity of using death certificates to estimate ALS epidemiological indicators (43). On the other hand, studies in England and Hong Kong showed that mortality rates were consistent with incidence rates for the same countries and periods of time (44,45). These studies applied most of the practice epidemiological criteria for ALS mortality studies that we followed. The use of death certificate is a convenient approach that could provide reliable data if strict methodological criteria are met.

Limitations and strengths

Some limitations have to be considered. First, it could be argued if cultural identity is a reliable method to classify ethnicity (official method in Ecuador census). In fact, a genetic study in Ecuador found that people identified as Mestizo (admixed), which is the predominant population, showed higher average genetic diversities with Indigenous and European ancestries (39). Hence, ethnic identity could be considered a reliable proxy of ancestral origin. Second, it is difficult to determine the influence of health care access or socioeconomic status. Further studies might consider the impact of these factors. Third, ethnic information of the population was only available for the 2009–2016 period, which limited the number of cases. On the other hand, this period reported the highest proportion of ALS cases.

Our study relies in several strengths. First, a population-based approach was used to assess ALS mortality between ethnic groups, which enables us to strengthen the possibility of including all persons in a defined population (46). Second, we considered a 27-year period to ensure a time frame long enough for sufficient numbers of events to be recorded. Third, physicians certified all ALS deaths reported, which is an important issue to assure a reliable ICD code classification. Lastly, the analyses took into account age and sex structure of the population per year during the study period. We reported standardized mortality rates that could contribute to clarify ALS variability.

Prospects

An international collaboration using homogenous and standardized methodology is needed to address the potential influence of ancestral origin along with environmental factors. Genetic studies in admixed population are needed to elucidate the potential influence of genetic factors, especially population's ancestries, admixture, along with genetic mutations, on ALS heterogeneity. Genetic markers could provide a more accurate image of biogeographic ancestry. Genetic analyses on ancestral origin must follow strict ethical standards and respect the principles of autonomy, privacy, confidentiality, and equity. A better understanding of the ALS variation in different populations will help to clarify potential gene-environmental determinants and the risk of developing the disease. Moreover, prospective population-based studies using multiple sources of case ascertainment should be encouraged in admixed populations.

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Chapter V. General discussion

V.1. Summary of thesis works and main findings

This dissertation offers an updated review concerning the epidemiology and clinical characteristics of ALS. The aim was to provide a critical overview of the current evidence and the potential implications of disease variability. As a scientific contribution of this work, original studies were performed to furnish reliable and standardized data in Africa and Latin America.

After a brief presentation of the disease in the first chapter, the subject of amyotrophic lateral sclerosis epidemiology was addressed by presenting the most relevant evidences since the first efforts to determine an overall estimation of epidemiological indicators around the world. The current data lead researchers to suggest a heterogeneous occurrence of ALS with a higher incidence in Europe and North America compared to other regions. Given that, the epidemiological variability is also observed between different populations. We reviewed studies assessing incidence and mortality among ethnic groups. Studies constantly showed higher risk to develop the disorder in whites or Caucasian populations compared with Hispanics, Africans and Asians. Therefore, it appears that ancestral origin could play a role in ALS variability.

A wide range of clinical features characterizes ALS. The distribution of clinical characteristics was described with regards to demographic characteristics, genetic variants, geographic regions and populations. We still do not fully understand how several factors are involved to determine phenotypic expression.

Certain methodological considerations need to be taken into account as potential biases and limitations that could explain ALS variability. We have discussed these points in a constructive way and put into perspective the next steps for further research regarding epidemiological and clinical studies in ALS.

It is clear that ALS data are scarce in several regions of the world. Most of the scientific information available comes from Europe and North America and therefore from Caucasian populations. The limited data makes difficult to draw firm conclusions on disease variability. This subject is of great importance because it could unravel associated factors to the risk of developing ALS along with the understanding of clinical variability. It was in that spirit that research initiatives were carried out in collaboration with our colleagues in Africa and Latin America.

In Africa, an international project named TROPALS ("Epidemiological study of ALS in the tropics") was launched and coordinated by our research team INSERM UMR 1094 NET. This multicenter hospital-based study was performed to describe and compare the sociodemographic, clinical features, treatments, and prognoses and survival times of patients with ALS. The TROPALS study was developed with the participation of nine hospital centers from eight countries, which enabled us to include an unprecedented sample size in Africa. Reliable data were obtained using standardized methods for data collection with a subsequent centralized certification of diagnosis. Certain specific characteristics were found in patients with ALS from Africa compared to patients from Europe and North America. We observed higher proportion of male cases, younger age at onset and lower proportion of bulbar onset. Survival is in line with Western reports, but it was far shorter than expected for a young cohort of ALS cases. This could be explained by the lack of specialized care and access to riluzole.

After reviewing ALS literature in Latin America, we have been entirely focused on a specific country. Given the scientific interest in working on multiethnic populations and previous collaborations between our research team and Ecuadorian researchers, a retrospective population-based study was performed to describe and compare mortality rates among ethnic groups in Ecuador. The national mortality register was used to identify ALS deaths thought the ICD codes following standard epidemiological criteria. A well-defined population at risk and broad time framework were used for the overall estimations and the analyses among ethnic groups. The age profile of ALS mortality was determined for this population. The standardized

mortality rates were lower compared to those reported from North America and Europe. When standardized rates were compared among ethnic groups, no statistical difference was found between admixed, white and black groups. Nevertheless, the differences between admixed and other ethnics (Indigenous, Asians and Arabs) were statistically significant.

This scientific work contributes to move forward in the understanding of ALS variability through epidemiological and clinical data from Africa and Latin America.

V.2. Potential factors related to ALS variability

Along this dissertation, we have presented evidence supporting ALS variability. Epidemiological and clinical heterogeneity could be explained by methodological issues related to variability of study design, biases, underrepresentation of cases, difficulties for case ascertainment and lack of health care access. On the other hand, these variations could be related to differences in terms of determinants of risk such as environmental factors, genetic mutations and ancestral origin of the populations.

V.2.1. Methodological issues

There are several methodological challenges to overcome to perform ALS biomedical research that are not only related to the number of people with the condition. To report accurate epidemiological and clinical data several factors need to be taken into account.

The representativeness is a vital concept in epidemiology mainly for descriptive purposes (Elwood, 2013; Rothman et al., 2013). This is a key factor in drawing conclusions with good external validity. Reliable epidemiological indicators should come from population-based studies. The source of case ascertainment is another important matter directly linked. Strategies could be used to assess the exhaustiveness of case ascertainment such as capture–recapture method (Hook and Regal, 1995). The reliability of the information available in the source is essential (e.g. validity of medico-administrative data). In addition, it is strongly recommended to provide standardized epidemiological data, which will allow us to compare between populations. An ideal methodological framework would be the use of multiple independent sources with complete ascertainment of cases that gather reliable data from the general population.

The use of reliable methodological criteria have proven to be an accurate instrument to describe ALS epidemiology in Europe (Beghi et al., 2006; Hardiman et al., 2017). This is illustrated by initiatives such as the French register of ALS in Limousin (FRALim register), the

Piemonte and Valle d'Aosta Register for ALS (PARALS), Sclerosis Lateral Amyotrophic – Puglia (SLAP) and the European amyotrophic lateral sclerosis consortium (EURALS).

To clarify the clinical variability of ALS, it is indispensable to furnish a detailed clinical description by well-trained neurologists and health care personnel using standardized criteria and valid tools (e.g. El Escorial criteria (Brooks, 1994; Brooks et al., 2000), the Edinburgh Cognitive and Behavioural ALS Screen (Abrahams and Bak, 2013)). Systematic errors in the recruitment process need to be limited. It has been shown that referral bias could have a major impact in ALS patient's characteristics including age of onset, type of onset, familial background and survival (Logroscino et al., 2018a). The establishment of ALS diagnosis from the medical records is generally poor in agreement among clinicians (Beghi et al., 2002) and it can be improved only after discussing the reasons for discordance. A central verification of clinical informations by a group of expert neurologists could be another robust point in order to achieve clinical consensus. Ideally, a prospective design brings the strength to collect data using standardized methods following a research protocol.

V.2.1.1. Methodological challenges to conduct studies in low- and middle-income countries

The low- and middle-income countries (LMICs) are underrepresented areas in ALS literature. Those countries are struggling with an epidemiological transition and double burden of disease that implies an increasing prevalence of non-communicable disorders while infectious illnesses still remains a great issue for public health (Naghavi et al., 2017). Several factors are involved in this phenomenon such as changes in mortality and fertility rates accompanied by population aging and better sanitary conditions. The burden of age-related conditions will progressively increase including neurodegenerative disorders. Unfortunately, limited information are available about the epidemiology, genetics, clinical features, management and health care access of these conditions in LMICs.

It is challenging to perform studies in LMICs, especially neurodegenerative disorders, owing to a several hurdles. The limited number of health care personal including very low number of

neurologists, lack of essential healthcare infrastructures and poor access to health care contribute to a deficiency of diagnosis and formal identification of cases. The lack of reliable data, for example administrative health data and population census, prevents a full assessment of these conditions (e.g. incidence, mortality). Geographic difficulties in the field, lack of logistical and financial support and misconceptions of neurological conditions make even more complicated the research work (Bharucha et al., 2014; Boumediene et al., 2018), adding to the fact that neurodegenerative disorders do not represent a public health priority in these countries.

In the recent years, new initiatives have been launched in Africa, Asia and Latin America to provide standardized and reliable data. However, several challenges remain to implement research projects in these areas (e.g. financing and logistic difficulties). It is for this reason that international support is essential to overcome the obstacles and difficulties to provide data and measure the burden of neurodegeneration in LMICs.

V.2.2. Ancestral origin of populations

V.2.2.1. Genetics and ancestral origin as determinants of risk

The insight that genetic background is a determinant of risk for certain medical conditions is not an innovative concept. Genetics play a role in the risk to develop several disorders. In fact, clinicians attempt to estimate health risk based on family history all the time (Gwinn-Hardy, 2005). To give an example, patients with family history of early heart disease will probably undergo to close follow-up of the cardiovascular status (Kolber and Scrimshaw, 2014). Epidemiologists also assess the risks associated with family medical history. A positive family history of depression is a consistent predictor of the disorder (Monroe et al., 2014).

Studies have revealed that certain mutations are common in some populations and, more recently, the origin of these mutations have been explored. For instance, sickle cell disease which is a genetic disorder caused by a mutation in the hemoglobin beta chain with a higher prevalence among the people of Sub-Saharan Africa, South Asia, Middle East, and the

Mediterranean (Sedrak and Kondamudi, 2019). A recent study investigated the origins of the sickle allele by using whole-genome-sequence data. The findings support an African origin of the sickle mutation approximately 7,300 years ago either in the Sahara or in west-central Africa (Shriner and Rotimi, 2018). These new discoveries may open the door for further understanding the origin of mutations, which could be essential to decrypt several disorders including neurodegeneration.

Neurodegeneration is a complex process that we still do not fully understand. Current evidence suggests an epidemiological variability among populations with regards to neurodegenerative disorders like Alzheimer disease (Anderson et al., 2004; Mehta et al., 2008), Parkinson's disease (Dahodwala et al., 2009; Wright Willis et al., 2010), and Huntington disease (Pringsheim et al., 2012). In addition, these disorders share common physiopathological mechanisms like protein aggregation and inclusion body formation (Ludolph and Brettschneider, 2015; Ross and Poirier, 2004). These are arguments suggest that genetics and ancestral origin might play a crucial role in neurodegenerative processes. Further research is necessary to understand neurodegeneration.

V.2.2.2. Amyotrophic lateral sclerosis: Ancestral origin

The role of ancestral origin of the population as a potential risk factor for ALS is an interesting hypothesis that has attracted scientific attention in the last decades. This idea is mainly supported by higher incidence and mortality rates in geographic regions with a predominant population of European origins (e.g. Europe, North America and New Zealand), and the higher risk of ALS described for Caucasians or whites compared to Hispanics, Asians and black populations in multiethnic studies.

Researchers also postulated that admixed populations from Latin America could have a lower risk to develop ALS due to their mixed genetic background. The demographic history of Latin America is marked by multiple migration and admixture events of different populations like Native Amerindians or Indigenous, Europeans, and Africans. A genetic study found that

admixed individuals from five Latin American countries (Colombia, Ecuador, Peru, Chile, and Argentina) have European and Native American ancestry components (Homburger et al., 2015). It is hypothesized that European populations share a variety of at-risk genes, which may increase ALS susceptibility. Admixed populations have a wider variety and different combinations of at-risk genes that leads to a lower risk of developing the disease (Zaldivar et al., 2009). Here, we could bring up the idea that certain at-risk genes are intrinsically linked to European genetic background, therefore, the probability to inherit these variants is higher in these populations resulting in a higher risk to develop ALS. Nevertheless, the specific genetics variants and mechanisms behind the potential differences of risk are not yet determined.

Genetic epidemiology is essential to understand ALS and their potential determinants of risk. Evidence already showed that genetic variants associated to ALS display a different distribution between Caucasians and Asians. However, it remains unclear whether these mutations variability is related to a lower occurrence in Asia. Further studies are needed to assess this important issue.

V.2.2.3. Ancestral origin assessment: Limits and prospects

Epidemiological studies assessing the ancestral origin are limited by the heterogeneity of terminology to categorize populations. There are no international consensus on this topic for biomedical research. In the USA, populations are categorized into “races” (white, black/African American, and Asian) and ethnicity (Hispanic and non-Hispanic). In the UK, studies use the continent of origin (e.g. European or African origin), while it is almost unthinkable to categorize individuals and populations in most European countries. In Latin America, there is a diversity of definitions for ethnicity. For instance, ethnicity is self-reported based on cultural and traditional aspects in Ecuador, while it is self-reported according to the skin color in Cuba. Ethnic self-identification based in these aspects is subjective.

Accurate and objective methods need to be used to assess ancestral origin. Molecular signature of ancestral origin using genetic markers (haploid markers or autosomal markers)

could provide a reliable way of assessing genetic biogeographic ancestry. Biogeographic ancestry is a person's origin associated with the geographic location of presumed ancestors inferred by comparison with contemporary populations living in these locations (Royal et al., 2010). An objective genetic approach could clarify the role of ancestral origin on the risk of developing ALS. However, the use of genetic studies is an approach that is not without difficulties. *Royal et al*. raise four interesting questions about inferring genetic ancestry: "*What do we mean by ancestry? How exactly is ancestry measured? How far back can such ancestry be defined and by which genetic tools? How do we validate inferences about ancestry in genetic research?*" (Royal et al., 2010). Efforts must be intensified to settle these questions in order to move forward in the subject.

Ancestral origin and ethnicity are extremely serious matters that must follow strict ethical standards and respect the principles of autonomy, privacy, confidentiality and equity. It is necessary to point out the potential risk of promoting divisiveness, allowing perpetuation of stereotypes, and encouraging prejudice from classifying people (Azuonye, 1996; Fullilove, 1998). This means it is extremely important to combat these problems to promote the benefits behind documenting genetic background. It can be useful for reporting healthcare disparities, assessing differential drugs effects on different populations, developing pharmacogenetics and genetic epidemiology, and moving forward to personalized medicine.

V.2.3. Gene-environment interaction

Environmental factors have been largely studied as potential risk factors for ALS. There is no strong evidence to support a replicable association between a particular environmental factor and ALS. The assessment of exposure to environmental factors is problematic because of several reasons, for example the difficulty to accurately estimate exposure throughout life. It is even more challenging to establish a causal relationship. Most of the evidence is based on case-control studies and retrospective cohort studies, usually limited by small sample size. However, the role of environmental factors cannot be dismissed. If environmental factors play a role in the occurrence of ALS, it does not seem to be the only contributing factor. On the

other hand, genetic variants have been clearly established as a factor to develop ALS. A model of gene-environment interaction could be supported for ALS. Gene-environment interaction is defined as "a different effect of an environmental exposure on disease risk in persons with different genotypes," or, alternatively, "a different effect of a genotype on disease risk in persons with different environmental exposures." (Ottman, 1996).

Several authors support a complex interaction between genetic predisposition and environmental determinants over time (Al-Chalabi and Hardiman, 2013). The risk to develop ALS could be modeled by diverse interactions between genetics and environment. The risk may vary depending on specific genetic variants and exposures, which raise ideas about different models of risk. For instance, a specific exposure may be associated with higher risk only in patients carrying certain genetic variant. Another possibility is that certain genes account for most of the risk with only a partial contribution of environmental factors. In contrast, a complex combination of multiple exposures that accumulate over time could determine higher risk with a modest contribution of genetics.

It is indispensable to understand gene-environment interactions to clarify the determinants of risk in ALS. In order to move forward, international collaboration is essential to launch prospective observational population-based studies investigating these interactions considering different genetic backgrounds in several regions of the world with diverse environments.

V.2.4. Further interrogations and unanswered questions in ALS variability

Many questions remain to be answered on this subject. There is a need to provide reliable data on ALS epidemiology in certain geographic areas and populations to confirm if the difference of risk is factual. If this is indeed the case, it is important to study the role of genetics (e.g. ancestral background, mutations) and environmental factors. A key point is to improve our understanding of gene–environment interaction. It is also essential to gain further insights into how genetic variants and ancestral origin are linked to ALS occurrence and phenotypic

expression. We might also ask ourselves, what are the inheritance patterns of certain variants and their relation with ancestral origin? How penetrance and gene expression play a role in ALS heterogeneity? What is the contribution of epigenetic changes?

This body of knowledge will increase our scientific understanding of risk to develop the disease, physiopathological mechanisms and the relation between genetics and environment. These advances might have an impact for therapeutic innovation. Multidisciplinary collaboration is crucial to clarify these key questions.

V.3. Prospects: epidemiological and clinical research on ALS

A recent study to project the epidemiological trend of ALS showed that the global number of individuals with ALS across the world would increase significantly from 222,801 in 2015 to 376,674 in 2040. According to these projections, the largest increase will be in Africa with 116%, followed by Asia with 81% and South America with 73%. This is mainly due to aging of the population (Arthur et al., 2016). In spite of this, there is limited data about epidemiology indicators, genetics, clinical features, management and prognosis in these continents. Several initiatives are in progress and new ones will be launched to improve the understanding of ALS in Africa, Latin America and Asia.

V.3.1. Prospects in Africa

Research programs should prioritize its efforts to determine epidemiological data on ALS in Africa. There is a need for population-based studies to describe epidemiological indicators in the continent. Only one population-based study have been performed in Libya to assess ALS incidence more than thirty years ago (Radhakrishnan et al., 1986). We recognize the challenge to implement this type of studies in Africa, especially for rare neurodegenerative disorders. A strong international collaboration could be a key to target a specific African country to develop a well-conducted epidemiological study.

Clinical information is another important issue in ALS variability. At this stage, our multicenter hospital-based study provides a useful approach to better understand clinical characteristics and prognosis of patients with ALS in Africa. We are aware that the study is hospital-based, and as a consequence, exposed to selection bias. Evidently, the implementation of population-based studies is essential to limit potential biases for future studies. Although at this moment, it is not very feasible to perform this type of studies in Africa.

We found in the TROPALS study that the subcontinent and the disease-modifying treatment were independent factors for survival. In an attempt to further clarification in terms of access

to treatment and management of these patients, a study is under way in African hospitals of the TROPALS collaboration. A digital survey was sent to the hospitals centers to gather information with regards to: i) health professionals involved in the management of ALS patients with a strong emphasis on respiratory, nutritional and palliative management, ii) cost and availability of complementary exams, symptomatic treatments, neuroprotective treatments, and traditional treatments, iii) use of management guidelines. This approach will allow us to put into perspective our previous findings and describe the whole picture of ALS in Africa hospital centers.

Genetic research must take a more comprehensive approach towards ALS in African populations. Current initiatives are ongoing to provide the first insight of ALS genetics in South Africa (Nel et al., 2019). Further research is important to describe ALS genetic architecture and the role of ancestral background.

V.3.2. Prospects in Latin America

Few population-based studies have been performed to assess ALS in Latin America. Among these studies, epidemiological programs with a strong methodological approach have been carried out in Uruguay (Vázquez et al., 2008) and Cuba (Zaldivar et al., 2009). These studies offer a reliable start to clarify the picture of this fatal neurodegenerative disorder in the region.

A call for action has been made to bring data and promote research (Bucheli et al., 2013). The team INSERM UMR 1094 Tropical Neuroepidemiology develop a robust research initiative in Ecuador. The first step has been adopted to report ALS mortality rates and assess differences among ethnic groups. Further steps will be taken to deliver additional epidemiological and clinical data in this predominant admixed population. In close collaboration with Ecuadorian neurologists, a retrospective population-based study will be implemented to describe ALS incidence in the most populated cities of the country (Quito, Guayaquil and Cuenca). Multiple sources will be used to identify cases (private/public hospitals and clinics, neurologists, insurances and patients' associations). At the same time, a cross-sectional survey will take

place to determine the clinical practices for diagnosis and management of patients with ALS. In a later phase, incident cases will be included using a prospective design with the aim to describe clinical features, environmental factors and genetics (e.g. ancestral origin, mutations). This ambitious strategy will led us to focus our efforts in a specific Latin America country to gain a clear insight of ALS in a predominant admixed population.

Other interesting projects are taking place in the continent. Researchers continue to provide relevant ALS data from Cuba and Uruguay (e.g. clinical and genetic variants). Another great initiative is the development of a register of neurodegenerative disorders including ALS in the Guadeloupe Island, located in the Caribbean. It is important to promote and support these research programs in the region as the shining light that might clarify ALS heterogeneity in admixed population.

V.3.3. Prospects in Asia

Asia is a very interesting region for ALS research. Several projects have provided relevant scientific data in this continent, but it is clear that most of the information remains limited to some countries, mainly in East Asia (Japan and China). Most of epidemiological data available support a low incidence of ALS in Asia populations (Fong et al., 2005, 1996; Lai and Tseng, 2008; Okumura, 2003), while another study have found an incidence consistent with Western studies (Doi et al., 2014). Genetic studies have shown that the genetic architecture of ALS in Asian population differ from the European population (Zou et al., 2017). A certain degree of variability has also been described for clinical characteristics and prognosis between Asian and European patients (Marin et al., 2016b). Interestingly, atypical presentations of motor neuron disorders have been reported in Asian patients (e.g. Madras motor neuron disease (Meenakshisundaram et al., 1970) and ALS-parkinsonism-dementia complex (Kimura, 1961; Shindo et al., 2014)).

ALS research is important in this part of the world due to Asian population represents more than 50% of the world population and it is characterized by a diverse ethnic background

(Shahrizaila et al., 2016). Several research teams are working to furnish more information in Asian population with initiatives such as the Pan-Asian Consortium for Treatment and Research in ALS (http://pactals.org/). Scientific research needs to continue to provide a wide description of ALS across the continent.

V.3.4. General insights

It is clear that efforts must be made to the advancement of knowledge in ALS. We must therefore encourage and support projects with strong scientific standards (e.g. standard methodological framework, appropriate diagnosis criteria and data collection, population-based approach) in several regions of the world.

Epidemiological indicators are indispensable to begin the scientific understanding of this disorder. Further studies have to investigate the implications of genetic along with environmental and lifestyle factors in the ALS occurrence. Clinical features in various geographical regions and populations must be identified to facilitate management of disease heterogeneity in clinical practice and improve the methodologies of therapeutic trials. Survivorship pattern across different ethnic groups needs to be addressed with high-quality studies. These steps forward will only be possible within an international support based on multidisciplinary collaboration.

V.4. ALS research: An humanitarian research for a rare fatal disorders

It has been brought to my attention, rightly, that neurodegenerative disorders including ALS are not a priority research in LMICs countries. This subject is not a main concern in these areas due to the high impact of other diseases with public health relevance (e.g. communicable diseases). The terrible impact of communicable disorders is undeniable and international actions have taking place to combat these priority illnesses in these regions. Several public health programs have served to reduce the burden of communicable disorders around the globe. Nevertheless, it must not be forgotten that these countries are experiencing an epidemiological transition with a constant increase of non-communicable disorders such as neurodegenerative disorders. In consequence, these disorders deserve further attention and analysis.

Often when we talk about a rare disorder such as amyotrophic lateral sclerosis, one cause for criticism is the fact that a limited impact could be envisaged with only a minority group of patients. We need to be convinced that the efforts have been well worth for individuals and their families. I strongly believe that hard work needs to be made to fight against diseases for every human being in conditions of equality regardless of age, sex, ethnic group, birthplace, socioeconomic status or disease, etc. Therefore, it is crucial that all members of the community work together to improve patients' quality of life and care for rare disorders. ALS patients around the world need to have a voice to bring to the light their presence, their suffering, and their fight for life. Scientific community and public health authorities need to give them the attention they merit. I am honored to be part of the scientific and medical community placing their best efforts to understand ALS.

Conclusion

The current evidence supports ALS variability in terms of incidence, mortality and clinical features between geographic areas and populations. Further researches need to confirm this hypothesis with good quality studies following a standard methodological framework in different areas around the world.

The original studies presented in this dissertation contribute to reliable epidemiological and clinical data of ALS in Africa and Latin America. The clinical data in Africa showed certain specific characteristics of African cases and illustrated the important role of riluzole treatment for survival. The epidemiological data in Ecuador supports the hypothesis that ALS occurrence is lower in admixed populations from Latin America. These findings provide unique insights into disease variability in two underrepresented areas in ALS literature.

Improving our understanding of the ALS variation in different populations could lead to important advances in the knowledge of risk factors, including the influence of genetic factors, especially ancestral origin and gene-environmental interactions, which may provide important insights of the pathogenic mechanisms.

A multidisciplinary approach involving clinicians, epidemiologists, geneticists, and researchers is necessary to understand ALS variability. It is essential to provide a more objective assessment of potential risk factors and the range of disease phenotypes. Innovative research projects using prospective population-based approach need to be encouraged. Given the potential implications of ALS variability, it is required to strengthen collaboration and partnerships to develop international research projects.

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Appendices

Appendix 1. The TROPALS study questionnaire

SLA et syndromes apparentés en zone tropicale

CRF

Pays :
Nom Investigateur :
Numéro patient : |__|__|__|

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

IDENTIFICATION DU PATIENT

NUMERO DU PATIENT : |__|__|__|

NOM DU PATIENT :
|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
|__|__|__|__|__|__|__|__||__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

NOM DE JEUNE FILLE DU PATIENT :
|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
|__|__|__|__|__|__|__|__||__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

PRENOM DU PATIENT :
|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
|__|__|__|__|__|__|__|__||__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

ADRESSE DU PATIENT|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
|__|__|__|__|__|__|__|__||__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

VILLE|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

TELEPHONE DU PATIENT |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

SEXE : 0 ☐ Féminin 1 ☐ Masculin

DATE DE NAISSANCE : |__|__| |__|__| |__|__|__|__| jj/mm/aaaa

OU AGE ACTUEL si date de naissance non connue : |__|__|__| ans

PAYS DE NAISSANCE : ....

PRESENCE D'AIDANT : 0 ☐ Non 1 ☐ Oui

Lien de parenté avec l'aidant : 0 ☐ Non 1 ☐ Oui

➲ **Si Oui** lequel

1 - ☐ Epoux / conjoint

2 - ☐ Enfant

3- ☐ Autre

NOM DE L'AIDANT
|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
|__|__|__|__|__|__|__|__||__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

PRENOM DE L'AIDANT
|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
|__|__|__|__|__|__|__|__||__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

TELEPHONE DE L'AIDANT |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

LIEU DE VIE DE L'AIDANT ....
....

1

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

NIVEAU D'ETUDE DU PATIENT :

Le patient est il allé à l'école ☐$_0$ non ☐$_1$ oui
➲ Si Oui, indiquer le niveau scolaire

☐ - PRIMAIRE (ECOLE PRIMAIRE)

☐ - SECONDAIRE (COLLEGE, LYCEE)

☐ - SUPERIEUR (UNIVERSITE)

LE PATIENT EST IL RETRAITE ☐$_0$ non ☐$_1$ oui

PROFESSION (actuelle ou passée si patient retraité :
|__|__|__|__|__|__|__|__||__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

STATUT MARITAL : 0 ☐ Célibataire 1 ☐ Marié/en concubinage 2 ☐ Divorcé 3 ☐ Veuf

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

ANTECEDENTS

ANTECEDENTS PERSONNELS :

☐ **Ne connaît pas les antécédents personnels du patient**

☐ **Aucune pathologie pertinente à retenir**

Antécédents cardiovasculaires

☐ Insuffisance cardiaque
☐ Coronaropathie
☐ Troubles du rythme
☐ Malaises, vertiges, P d C, chutes
☐ Hypertension artérielle
☐ Accidents vasculaires cérébraux

Affections Neurologiques et Psychiatriques

☐ Poliomyélite
☐ Syndrome démentiel
☐ Comitialité focale et généralisée
☐ Syndrome parkinsonien
☐ Syndrome confusionnel aigu
☐ Troubles chroniques du comportement
☐ Etats dépressifs
☐ Etats anxieux
☐ Psychose
☐ Délires, hallucinations

☐ Maladie infectieuse ou complication de maladie infectieuse, touchant le Système Nerveux

➲ Si Maladie infectieuse ou complication de maladie infectieuse, touchant le Système Nerveux, préciser :

☐ Méningite
☐ Méningo-encéphalite
☐ Radiculite
☐ Myélite
☐ Neuropathie

Antécédents Traumatiques

☐ Traumatisme crânien
☐ Traumatisme rachidien

➲ **Si traumatisme crânien ou rachidien,** indiquer le niveau du traumatisme :.....
.....

Autres antécédents

☐ Infection par le VIH
☐ Diabète

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

☐ Syndromes infectieux

☐ Pathologies osseuses et articulaires

☐ Syndromes digestifs

☐ Affection hépatique, biliaire, pancréatique

☐ Dénutrition et troubles de l'hydratation

☐ Insuffisance rénale

☐ Cancer

➲ **Si cancer,** indiquer le niveau et le type de cancer :.....
.....

Autres pathologies, préciser : .....

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

ANTECEDENTS FAMILIAUX :

☐ **Ne connaît pas les antécédents familiaux du patient**

ANTECEDENTS FAMILIAUX :

Cas de SLA dans la famille ☐$_0$ **non** ☐$_1$ **oui**
➲ **Si Oui,** indiquer le lien de parenté
.....
.....

Cas de Maladie de Parkinson dans la famille ☐$_0$ **non** ☐$_1$ **oui**
➲ **Si Oui,** indiquer le lien de parenté
.....
.....

Cas de Démence dans la famille ☐$_0$ **non** ☐$_1$ **oui**
➲ **Si Oui,** indiquer le lien de parenté
.....
.....

Y a-t-il une consanguinité connue dans la famille ☐$_0$ **non** ☐$_1$ **oui**
➲ **Si Oui,** indiquer laquelle
.....
.....

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SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

DEBUT DE LA MALADIE

DATE DES PREMIERS SYMPTOMES : |__|__| |__|__|__|__| mm/aaaa

POIDS DE FORME AVANT LA MALADIE : |__|__|__| kg - (poids estimé 6 mois avant le début des symptômes)

SITE DES SYMPTOMES DE DEBUT :

0 ☐ Spinal
➲ **Si Spinal,** préciser :

☐ Atteinte Membre Supérieur

☐ Proximale
☐ Distale

☐ Unilatérale
☐ Bilatérale

☐ Atteinte Membre Inférieur

☐ Proximale
☐ Distale

☐ Unilatérale
☐ Bilatérale

1 ☐ Bulbaire
➲ **Si Bulbaire,** préciser :

☐ Troubles de la phonation
☐ Troubles de la déglutition

2 ☐ Respiratoire

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

DIAGNOSTIC

DATE DE DIAGNOSTIC |__|__| |__|__|__|__| mm/aaaa

POIDS LORS DU DIAGNOSTIC : |__|__|__|,|__| kg

TAILLE |__|__|__| cm

EXAMEN NEUROLOGIQUE

a) Signes d'atteinte du NEURONE MOTEUR PERIPHERIQUE ☐$_0$ non ☐$_1$ oui ☐ Ne Sait Pas

a.1 - Atrophie musculaire ☐$_0$ non ☐$_1$ oui
➲ Si atrophie, préciser le siège

- ☐ Langue
- ☐ Membre supérieur
- ☐ Membre inférieur

a.2 - Fasciculations ☐$_0$ non ☐$_1$ oui
➲ Si fasciculations, préciser le siège

- ☐ Langue
- ☐ Thorax
- ☐ Membre supérieur
- ☐ Membre inférieur

b) Signes d'atteinte du NEURONE MOTEUR CENTRAL ☐$_0$ non ☐$_1$ oui ☐ Ne Sait Pas

b.1 - Réflexe masséterin

- ☐ vif
- ☐ normal

b.2 - Réflexes ostéotendineux

Bicipital

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs
☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

Tricipital

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs
☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

Stylo-radial

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs
☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

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SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

Rotulien

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs
☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

Achilléen

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs
☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

b.3 - Réflexes cutanéoplantaires

Coté GAUCHE	**Coté DROIT**
☐ Flexion	☐ Flexion
☐ Extension	☐ Extension
☐ Indifférent	☐ Indifférent

b.4 – Signe de Hoffman

Coté GAUCHE	**Coté DROIT**
☐ Présent	☐ Présent
☐ Absent	☐ Absent

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

c) Signes ATYPIQUES ☐$_0$ non ☐$_1$ oui ☐ Ne Sait Pas
➲ Si signes atypiques, préciser

c.1 - Troubles cognitifs ☐$_0$ non ☐$_1$ oui
➲ Si troubles cognitifs, préciser

- ☐ Troubles de la mémoire
- ☐ Troubles du langage
- ☐ Troubles des fonctions exécutives

c.2 - Troubles sensitifs ☐$_0$ non ☐$_1$ oui
➲ Si troubles sensitifs, préciser

- ☐ Troubles subjectifs
  - ☐ Paresthésie
  - ☐ Dysesthésie
- ☐ Troubles objectifs

➲ Si troubles sensitifs objectifs, préciser le type et le siège : .....
.....

c.3 - Troubles dysautonomiques ☐$_0$ non ☐$_1$ oui
➲ Si troubles dysautonomiques, préciser

- ☐ Troubles digestifs
- ☐ Troubles sexuels
- ☐ Hypotension orthostatique

c.4 - Troubles vésicosphinctériens ☐$_0$ non ☐$_1$ oui

c.5 - Troubles extrapyramidaux ☐$_0$ non ☐$_1$ oui

c.6 - Troubles occulomoteurs ☐$_0$ non ☐$_1$ oui

c.7 – Autres signes atypiques ☐$_0$ non ☐$_1$ oui
➲ Si autres signes atypiques, préciser le type et le siège : .....
.....

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SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

d) SYMPTOMES PRESENTS A LA DATE DE DIAGNOSTIC

Symptômes ou signes cliniques	Non	Oui	Ne Sait Pas
Asthénie/fatigue	0 ☐	1 ☐	9 ☐
Crampes	0 ☐	1 ☐	9 ☐
Déficit moteur	0 ☐	1 ☐	9 ☐
Spasticité	0 ☐	1 ☐	9 ☐
Douleurs	0 ☐	1 ☐	9 ☐
Troubles de la parole	0 ☐	1 ☐	9 ☐
Troubles de la déglutition	0 ☐	1 ☐	9 ☐
Hypersalivation	0 ☐	1 ☐	9 ☐
Dyspnée	0 ☐	1 ☐	9 ☐
Anxiété/dépression	0 ☐	1 ☐	9 ☐
Laryngospasmes	0 ☐	1 ☐	9 ☐
Hypersécrétions bronchiques	0 ☐	1 ☐	9 ☐
Rires et pleurs spasmodiques	0 ☐	1 ☐	9 ☐
Troubles du sommeil	0 ☐	1 ☐	9 ☐

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

d) ALS Functional Rating Scale

1. Parole	4 – normale 3 – perturbations détectables 2 – intelligible avec répétition 1 – utilise occasionnellement une communication non verbale 0 – perte de la parole
2. Salivation	4 – normale 3 – hypersialorrhée discrète avec bavage nocturne 2 – hypersialorrhée modérée mais permanente 1 – hypersialorrhée gênante 0 – bavage continu nécessitant l'utilisation d'un mouchoir
3. Déglutition	4 – alimentation normale 3 – quelques fausses routes 2 – consistance des aliments modifiée 1 – suppléments alimentaires 0 – alimentation parentérale exclusive
4. Ecriture / Bricolage	4 – normal 3 – écriture : lente et imprécise mais compréhensible / bricolage : ralenti mais réalisable 2 – écriture : tous les mots ne sont pas compréhensibles / bricolage : ne parvient pas toujours à réaliser l'opération souhaitée 1 – écriture : tient un stylo mais incapable d'écrire / bricolage : tient un outil mais incapable d'utiliser l'outil 0 – incapable de tenir un stylo / outil
5. Hygiène	4 – normale 3 – autonome mais avec efficacité diminuée 2 – assistance occasionnelle ou substitution 1 – assistance d'une tierce personne requise 0 – assistance permanente totale
6a. Préparation des aliments et ou capacité de s'alimenter seul	4 – normale 3 – lente et maladroite mais seul 2 – aide occasionnelle pour couper les aliments 1 – aide systématique pour couper les aliments mais mange seul 0 – doit être nourri
6b. En cas de gastronomie	4 – utilisation normalement autonome de gastrostomie 3 – maladroit mais toutes les manipulations sont effectuées seul 2 – aide nécessaire pour la mise en place 1 – fourni une aide minime aux soignants 0– doit être nourri
7 Mobilisation au lit	4 – normale 3 – lenteur et maladresse mais autonome 2 – ajuste les draps avec difficulté 1 – peut bouger mais pas se retourner dans le lit 0 – dépendant
8 Marche	4 – normale 3 – difficultés de déambulation 2 – marche avec assistance 1 – mouvements sans déambulation 0 – pas de mouvement des jambes

SLA et syndromes apparentés en zones tropicales Pays : Numéro patient :	
9 Montée d'escaliers	4 – normale 3 – lente 2 – fatigue 1 – aide nécessaire 0 – impossible
10 Dyspnée	4 – absente 3 – à la marche 2 – dans une ou plus des situations suivantes : repas, toilette, habillage 1 – au repos, difficultés respiratoires en position assise ou allongée 0 – difficulté importante, envisage l'utilisation d'un appareil de ventilation mécanique
11 Orthopnée	4 – absente 3 – quelques difficultés pour dormir la nuit en raison d'un souffle court, n'utilise habituellement pas plus de 2 oreillers 2 – besoin de plus de 2 oreillers pour dormir 1 – ne peut dormir qu'assis 0 – ne peut pas dormir
12 Insuffisance respiratoire	4 – absente respiratoire 3 – utilisation intermittente d'une assistance ventilatoire 2 – utilisation continue d'une VNI la nuit 1 – utilisation continue d'une VNI jour et nuit 0 – ventilation mécanique invasive par intubation ou trachéotomie

Total |__|__| / 48

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

EXAMENS COMPLEMENTAIRES REALISES POUR CONFIRMER LE DIAGNOSTIC DE SLA

Electroneuromyographie réalisée ☐$_0$ non ☐$_1$ oui
➲ Si Oui, préciser date |__|__| |__|__| |__|__|__|__| jj/mm/aaaa
➲ Si Oui, préciser

Tracé neurogène
Membre supérieur Droit ☐$_0$ non ☐$_1$ oui
Membre supérieur Gauche ☐$_0$ non ☐$_1$ oui
Membre inférieur Droit ☐$_0$ non ☐$_1$ oui
Membre inférieur Gauche ☐$_0$ non ☐$_1$ oui
Bulbaire ☐$_0$ non ☐$_1$ oui

Vitesse de conduction nerveuse normale ☐$_0$ non ☐$_1$ oui

Examen Morphologique ENCEPHALIQUE réalisé ☐$_0$ non ☐$_1$ oui
➲ Si Oui lequel :

☐IRM
➲ Préciser date |__|__| |__|__| |__|__|__|__| jj/mm/aaaa
➲ Préciser résultat ☐$_0$ normal ☐$_1$ anormal
➲ Si anormal, préciser résultat : .....
.....

☐ Scanner
➲ Préciser date |__|__| |__|__| |__|__|__|__| jj/mm/aaaa
➲ Préciser résultat ☐$_0$ normal ☐$_1$ anormal
➲ Si anormal, préciser résultat : .....
.....

Examen Morphologique MEDULLAIRE réalisé ☐$_0$ non ☐$_1$ oui
➲ Si Oui lequel :

☐ Scanner
➲ Préciser date |__|__| |__|__| |__|__|__|__| jj/mm/aaaa
➲ Préciser résultat ☐$_0$ normal ☐$_1$ anormal
➲ Si anormal, préciser résultat : .....
.....

☐ IRM
➲ Préciser date |__|__| |__|__| |__|__|__|__| jj/mm/aaaa
➲ Préciser résultat ☐$_0$ normal ☐$_1$ anormal
➲ Si anormal, préciser résultat : .....
.....

☐ Radiographie du rachis cervical
➲ Préciser date |__|__| |__|__| |__|__|__|__| jj/mm/aaaa
➲ Préciser résultat ☐$_0$ normal ☐$_1$ anormal
➲ Si anormal, préciser résultat : .....
.....

EXAMEN Liquide Céphalo-Rachidien réalisé ☐$_0$ non ☐$_1$ oui
➲ Si oui, préciser date |__|__| |__|__| |__|__|__|__| jj/mm/aaaa
➲ Si oui, préciser résultat ☐$_0$ normal ☐$_1$ anormal

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

➲ Si anormal, préciser résultat : .....
.....

TRAITEMENTS

Le patient prend t-il un ou plusieurs traitements ? ☐$_0$ **non** ☐$_1$ **oui**

TRAITEMENT DE TYPE OCCIDENTAL ☐$_0$ **non** ☐$_1$ **oui**

➲ Si Oui lequel

.....
.....

Traitement mis en place par vous ou collègues de votre service/hôpital :

.....
.....

Traitement mis en place par un autre médecin (n'exerçant pas dans votre hôpital) :

.....
.....

TRAITEMENT TRADITIONNEL ☐$_0$ **non** ☐$_1$ **oui**

➲ Si Oui lequel

.....
.....

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

VISITE 1

DATE DE LA VISITE : |__|__| |__|__| |__|__|__|__| jj/mm/aaaa

POIDS : |__|__|__| kg

EXAMEN NEUROLOGIQUE

a) Signes d'atteinte du NEURONE MOTEUR PERIPHERIQUE ☐$_0$ non ☐$_1$ oui

a.1 - Atrophie musculaire ☐$_0$ non ☐$_1$ oui
➲ Si atrophie, préciser le siège

- ☐ Langue
- ☐ Membre supérieur
- ☐ Membre inférieur

a.2 - Fasciculations ☐$_0$ non ☐$_1$ oui
➲ Si fasciculations, préciser le siège

- ☐ Langue
- ☐ Thorax
- ☐ Membre supérieur
- ☐ Membre inférieur

b) Signes d'atteinte du NEURONE MOTEUR CENTRAL ☐$_0$ non ☐$_1$ oui

b.1 - Réflexe masséterin

- ☐ vif
- ☐ normal

b.2 - Réflexes ostéotendineux

Bicipital

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs
☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

Tricipital

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs
☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

Stylo-radial

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs
☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

Rotulien

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs

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SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

Achilléen

Coté GAUCHE	**Coté DROIT**
☐ vifs	☐ vifs
☐ diffusés	☐ diffusés
☐ normaux	☐ normaux
☐ abolis	☐ abolis

b.3 - Réflexes cutanéoplantaires

Coté GAUCHE	**Coté DROIT**
☐ Flexion	☐ Flexion
☐ Extension	☐ Extension
☐ Indifférent	☐ Indifférent

b.4 – Signe de Hoffman

Coté GAUCHE	**Coté DROIT**
☐ Présent	☐ Présent
☐ Absent	☐ Absent

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SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

c) Signes ATYPIQUES ☐0 non ☐1 oui

➲ Si signes atypiques, préciser

c.1 - Troubles cognitifs ☐0 non ☐1 oui

➲ Si troubles cognitifs, préciser

- ☐ Troubles de la mémoire
- ☐ Troubles du langage
- ☐ Troubles des fonctions exécutives

c.2 - Troubles sensitifs ☐0 non ☐1 oui

➲ Si troubles sensitifs, préciser

- ☐ Troubles subjectifs
  - ☐ Paresthésie
  - ☐ Dysesthésie
- ☐ Troubles objectifs

➲ Si troubles sensitifs objectifs, préciser le type et le siège : .....

.....

c.3 - Troubles dysautonomiques ☐0 non ☐1 oui

➲ Si troubles dysautonomiques, préciser

- ☐ Troubles digestifs
- ☐ Troubles sexuels
- ☐ Hypotension orthostatique

c.4 - Troubles vésicosphinctériens ☐0 non ☐1 oui

c.5 - Troubles extrapyramidaux ☐0 non ☐1 oui

c.6 - Troubles occulomoteurs ☐0 non ☐1 oui

c.7 – Autres signes atypiques ☐0 non ☐1 oui

➲ Si autres signes atypiques, préciser le type et le siège : .....

.....

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SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

d) SYMPTOMES PRESENTS LORS DE LA VISITE

Symptômes ou signes cliniques	Non	Oui
Asthénie/fatigue	0 ☐	1 ☐
Crampes	0 ☐	1 ☐
Déficit moteur	0 ☐	1 ☐
Spasticité	0 ☐	1 ☐
Douleurs	0 ☐	1 ☐
Troubles de la parole	0 ☐	1 ☐
Troubles de la déglutition	0 ☐	1 ☐
Hypersalivation	0 ☐	1 ☐
Dyspnée	0 ☐	1 ☐
Anxiété/dépression	0 ☐	1 ☐
Laryngospasmes	0 ☐	1 ☐
Hypersécrétions bronchiques	0 ☐	1 ☐
Rires et pleurs spasmodiques	0 ☐	1 ☐
Troubles du sommeil	0 ☐	1 ☐

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SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

d) ALS Functional Rating Scale

6. Parole	4 – normale 3 – perturbations détectables 2 – intelligible avec répétition 1 – utilise occasionnellement une communication non verbale 0 – perte de la parole
7. Salivation	4 – normale 3 – hypersialorrhée discrète avec bavage nocturne 2 – hypersialorrhée modérée mais permanente 1 – hypersialorrhée gênante 0 – bavage continu nécessitant l'utilisation d'un mouchoir
8. Déglutition	4 – alimentation normale 3 – quelques fausses routes 2 – consistance des aliments modifiée 1 – suppléments alimentaires 0 – alimentation parentérale exclusive
9. Ecriture / Bricolage	4 – normal 3 – écriture : lente et imprécise mais compréhensible / bricolage : ralenti mais réalisable 2 – écriture : tous les mots ne sont pas compréhensibles / bricolage : ne parvient pas toujours à réaliser l'opération souhaitée 1 – écriture : tient un stylo mais incapable d'écrire / bricolage : tient un outil mais incapable d'utiliser l'outil 0 – incapable de tenir un stylo / outil
10. Hygiène	4 – normale 3 – autonome mais avec efficacité diminuée 2 – assistance occasionnelle ou substitution 1 – assistance d'une tierce personne requise 0 – assistance permanente totale
6a. Préparation des aliments et ou capacité de s'alimenter seul	4 – normale 3 – lente et maladroite mais seul 2 – aide occasionnelle pour couper les aliments 1 – aide systématique pour couper les aliments mais mange seul 0 – doit être nourri
6b. En cas de gastronomie	4 – utilisation normalement autonome de gastrostomie 3 – maladroit mais toutes les manipulations sont effectuées seul 2– aide nécessaire pour la mise en place 1 – fourni une aide minime aux soignants 0– doit être nourri
7 Mobilisation au lit	4 – normale 3 – lenteur et maladresse mais autonome 2 – ajuste les draps avec difficulté 1 – peut bouger mais pas se retourner dans le lit 0 – dépendant
8 Marche	4 – normale 3 – difficultés de déambulation 2 – marche avec assistance 1 – mouvements sans déambulation 0 – pas de mouvement des jambes

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SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

9 Montée d'escaliers	4 – normale 3 – lente 2 – fatigue 1 – aide nécessaire 0 – impossible
10 Dyspnée	4 – absente 3 – à la marche 2 – dans une ou plus des situations suivantes : repas, toilette, habillage 1 – au repos, difficultés respiratoires en position assise ou allongée 0 – difficulté importante, envisage l'utilisation d'un appareil de ventilation mécanique
11 Orthopnée	4 – absente 3 – quelques difficultés pour dormir la nuit en raison d'un souffle court, n'utilise habituellement pas plus de 2 oreillers 2 – besoin de plus de 2 oreillers pour dormir 1 – ne peut dormir qu'assis 0 – ne peut pas dormir
12 Insuffisance respiratoire	4 – absente respiratoire 3 – utilisation intermittente d'une assistance ventilatoire 2 – utilisation continue d'une VNI la nuit 1 – utilisation continue d'une VNI jour et nuit 0 – ventilation mécanique invasive par intubation ou trachéotomie

Total |__|__| / 48

SLA et syndromes apparentés en zones tropicales

Pays :

Numéro patient :

TRAITEMENTS

Le ou les traitement(s) du patient ont-ils été modifiés ? ☐$_0$ **non** ☐$_1$ **oui**

Si oui, mentionnez le traitement actuel du patient :

TRAITEMENT DE TYPE OCCIDENTAL ☐$_0$ **non** ☐$_1$ **oui**

➲ Si Oui lequel

.....

.....

Traitement mis en place par vous ou collègues de votre service/hôpital :

.....

.....

Traitement mis en place par un autre médecin (n'exerçant pas dans votre hôpital) :

.....

.....

TRAITEMENT TRADITIONNEL ☐$_0$ **non** ☐$_1$ **oui**

➲ Si Oui lequel

.....

.....

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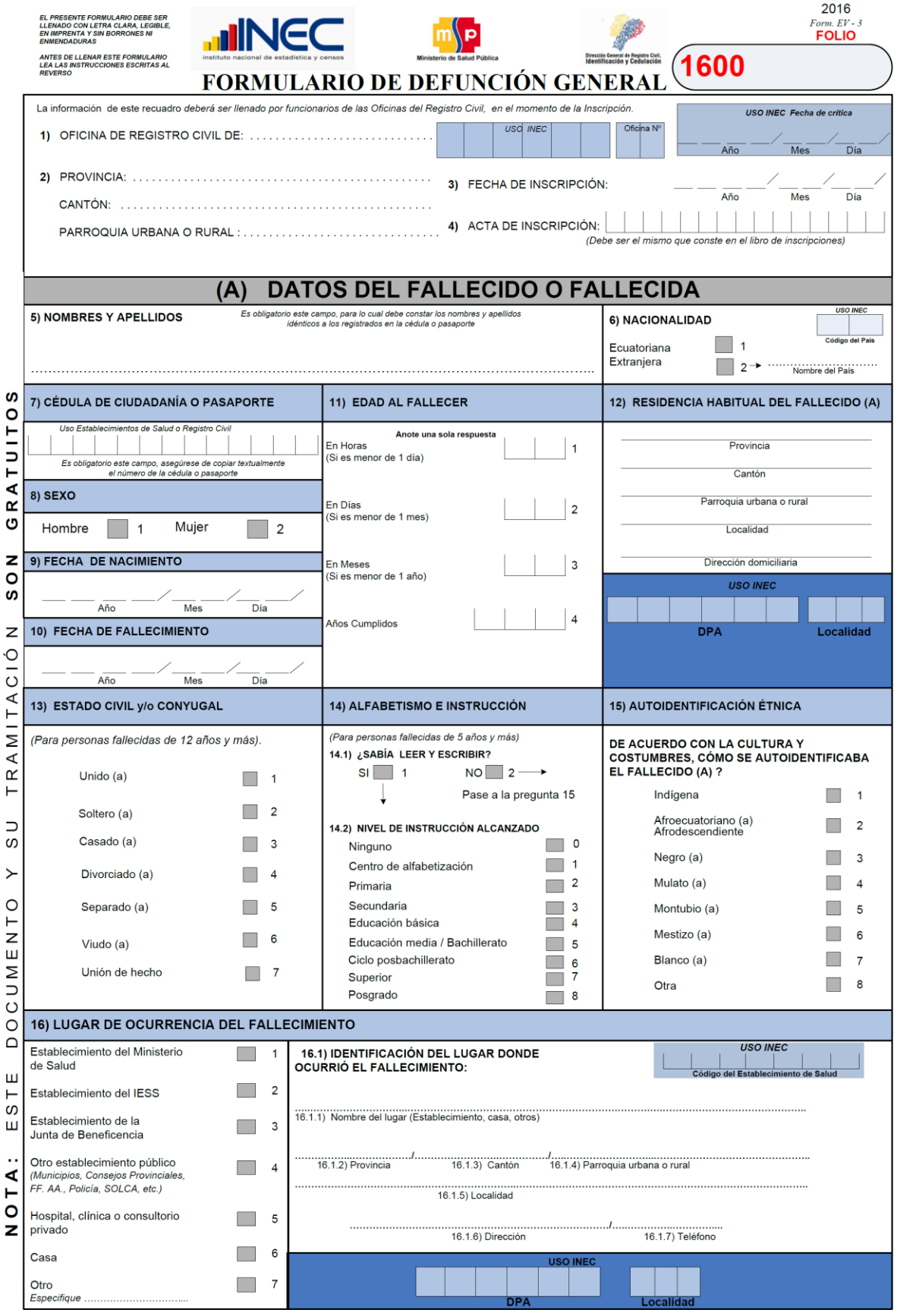
Appendix 2. Death certificate in Ecuador



EL PRESENTE FORMULARIO DEBE SER LLENADO CON LETRA CLARA, LEGIBLE, EN IMPRENTA Y SIN BORRONES NI ENMENDADURAS

ANTES DE LLENAR ESTE FORMULARIO LEA LAS INSTRUCCIONES ESCRITAS AL REVERSO

instituto nacional de estadística y censos

Ministerio de Salud Pública

Dirección General de Registro Civil, Identificación y Cedulación

2016

Form. EV - 3

FOLIO 1600

FORMULARIO DE DEFUNCIÓN GENERAL

La información de este recuadro deberá ser llenado por funcionarios de las Oficinas del Registro Civil, en el momento de la Inscripción.

1) OFICINA DE REGISTRO CIVIL DE: ..... USO INEC ..... Oficina Nº

USO INEC Fecha de crítica: Año / Mes / Día

2) PROVINCIA: .....

CANTÓN: .....

PARROQUIA URBANA O RURAL : .....

3) FECHA DE INSCRIPCIÓN: Año / Mes / Día

4) ACTA DE INSCRIPCIÓN: (Debe ser el mismo que conste en el libro de inscripciones)

(A) DATOS DEL FALLECIDO O FALLECIDA

5) NOMBRES Y APELLIDOS — Es obligatorio este campo, para lo cual debe constar los nombres y apellidos idénticos a los registrados en la cédula o pasaporte

.....

6) NACIONALIDAD — USO INEC: Código del País

Ecuatoriana 1

Extranjera 2 → Nombre del País

7) CÉDULA DE CIUDADANÍA O PASAPORTE

Uso Establecimientos de Salud o Registro Civil

Es obligatorio este campo, asegúrese de copiar textualmente el número de la cédula o pasaporte

8) SEXO

Hombre 1 Mujer 2

9) FECHA DE NACIMIENTO

Año / Mes / Día

10) FECHA DE FALLECIMIENTO

Año / Mes / Día

11) EDAD AL FALLECER

Anote una sola respuesta

En Horas (Si es menor de 1 día) 1

En Días (Si es menor de 1 mes) 2

En Meses (Si es menor de 1 año) 3

Años Cumplidos 4

12) RESIDENCIA HABITUAL DEL FALLECIDO (A)

Provincia

Cantón

Parroquia urbana o rural

Localidad

Dirección domiciliaria

USO INEC: DPA / Localidad

13) ESTADO CIVIL y/o CONYUGAL

(Para personas fallecidas de 12 años y más).

Unido (a) 1

Soltero (a) 2

Casado (a) 3

Divorciado (a) 4

Separado (a) 5

Viudo (a) 6

Unión de hecho 7

14) ALFABETISMO E INSTRUCCIÓN

(Para personas fallecidas de 5 años y más)

14.1) ¿SABÍA LEER Y ESCRIBIR?

SI 1 NO 2 → Pase a la pregunta 15

14.2) NIVEL DE INSTRUCCIÓN ALCANZADO

Ninguno 0

Centro de alfabetización 1

Primaria 2

Secundaria 3

Educación básica 4

Educación media / Bachillerato 5

Ciclo posbachillerato 6

Superior 7

Posgrado 8

15) AUTOIDENTIFICACIÓN ÉTNICA

DE ACUERDO CON LA CULTURA Y COSTUMBRES, CÓMO SE AUTOIDENTIFICABA EL FALLECIDO (A) ?

Indígena 1

Afroecuatoriano (a) Afrodescendiente 2

Negro (a) 3

Mulato (a) 4

Montubio (a) 5

Mestizo (a) 6

Blanco (a) 7

Otra 8

16) LUGAR DE OCURRENCIA DEL FALLECIMIENTO

Establecimiento del Ministerio de Salud 1

Establecimiento del IESS 2

Establecimiento de la Junta de Beneficencia 3

Otro establecimiento público (Municipios, Consejos Provinciales, FF. AA., Policía, SOLCA, etc.) 4

Hospital, clínica o consultorio privado 5

Casa 6

Otro 7 Especifique .....

16.1) IDENTIFICACIÓN DEL LUGAR DONDE OCURRIÓ EL FALLECIMIENTO:

USO INEC: Código del Establecimiento de Salud

16.1.1) Nombre del lugar (Establecimiento, casa, otros)

16.1.2) Provincia / 16.1.3) Cantón / 16.1.4) Parroquia urbana o rural

16.1.5) Localidad

16.1.6) Dirección / 16.1.7) Teléfono

USO INEC: DPA / Localidad

NOTA: ESTE DOCUMENTO Y SU TRAMITACIÓN SON GRATUITOS

(B) CERTIFICADO MÉDICO DE DEFUNCIÓN

El presente certificado debe ser llenado con letra clara, legible y en imprenta

17) CAUSAS DE LA DEFUNCIÓN CERTIFICADAS POR MÉDICO: ***Anote sólo una causa por línea.***

		Tiempo aproximado entre el comienzo de cada causa y la muerte (en minutos, horas, días, semanas, meses o años)	Código CIE – 10 *USO INEC*
PARTE I Enfermedad o estado fisiopatológico que produjo la muerte directamente.	a)		
	debido a (o como consecuencia de)		
CAUSAS ANTECEDENTES: *Estados morbosos, si existiera alguno, que produjeron la causa arriba consignada, mencionándose en último lugar, la CAUSA BÁSICA o fundamental.*	b)		
	debido a (o como consecuencia de)		
	c)		
	debido a (o como consecuencia de)		
	d)		
PARTE II OTROS ESTADOS PATOLÓGICOS SIGNIFICATIVOS, que contribuyeron a la muerte, pero no relacionados con la enfermedad o estado morboso que la condujo.	.....		
	.....		

USO INEC
Código Causa Básica CIE-10

18) MORTALIDAD MATERNA

En el caso de que la defunción corresponda a una MUJER en edad fértil (de 10 a 49 años),

Marque el periodo en el que ocurrió la muerte:
(Solo marcar una opción)

- Embarazo ☐ 1
- Parto ☐ 2
- Puerperio (hasta 42 días) ☐ 3
- Entre 43 días y 11 meses después del parto o aborto ☐ 4
- No estuvo embarazada durante los 11 meses previo a la muerte ☐ 5

19) MUERTES ACCIDENTALES Y/O VIOLENTAS

(Esta información es valiosa para facilitar la determinación del código CIE-10 específico).

19.1) Si la muerte fue accidental o violenta, Señale el tipo presuntivo:
(solo marcar una opción)

- Accidentes de transporte ☐ 1
- Otros accidentes ☐ 2
- Homicidio ☐ 3
- Suicidio ☐ 4

19.2) Lugar donde ocurrió el hecho.

- Vivienda ☐ 0
- Institución residencial ☐ 1
- Escuela u oficina pública ☐ 2
- Áreas deportivas ☐ 3
- Calle o carretera (vía pública) ☐ 4
- Área comercial o de servicios ☐ 5
- Áreas industriales (taller, fábrica u obra) ☐ 6
- Área Agrícola (hacienda, rancho, granja, terreno de sembrío) ☐ 7
- Otro ☐ 8
- Se ignora ☐ 9

Descripción: *Describa brevemente la situación, circunstancia o motivos en que se produjo el hecho accidental y/o violento.*

.....

.....

.....

20) SE REALIZÓ NECROPSIA / AUTOPSIA? SÍ ☐ 1 NO ☐ 2

(C) PARA MUERTES SIN CERTIFICACIÓN MÉDICA

21) CAUSA PROBABLE DE LA MUERTE: .....

Síntomas: .....

Informantes o Testigos

Nombres y apellidos	Firma	Dirección	Teléfono
.....	.....	.....	.....
.....	.....	.....	.....

(D) DATOS DE LA INSCRIPCIÓN DE LA DEFUNCIÓN

22) CERTIFICADO POR:

- Médico Tratante ☐ 1
- Médico no Tratante ☐ 2
- Médico Legista ☐ 3
- Autoridad Civil o de Policía ☐ 4
- Funcionario del Registro Civil ☐ 5

22.1) IDENTIFICACIÓN DE QUIEN CERTIFICA LA DEFUNCIÓN:

..... / .....
Nombres y apellidos — No. cédula de ciudadanía/pasaporte

..... / .....
Dirección de consultorio o domicilio — Teléfono

.....
Firma y sello

23) Nombres y apellidos de quien solicita la inscripción:

.....

Edad ..... años cumplidos

24) RELACIÓN DE PARENTESCO CON EL FALLECIDO/A

- Cónyuge ☐ 1
- Hijo (a) ☐ 2
- Yerno o Nuera ☐ 3
- Nieto (a) ☐ 4
- Padres o Suegros ☐ 5
- Otros parientes ☐ 6
- Otros no parientes ☐ 7

Observaciones: *Este espacio está destinado para que se pueda anotar cualquier comentario que sirva para clarificar algún dato o circunstancia sobre la defunción ocurrida.*

.....

.....

USO INEC
Código crítico - codificador

Appendix 3. The number of ALS cases and population at risk in Ecuador by age and sex from 1900 to 2016.

ALS deaths in Ecuador by age and sex from 1990 to 2016: ALS mortality study in Ecuador

Age	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	≥80	Total
Sex																		
Male	0	0	0	3	2	0	5	13	21	24	43	43	41	44	25	28	17	309
Female	0	0	0	0	1	4	1	7	13	20	25	35	32	30	32	28	33	261
Total	0	0	0	3	3	4	6	20	34	44	68	78	73	74	57	56	50	570

Population at risk in Ecuador by age and sex from 1990 to 2016: ALS mortality study in Ecuador

Age	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	≥80	Total
Sex																		
Male	20,206,198	19,966,823	19,371,725	18,006,041	16,331,286	14,429,271	12,721,301	11,083,730	9,538,229	7,958,410	6,652,880	5,345,413	4,254,881	3,313,022	2,475,784	1,713,122	1,761,679	175,129,795
Female	19,410,380	19,250,877	18,715,173	17,620,337	16,210,398	14,503,553	12,910,835	11,400,180	9,825,440	8,236,478	6,904,685	5,579,909	4,496,786	3,579,060	2,746,653	1,969,881	2,185,068	175,545,693
Total	39,616,578	39,217,700	38,086,898	35,626,378	32,541,684	28,932,824	25,632,136	22,483,910	19,363,669	16,194,888	13,557,565	10,925,322	8,751,667	6,892,082	5,222,437	3,683,003	3,946,747	350,675,488

Appendix 4. The number of ALS cases and population at risk (INEC census 2010) in Ecuador by ethnic groups, sex and age

ALS cases in Ecuador by age, sex and ethnic group from 2009 to 2016: ALS mortality study in Ecuador

Age	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-100	>100	Total
Ethnic group																						
Admixed Male	0	0	0	0	0	0	3	5	10	9	16	18	19	25	10	13	6	2	1	0	0	137
Admixed Female	0	0	0	0	1	1	0	3	7	11	15	16	15	12	16	15	14	5	2	2	0	135
Admixed Total	0	0	0	0	1	1	3	8	17	20	31	34	34	37	26	28	20	7	3	2	0	272
White Male	0	0	0	0	0	0	0	1	0	1	0	0	1	2	3	0	0	0	0	0	0	8
White Female	0	0	0	0	0	0	0	1	0	1	1	1	1	1	1	2	2	1	0	0	0	12
White Total	0	0	0	0	0	0	0	2	0	2	1	1	2	3	4	2	2	1	0	0	0	20
Black Male	0	0	0	0	0	0	0	0	0	1	2	0	0	1	0	1	0	1	0	0	0	6
Black Female	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Black Total	0	0	0	0	0	0	0	0	0	2	2	0	0	1	0	1	0	1	0	0	0	7
Others Male	0	0	0	0	0	0	0	0	1	0	0	2	0	0	0	0	0	1	0	0	0	4
Others Female	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	1	0	0	0	0	0	4
Others Total	0	0	0	0	0	0	0	0	1	0	0	2	1	2	0	1	0	1	0	0	0	8
Total Male	0	0	0	0	0	0	3	6	11	11	18	20	20	28	13	14	6	4	1	0	0	155
Total Female	0	0	0	0	1	1	0	4	7	13	16	17	17	15	17	18	16	6	2	2	0	152
Total	0	0	0	0	1	1	3	10	18	24	34	37	37	43	30	32	22	10	3	2	0	307

Ecuador population by ethnic groups, age and sex in 2010 Census

Age	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-100	>100	Total
Ethnic group																						
Admixed Male	576,506	602,321	617,379	564,939	504,649	462,361	413,958	365,110	322,527	297,077	241,792	204,060	157,631	124,558	92,074	62,874	42,642	21,912	8,730	2,607	551	5,686,258
Admixed Female	554,710	583,247	594,772	557,592	519,338	488,189	439,016	390,781	342,837	313,177	252,969	212,238	162,618	131,396	97,464	67,959	49,193	27,185	12,110	3,993	985	5,801,769
Admixed Total	1,131,216	1,185,568	1,212,151	1,122,531	1,023,987	950,550	852,974	755,891	665,364	610,254	494,761	416,298	320,249	255,954	189,538	130,833	91,835	49,097	20,840	6,600	1,536	11,488,027
White Male	47,513	46,266	40,745	37,834	34,449	32,433	30,269	27,854	24,840	23,292	19,864	17,152	14,266	12,143	9,589	6,687	4,727	2,475	922	264	59	433,643
White Female	46,695	45,333	39,812	38,244	33,449	31,905	30,938	29,009	25,886	24,996	21,629	18,970	16,225	14,056	11,103	8,363	6,370	3,582	1,566	492	117	448,740
White Total	94,208	91,599	80,557	76,078	67,898	64,338	61,207	56,863	50,726	48,288	41,493	36,122	30,491	26,199	20,692	15,050	11,097	6,057	2,488	756	176	882,383
Black Male	55,070	57,934	59,309	53,905	52,961	49,859	42,464	34,320	27,948	24,436	19,478	15,910	11,366	8,943	6,475	3,835	2,508	1,089	443	149	45	528,447
Black Female	53,373	56,608	57,752	52,950	50,888	48,841	40,723	32,699	26,702	23,226	18,493	15,452	11,258	9,038	6,341	3,940	2,592	1,322	621	218	75	513,112
Black Total	108,443	114,542	117,061	106,855	103,849	98,700	83,187	67,019	54,650	47,662	37,971	31,362	22,624	17,981	12,816	7,775	5,100	2,411	1,064	367	120	1,041,559
Others Male	65,216	67,369	65,544	56,870	47,081	42,297	34,200	28,918	23,915	21,643	17,594	15,984	13,151	11,160	8,065	5,206	3,280	1,258	428	113	43	529,335
Others Female	63,194	67,728	64,029	57,203	49,311	44,679	35,721	30,035	24,347	22,294	18,313	16,127	14,244	12,523	8,980	6,354	4,240	1,912	680	203	78	542,195
Others Total	128,410	135,097	129,573	114,073	96,392	86,976	69,921	58,953	48,262	43,937	35,907	32,111	27,395	23,683	17,045	11,560	7,520	3,170	1,108	316	121	1,071,530
Male population	744,305	773,890	782,977	713,548	639,140	586,950	520,891	456,202	399,230	366,448	298,728	253,106	196,414	156,804	116,203	78,602	53,157	26,734	10,523	3,133	698	7,177,683
Female population	717,972	752,916	756,365	705,989	652,986	613,614	546,398	482,524	419,772	383,693	311,404	262,787	204,345	167,013	123,888	86,616	62,395	34,001	14,977	4,906	1,255	7,305,816
Total Population	1,462,277	1,526,806	1,539,342	1,419,537	1,292,126	1,200,564	1,067,289	938,726	819,002	750,141	610,132	515,893	400,759	323,817	240,091	165,218	115,552	60,735	25,500	8,039	1,953	14,483,499

Epidemiological and clinical variability of amyotrophic lateral sclerosis between geographic areas and populations: focus on Africa and Latin America.

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder with an invariable fatal outcome. Current evidence supports ALS variability in terms of incidence, mortality and clinical features between geographic areas and populations. This dissertation offers an updated review of ALS heterogeneity along with two original epidemiological and clinical studies in Africa and Latin America. First, a multicenter hospital-based study in eight African countries that described and compared the sociodemographic characteristics, clinical features, treatments, prognoses and survival times of patients with ALS. Certain specific characteristics were different in African cases compared to Western cases like higher proportion of male patients, younger age at onset, lower proportion of bulbar onset and shorter survival than expected. Subcontinental location and riluzole treatment are independently associated with survival. Second, a population-based study estimated ALS mortality rates in Ecuador, a predominant admixed population. The findings support a lower ALS occurrence in admixed populations from Latin America compared to European and Northern American populations. Standardized mortality rates were compared among ethnic groups with significant differences between admixed and other ethnic groups (Indigenous, Asians and Arabs). This work provides original and reliable data to improve our knowledge of ALS in Africa and Latin America. An international and multidisciplinary collaboration is crucial to understand ALS variability in different populations.

Keywords: Amyotrophic lateral sclerosis, variability, epidemiology, clinical features, methodology, Africa, Latin America, Ecuador.

Variabilité épidémiologique et clinique de la sclérose latérale amyotrophique entre les zones géographiques et les populations : focus sur l'Afrique et l'Amérique latine

La sclérose latérale amyotrophique (SLA) est une maladie neurodégénérative fatale. De récents travaux suggèrent une variabilité en termes d'incidence, de mortalité et de caractéristiques cliniques selon les régions géographiques et les populations. Cette thèse offre une mise à jour sur l'hétérogénéité de la SLA, accompagnée de deux études épidémiologiques et cliniques originales en Afrique et en Amérique latine. La première est une étude hospitalière multicentrique dans huit pays africains qui décrit et compare les caractéristiques sociodémographiques et cliniques, les traitements, les facteurs pronostics et la durée de survie chez les patients atteints de la SLA. Certaines caractéristiques sont plus spécifiques aux cas africains par rapport aux occidentaux, telles qu'une proportion plus élevée de patients masculins, un âge de début plus jeune, une proportion plus faible de début bulbaire et une survie plus courte que prévue. Le sous-continent et le traitement par riluzole sont des facteurs indépendamment liés à la survie du patient. La seconde étude en population générale a estimé les taux de mortalité en Équateur, pays composé d'une population majoritairement métisse. Ces résultats soutiennent l'hypothèse d'une survenue plus faible de cas SLA dans les populations métisses d'Amérique latine comparée aux populations caucasiennes d'Europe et d'Amérique du Nord. Les taux de mortalité standardisés ont été comparés entre les groupes ethniques, montrant des différences significatives entre le groupe métisse et le groupe comprenant les autres ethnies (indigènes, asiatiques et arabes). Ce travail fournit des données originales et fiables pour améliorer nos connaissances sur la SLA en Afrique et en Amérique latine. Une collaboration internationale et multidisciplinaire est cruciale pour comprendre la variabilité de la SLA dans différentes populations.

Mots-clés : Sclérose latérale amyotrophique, variabilité, épidémiologie, caractéristiques cliniques, méthodologie, Afrique, Amérique latine, Équateur.