



**HAL**  
open science

## Care pathway heterogeneity in Amyotrophic Lateral Sclerosis: effects of gender, age and onset

Marc Dibling, Juliette Ortholand, François Salachas, Adèle Hesters, Sophie Tezenas Du Montcel

### ► To cite this version:

Marc Dibling, Juliette Ortholand, François Salachas, Adèle Hesters, Sophie Tezenas Du Montcel. Care pathway heterogeneity in Amyotrophic Lateral Sclerosis: effects of gender, age and onset. *Neuroepidemiology*, 2024, pp.1-22. <10.1159/000542300>. <hal-05133639>

**HAL Id: hal-05133639**

**<https://hal.science/hal-05133639v1>**

Submitted on 27 Jun 2025

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

# Care pathway heterogeneity in Amyotrophic Lateral Sclerosis: effects of gender, age and onset.

Short title: Care pathway heterogeneity in Amyotrophic Lateral Sclerosis

Authors: Marc Dibling (1), Juliette Ortholand (1), François Salachas (2), Adèle Hesters (2), Sophie Tezenas Du Montcel (1)

(1) ARAMIS, Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM, CNRS, Inria, Inserm, AP-HP, Hôpital de la Pitie Salpêtrière

(2) Centre de Référence Maladies Rares SLA Ile de France, Département de Neurologie, GHU Pitié-Salpêtrière

Corresponding author: Sophie Tezenas du Montcel [sophie.tezenas@aphp.fr](mailto:sophie.tezenas@aphp.fr)

## ABSTRACT

**Background and objectives:** Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive motor neuron degeneration resulting in loss of muscle function. Care management is restricted to symptomatic and palliative strategies, while clinical manifestations are heterogeneous. However, assessing the timing and benefits of ALS major clinical interventions remains challenging, with varying and nonspecific time-to-events estimates reported in the literature. Consequently, we proposed a retrospective cohort study leveraging healthcare system data to investigate ALS patients care pathway stratified by gender, age class and onset site to describe strategies diversity and temporality.

**Methods:** We developed an algorithm to identify incident ALS patients in the French hospitalization registry and assessed its quality through comparison with literature. We described 7 states, encompassing patient status regarding clinical intervention history, considered 15 transitions and stratified the analysis depending on 12 different patient profiles, defined according to gender, the presence of symptoms indicative of disease onset site and age class, to model profile-specific care pathway trajectories. Alongside analysis of median time before transition, we compared acceleration factors resulting from Accelerated Failure Time (AFT) and time-inhomogeneous models.

**Results:** We identified 21,153 incident patients with ALS between 2013 and 2022 with a mean age of  $67.7 \pm 13.1$  years at time of in-registry detection, male/female and spinal/bulbar ratios of 1.2 and 1.9, respectively. Non-invasive ventilation (NIV), gastrostomy, tracheostomy or death at hospital was recorded for 55.24% of the study population. We identified significant variations in utilization based on gender, age class, and onset site. Notably, older age and bulbar onset site

accelerated gastrostomy use and spinal onset site was associated with delayed NIV initiation while tracheostomy, mainly considered for younger patients (<64 years), is rarely indicated in ALS care management. Alongside investigation of time-to-event speed, we report extensively the patient profile-specific estimated median delay before clinical event start.

Conclusion: Leveraging real-world data from hospital registries provides a large sample size to investigate low prevalence diseases. In conjunction with multi-state models such data enables a comprehensive analysis of care pathways which revealed variations in ALS management strategies based on patient profiles. By identifying these disparities, our study contributes to enhancing the foreseeability of support strategies for ALS patients.

*Keywords: Amyotrophic Lateral Sclerosis (ALS), care pathway, multi-state analysis, hospitalization registry, Population-based studies.*

## **INTRODUCTION**

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease which affects upper and lower motor neurons, resulting in gradual motor weakness and affecting basic and vital needs such as breathing, mobility and swallowing. Median survival ranges from 20 to 48 months after first onset symptoms, mainly due to respiratory failure, with a fraction of patients surviving over 10 years<sup>1-3</sup>. Incidence increases at the age of 40, is maximal for patients aged 60 to 70 years old<sup>4</sup> and is expected to rise due to ageing of the population<sup>5</sup>.

Different disease forms have been described depending on family history of the disease and the somatic region of involvement first affected at disease onset: spinal and bulbar onset sites. Bulbar onset site affects 30% of patients and is characterized by affliction of muscles involved in speech, chewing, and swallowing, at the early stages of the disease. Signs of muscle atrophy and weakness in the torso and limbs at disease onset are characteristic of spinal onset, with 85% of patients presenting this form exhibiting bulbar changes over time<sup>6,7</sup>. Alongside variable onset site and mix of upper and lower motor neurons involvement, genetic mutations, sexual dimorphism and age also influence disease progression<sup>8,9</sup> and lead to heterogeneous clinical manifestations.

Pathophysiology and etiology research suggests the involvement of multiple underlying complex molecular pathways and remains under investigation. Incurability persists with drug development limited to Riluzole, the only treatment on the market in Europe which has shown significant survival improvement of 3 months on average<sup>10,11</sup>. Care management of ALS requires a multidisciplinary approach<sup>12-14</sup> but remains restricted to palliative strategies which are therefore paramount to investigate. They mainly involve three major life-support clinical

procedures, all individually associated with acceptable Quality Of Life score<sup>15-19</sup>. Non-Invasive Ventilation (NIV) or tracheostomy provide ventilatory support. Tracheostomy is an invasive procedure which might be considered for critically sick patients in need of prolonged continuous ventilation. On the other hand, NIV is non invasive, less secure, more flexible and considered as the reference treatment to alleviate respiratory failure. Nutritional support is provided via a gastrostomy tube when malnutrition occurs or when swallowing or eating safely is no longer possible<sup>12</sup>.

However, benefits assessment and timing anticipation of all three major clinical events remain challenging for patients and clinicians. Heterogeneous clinical manifestations, along with unspecific and different reports found in scientific literature amplify this challenge. Indeed, studies report widely different survival benefits and guidelines for indication rather than expected initiation timings. According to the literature, gastrostomy provides controversial survival benefits on survival with no up to 20 months survival benefit<sup>20,21,20,21</sup>. For tracheostomy, reported survival benefits range from 16 up to 48.5 months<sup>8,21-238,21-2322,23</sup>. A 2006 randomized controlled trial of NIV use with 41 patients without severe bulbar symptoms indicated a 7-month survival prolongation<sup>24</sup> while more recent studies, taking into account improved healthcare conditions, report survival benefit ranging from 11<sup>25</sup> up to 15 months<sup>26</sup> from time of NIV prescription. Such variations can be partially explained by study design differences, equipment diversity, limited sample sizes and most likely by lack of consideration regarding sources of heterogeneity affecting disease progression. One study<sup>27</sup>, capturing onset site as a source of heterogeneity and relying on the electronic health record of 250 ALS patients, to investigate ALS clinical event timeline, has already demonstrated disparities in clinical intervention initiation.

Consequently, to specifically analyze ALS care strategy diversity, we propose a multi-state model approach applied to a nation-wide hospital registry and designed to investigate the influence of gender, presence of symptoms indicative of onset and age class on care pathway strategies. We leveraged real-world data from the extensive French hospitalization registry to identify patients and their characteristics of interest, track their vital status along with clinical interventions to conduct an overall and patient profile stratified analysis of median time-to-clinical events. Additionally, we defined states, encompassing all detectable statuses regarding clinical intervention, and used multi-state and Accelerated Failure Time (AFT) models to compare the speed of transition from one state to the next. Our models accommodate for gender, age group at first detected hospitalization of interest, the presence of bulbar or spinal onset site-related symptoms and their interactions as covariables to capture potential differences in care strategies. Furthermore, we assessed overall and stratified survival and confirmed population characteristics with scientific literature to confirm validity of the study population.

## METHODS

### Dataset and study population

We conducted a retrospective analysis leveraging the French national hospitalization registry: Programme de Médicalisation des Systèmes d'Information (PMSI). Originally created in 1982 to monitor allocated funding to care facilities and oversee hospital activity, this exhaustive medico-administrative database stores anonymized medical data registered at discharge from hospital for all patient stays. The PMSI database only covers inpatients visits, meaning that it excludes medical information from consultations wether in town or at hospital. Consequently, no data on out-of-hospital deaths, general practitioner consultations or other external healthcare providers are included. Access to data recorded between 2013 and 2022, both included, is granted by the Agence technique de l'information sur l'hospitalisation. Patient data is restricted to gender and age, while stay-specific data includes dates and modes of admission and discharge including in-hospital deaths, diagnoses, clinical procedures, and the associated dates<sup>28</sup>. Diagnoses and clinical procedures are coded by physicians via the International Classification of Diseases 10th revision (ICD-10) and the Common French Classification of Medical Acts (CCAM), respectively.

### Patient identification

The most precise ICD-10 diagnosis code referring to ALS is G12.2 and encompasses all “motor neuron diseases”. Consequently, we developed a selection algorithm to refine the ALS patient identification. The patient identification and data extraction processes were conducted using SAS Software and are described in *Figure 1*.

First, we identified patients who were assigned a G12.2 diagnosis code during a hospitalization stay beginning between 2013 up to 2022, both years included. All available stays related to the resulting list of patients were then retrieved to study the complete hospitalization history. Forty-seven invalid stays, due to undefined Diagnosis Related Groups (DRG), and 764 invalid identification code were removed from the analysis. Secondly, for each stay, we extracted the admission and discharge dates, discharge modes and registered diagnoses, along with the age, gender, last available stay and potential death-related discharge mode. Dialysis-specific stays were not considered. Additionally, the death-related discharge mode of 444 patients and last available datapoint of 1,299 patients were collected through the home-based hospitalization and post-op or rehabilitation sub-datasets. Third, to specifically identify patients of interest, we developed exclusion criteria which relied exclusively on the following available data: age, hospital stay characteristics, and diagnoses. The exclusion criteria were set to refine the study population to newly diagnosed adult patients with mostly ALS compatible diagnoses and an appropriate proportion of G12.2 diagnosis-coded stays. We defined them as follows:

- Patients who were less than 18 years old at the first recorded G12.2 diagnosis code.

- Non incident patients (patients with NIV, gastrostomy or tracheostomy code preceding the first detected G12.2 diagnosis code or a detected G12.2 diagnosis code before 01/01/2017 which is not preceded by a prior hospitalization).
- Patients exhibiting a proportion of G12.2 diagnosis-coded hospital stays, out of all their stays which lasted at least one day, inferior to 1/3 and more than 10 hospital stays separating the last G12.2 diagnosis-coded stay and the last available hospitalization stay.
- Patients with most diagnosis codes associated with neurological diseases incompatible with an ALS diagnosis, across all available stays.

Relevant ICD-10 diagnosis codes are listed in *Supplementary Material 1 (Table 1)*.

### Data extraction

Clinical expertise and exploratory analysis of the prevailing codes guided the definition of a list of ICD-10 diagnosis and CCAM clinical interventions codes relevant to three clinical procedures of interest: NIV, gastrostomy, and tracheostomy. All clinical procedures and diagnoses, including and following the first hospital stay with a G12.2 diagnosis code were considered and crossed to consolidate the occurrence of the clinical interventions. The list of ICD-10 and CCAM codes used in this data extraction step are provided in *Supplementary Material 1 (Table 2-4)*.

The onset site was defined through investigation of symptoms related to onset site one year prior and one year after the first G12.2-coded hospitalization as follows:

- We defined spinal onset site patients as patients presenting exclusively spinal onset-related diagnosis codes during the first hospital stay characterized by a G12.2 code or a majority of spinal onset site-related diagnosis codes across all hospital stays within the 2-year period.
- Bulbar onset site patients were defined as patients presenting exclusively bulbar onset-related diagnosis codes during the first hospital stay characterized by a G12.2 diagnosis code or a majority of bulbar onset site-related diagnosis codes across all hospital stays within the 2-year period.
- Undetermined onset site patients include the remaining patients. Consequently, for these patients, we either could not retrieve information regarding symptoms indicative of onset site or detected the same number of bulbar and spinal onset site-related diagnosis and a mix of onset site-related diagnosis codes at first detected hospital stay characterized by a G12.2 diagnosis code.

Consequently, for each patient, the following data was extracted: birth year, gender, date of admission associated with the first detected G12.2 diagnosis-coded hospitalization and the discharge date of the last available hospital stay. Patients leaving the hospital alive are considered as lost to follow-up the day of the last detected available hospital stay. Additionally, for some

patients, presence of onset-related symptoms, date of death registered at hospital, clinical procedures and their corresponding dates were also collected.

Given that gastrostomy and tracheostomy procedures necessitate specialized surgical skills, while NIV typically requires a hospital visits for training patients or caregivers on potential autonomous use in non-hospital settings<sup>29</sup>, the likelihood of capturing initiation of either clinical procedure in the PMSI dataset is high.

### Outcomes

The aim of this study is to describe profile-specific time-to-clinical events and compare transition dynamics. Consequently, the primary study outcomes were the detection of speed differences in state transition depending on patient profile and the profile-specific median time-to-clinical event for each transition of interest. We defined the states depending on patient status regarding performed clinical procedures after the first detected G12.2 diagnosis-coded hospital stay:

- State 0: the patient has never received NIV and is currently neither receiving support through gastrostomy or tracheostomy.
- NIV: the patient has received NIV and is currently receiving neither support through gastrostomy nor tracheostomy.
- Gastrostomy: the patient is currently receiving gastrostomy support and has never received NIV support.
- Tracheostomy: the patient is currently tracheotomized.
- Gastrostomy and NIV: the patient is currently receiving gastrostomy support and has received NIV.
- Gastrostomy and tracheostomy: the patient is currently receiving both gastrostomy and tracheostomy support.
- Death: the patient is dead.

We consider NIV use history instead of tracking NIV use. Additionally, patients were censored at the discharge date of the last available hospital stay or after a follow-up of 4 years since clinical acts and diagnosis codes referring to NIV discontinuation are nonexistent.

### Statistical analysis

First, we evaluated the quality of the extracted study population. We estimated overall survival and compared group population characteristics with literature. More specifically, we compared subgroup mean age through Student t-tests and estimated the overall and subgroup survival rates through the Kaplan-Meier method. We compared survival between subgroups using the Log-rank test after confirming lack of hazard proportionality through computation of the scaled

Schoenfeld residuals to estimate the time dependence of the coefficient for all three covariates (age class, gender and presence of symptoms related to bulbar and spinal onset site) individually.

Second, we assessed the validity and relevancy of the states and transition of the model. We carried out an exploratory process mining approach to identify all care pathway profiles, quantify the number of patients transitioning from one state to another and estimate the median length of stay in each state before transition. Gastrostomy and tracheostomy removal were dynamically tracked to study patient status and capture the full care pathway. This primary analysis served as a first assessment of the patient trajectories and provided background for the definition of the transition matrix of the survival model. The results of this primary analysis are detailed in *Supplementary material 2*.

Third, we estimated median time-to-clinical event for each patient profile and transition. Additionally, we developed a time-inhomogeneous multi-state model to describe simultaneously the care trajectories along ALS disease progression from longitudinal natural history data. Such a model provides a generalized framework to study the complete trajectory analysis of dynamic processes by considering intermediate events of interest that occur through disease progression, estimate transition-specific hazard rates and allow for comparison between patient profile<sup>30</sup>. We considered 7 states, 15 transitions of interest and a unidirectional model due to rare gastrostomy or tracheostomy removal events and lack of codes related to NIV discontinuation. At time of recruitment (admission date into the first detected stay characterized by a G12.2 diagnosis code), patients are included in “State 0” and remain in this state until they initiate a care pathway and enter other transient states or die at the hospital and therefore transition to the absorbing “Death” state. Depending on personal care strategy, patients can exit “State 0” and initiate “NIV”, “Gastrostomy” or “Tracheostomy” and further combine both ventilation supports with a nutrition support (“Gastrostomy and NIV” and “Gastrostomy and Tracheostomy”). To improve model fit, maximize statistical power and enhance the clinical relevance of the results, we restricted the follow-up period to 0-4 years after the first detected G12.2 diagnosis, as most events (97%) occurred within this timeframe. As a result, patients’ trajectories were censored at the discharge date of the last recorded hospital visit or after 4 years of follow-up. We studied clinical activity up to 4 years after the first G12.2-coded hospitalization to capture 97% of detected transitions of interest and keep sufficient statistical power. The distribution of the instantaneous hazard rates which provided the lowest Akaike Information Criterion (AIC), and therefore maximizes the likelihood for each transition, was determined to define the time-dependent transition intensity matrixes and confirm violation of the risk proportionality assumption. Gender, age class at first detected hospitalization with a G12.2 diagnosis, and onset site were included in the models to allow for comparison between patient profiles. Detailed model selection and definition are described in *Supplementary Material 3*. Due to violation of the risk proportionality assumption, we chose an AFT model to directly assess the effect of covariates

on the survival time for each transition and each of the 12 patient profiles. Consequently, we reported Acceleration Factors (AF), indicating deceleration or acceleration of the course of the time-to-event in order to compare speed of entry into states depending on the three covariables of interest which uniformly shift the transition-specific survival curve. The reference group was defined as men aged [64;74) with spinal onset site and remains constant across all transitions to simplify result interpretation with easier comparison of acceleration factors. This group includes the most patients and was chosen to minimize variances from smaller sample sizes leading to more precise estimates and a greater likelihood of detecting significant differences. AF were defined as the inverse of the ratio of failure times between a patient profile and this reference group. Consequently, an AF equal to 2 indicates a time-to-event twice as fast for the group compared to the reference class<sup>31</sup>.

All statistical analyses were conducted using R software with *mstate*<sup>32</sup> and *flexsurv*<sup>33</sup> packages.

### Standard Protocol Approvals, Registrations, and Patient Consents

This retrospective cohort study leveraging healthcare system data was conducted according to the national recommendations and current legislation. PMSI data is provided by the Technical Agency for Information on Hospital care (ATIH) and use was authorized by the National Commission for Data Processing and Civil Liberties (CNIL) (regulatory decision: DE-2011-078).

### Data Availability

Data cannot be shared publicly for legal reasons. Access is regulated by French legislation and applications can be submitted to the ATIH ([www.atih.sante.fr](http://www.atih.sante.fr)).

## **RESULTS**

### Assessment of study population extraction quality

#### *Population description*

We identified 21,153 patients who fit the eligibility criteria (*Table 1*) and estimated an onset site for 57.8% of the study population (*Supplementary Material 4: Table 1*). For most (91%) patients with an undetermined onset, no symptom of interest was observed. Considering the absence of significant differences in mean age (Student t-test,  $p = 0.38$ ) and similar survival curve, we classified patients with undetermined onset and no symptoms as spinal onset patients. Similarly, considering the survival curves (*Supplementary material 4: Figure 1*), we classified the remaining

743 patients with undetermined onset and both bulbar and spinal onset-site related diagnosis codes, as bulbar onset patients. Consequently, in total, we identified 65.6% of spinal onset patients and 34.4% of bulbar onset patients (*Table 1*). Age classes were defined to ensure equitable distribution of patients across classes and provide improved statistical power.

### *Survival analysis*

Median in-hospital survival, from the first G12.2 coded hospitalization stay, was 2.44 [2.35; 2.53] years (Figure 2A). Although survival rates differ significantly (Log-rank,  $p < 0.01$ ), median survival difference between men (2.51 [2.41;2.63] years) and women (2.35 [2.25;2.48] years) (Figure 2B) is lower than two months. Younger age class is associated with better survival rates (Log-rank,  $p < 0.01$ ) (Figure 2C). Patients with bulbar onset site had a median survival equal to 1.34 [1.30;1.41] years while spinal onset site patients had a median survival of 3.53 [3.35; 3.72] years (Figure 3D).

### Care pathway description

#### *States definition*

Overall care pathway description is represented in *Figure 3*. At least one hospital event (i.e. as death, NIV, gastrostomy or tracheostomy) was detected in 55.24% of the cohort and a pathway initiation was detected for 36.52% of the cohort.

#### *Time-to-event median and AFT coefficient comparison:*

Comparative transition-specific analyses of median and acceleration factors depending on patient profile are provided in *Figure 4*, *Figure 5* and *Supplementary Material 5: Figure 1*. All acceleration factors are reported comparatively to the reference class defined as men aged [64;74) with spinal onset site.

Care pathway initiation through NIV was 2.12 [1.59;2.83] times faster for men aged [64;74) with bulbar onset after the initial report of ALS in the hospital registry, compared to the reference group. More generally, men with bulbar onset also were characterized by higher acceleration factors with a significant difference exclusively for the [64;74) age class ([18;64) : AF = 1.44 [0.57;3.66], [64;74) : AF = 2.12 [1.59;2.83] and [74;103] : AF = 1.45 [0.52;4.01]) while other patients significantly delayed NIV initiation from 0.34[0.13;0.88] (for women aged [18;64) with spinal onset-site) up to 0.66 [0.51;0.87] (for men aged [74;103] with spinal onset site) times faster than the reference group. Increased age class was also associated with significantly lower median

time to NIV initiation (e.g. 3.02 [2.07;4.23] months for men aged [74;103] with spinal onset site against 11.47 [10;12.93] months for men aged [18;64] with spinal onset site).

Initiation of care pathway through gastrostomy for bulbar onset patients was frequent and significantly faster than the reference class. Initiation time ranged from 11.01 [3.97;30.47] up to 24.47 [1.24;482.92] times faster than the reference group. For the same age class, women with bulbar onset site were always characterized by higher AF than men. Although rarely performed and significantly delayed for men with spinal onset site aged [74;103] (AF = 0.58 [0.39;0.87]), gastrostomy support was also provided 2.52 [1.84;3.46] times more rapidly to women aged [64;74] with spinal onset compared to the reference class. Additionally, among patients who initiated their care pathway with NIV, resorting to gastrostomy seemed fast among bulbar onset site patients with high AF ranging from 4.69 [0.3;73.88] up to 24.62 [2.09;289.67] and some detected significant differences (men aged [64;74] with bulbar onset-site : AF = 10.8 [5.53;21.08] and women aged [64;74] with bulbar onset-site : AF = 24.62 [2.09;289.67]). Increased age class is also associated with lower median time to gastrostomy initiation (e.g. 14.6 [12.2;16.3] months for women aged [18;64] with spinal onset site against 3.77 [2.1;5.1] months for women aged [74;103] with spinal onset site).

Tracheostomy was more frequently indicated among patients aged [18;64]. No significant difference in timing dynamics involving tracheostomy were detected, apart among patients who already received NIV support with women aged [64;74] with spinal onset site who delayed and resorted to tracheostomy use 0.03[0;0.42] time faster than the reference class.

Except for death after requiring gastrostomy and tracheostomy, increased age class was mostly associated with increased AF. Apart from one exception, all significant delays before death were observed among patients aged [18;64] while all significantly shorter survival times were observed for patients aged [74;103]. Among patients who did not resort to any of the three life-support procedure, men aged [64;74] with bulbar onset site who died 2.22 [1.75;2.82] times significantly faster than the reference class.

## **DISCUSSION**

This retrospective study based on real-world data, demonstrated the influence of gender, symptoms indicative of onset site, and age class on ALS care pathway strategy heterogeneity and provides insights for improved profile-specific care pathway anticipation.

Notably, we observed wide variation in median time-to-event by patient gender, age group, and initiation for most of the transitions of interest. For instance, among all patients who initiated their care pathway with a gastrostomy, half received a gastrostomy support after 5.97 months.

However, a stratified analysis shows a median initiation time of only 1.9 months for men aged [74;103] with bulbar onset site and up to 14.9 months for men aged [18;64) with spinal onset site.

Additionally, we shed light on significant transition speed differences depending on patient profile.

NIV seemed to be initiated faster among men with bulbar onset site, compared to other patient profiles and mostly spinal onset site patients with significantly lower AF than the reference class. Faster decline in respiratory function and significant weight loss for men might explain this observation which has also been reported in two studies<sup>9,34</sup>. It is however worth noting that this difference might also partially be explained by the inclusion of symptoms related exclusively to respiratory insufficiency in the chosen definition of bulbar onset site patients. Consequently, although extremely rare and primarily observed in men, patients affected by respiratory onset might drive this early NIV initiation<sup>35</sup>. Additionally, as previously reported in literature<sup>27</sup>, gastrostomy initiation and resort to gastrostomy after NIV is faster among bulbar onset site patients and even greater among women with bulbar onset site. Important weight and appetite loss, characteristic of ALS, could explain this prompt gastrostomy indication since inter-sex and inter-age group differences in metabolism and body fat percentage between the two genders are reported to play a role in disease progression<sup>36</sup>. Alongside explanatory biological processes, sex-differential decision-making processes, stemming from personal experiences, family support or autonomy perception for instance could also provide explanations towards willingness to accept such procedures<sup>37,38</sup>.

Older age is also associated with significantly lower NIV and gastrostomy initiation medians. Older individuals, especially those who are frail or have multiple comorbidities<sup>39</sup>, may exhibit a faster decline in functional status<sup>40,41</sup>, nutritional health<sup>42</sup> and physiological reserve capacity<sup>43,44</sup>. Rapid initiation of gastrostomy may stem from concerns regarding the patient's capability to sustain sufficient oral nutrition. Similarly, the need for NIV may arise swiftly due to respiratory compromise associated with age-related decline or chronic illnesses. These reasons can also explain why older age is sometimes associated with significantly lower survival and lower survival medians, while patients aged [18;64) survive longer.

Tracheostomy remains a rare event, mainly considered for patients aged [18;64) mainly indicated in emergency situations and after unsuccessful NIV initiation<sup>45</sup>.

Our study relied on longitudinal natural history data which, on top of enhancing relevance of findings to real-world situations compared to controlled experiments, offered a nation-wide sample size and large temporal coverage. The use of multi-state models provided a flexible statistical framework to study complex systems characterized by censored data, to examine

multiple events simultaneously, and to account for intermediate states involved in disease progression. Taking advantage of the large sample size, we stratified the timeline analysis by patient profile to capture the heterogeneity of the dynamics by time-to-event median and AF, thus assuming the covariates have a multiplicative effect on the time scale of the event.

Despite the strengths associated with the use of real-world data in conjunction with multi-state models, our study has several limitations mainly inherent to claims database.

In spite of its comprehensive hospital-based coverage, the PMSI does not capture healthcare interactions occurring in outpatient care and limits data to in-hospital treatments and procedures within France. This resulted in 36.52% of the cohort having an initiated care pathway including at least one event among NIV, gastrostomy and tracheostomy at hospital. When considering hospital deaths, along with the three clinical procedures of interest, the activity of only 55.24% of the study population was recorded. This low percentage can largely be attributed to the lack of available data on out-of-hospital deaths and the study's 4-year washout period, during which more recent incident patients may not have had time to experience the events of interest. Other contributing factors include patient preferences, treatment refusals, the inclusion of patients with other motor neuron diseases, and treatments occurring outside France. While gastrostomy and tracheostomy require specialized surgical expertise, and NIV initiation typically involves hospital visits, suggesting these procedures were likely captured in the PMSI dataset, it lacks the detail to clarify the decision-making processes of both patients and clinicians regarding the timing and initiation of care. Consequently, this study does not quantify the impact of factors such as unreasonable obstinacy or treatment refusal and is based on the hypothesis that ALS requires inpatient visits. While the overall estimated incidence aligns with the one reported in literature<sup>46</sup>, short survival, potential diagnostic uncertainty, and a desire to avoid hospital visits may result in some patients not being captured in this analysis. Estimating the proportion of patients who were never hospitalized is challenging and has not been reported in the literature.

We mitigated coding heterogeneity by conducting an exploratory analysis of the prevailing codes and consolidated clinical interventions codes with registered diagnoses codes to maximize patients' statuses tracking. Additionally, up to 2018, the exact date of admission and discharge of the stay were not provided (only the month and year) which can lead to biased estimations since the first day of the month was systematically chosen as a replacement to the real date. Similarly, disease onset or date of first diagnosis are challenging to identify and only a proxy (date of admission of the first detected hospital stay characterized by a G12.2 diagnosis code) with limited clinical relevance was determined as index date.

Furthermore, we could only assess the quality of our selection algorithm through comparison with literature. Consequently, we chose to define this algorithm with lenient exclusion criteria and a 4-year wash-out window, corresponding to the maximal median survival reported in

literature, which limits the inclusion of non-newly diagnosed patients with already initiated care pathways that would skew the results. We identified 21,153 newly diagnosed patients over 10 years which corresponds to an incidence of 3.36 per 100,000 person-years, coherent with estimated crude ALS incidence in France 3.19 [2.81;3.56] per 100,000 person-years<sup>46</sup> and more than half (54.9%) of the population are men (53.7%). Overall mean age at first detected ALS diagnosis is  $67.7 \pm 13.1$  years and mean age at diagnosis in Europe is reported as  $64.4 \pm 12.3$  years<sup>47</sup>. Regarding the definition of onset, we assumed that patients who did not have a majority of bulbar onset symptoms one year before and one year after the first hospitalization were spinal onset patients. They represented 65.6% of the identified population. It is estimated that 70% of patients have spinal onset, 25% have bulbar onset, and 5% have rare and atypical forms<sup>48</sup>, although phenotypes may vary by country (22.8% and 35.9% of bulbar patients in China and Germany, respectively<sup>49</sup>). Observed median overall survival is equal to 2.44 [2.35; 2.53] years after the first detected G12.2-coded hospitalisation and is included in the widely variable reported 2 to 4 years survival<sup>3,50</sup>. Additionally, as reported in literature, higher death rates for men are observed<sup>51</sup> and bulbar onset survival (1.33 [1.28;1.38] years) is inferior to spinal onset survival (3.40 [3.25; 3.59] years)<sup>50</sup>. Consequently, our study population has characteristics consistent with populations described in literature. However, the ICD-10 diagnosis code "G12.2" also includes patients affected by two X-linked conditions: Kennedy's Disease and PLS. Failing to remove patients affected by these conditions, which affect exclusively males and are not associated with reduced life expectancy, can lead to an overestimated male/female ratio as well as median survival estimates. Similarly, time-to-clinical event measures (e.g., NIV, gastrostomy, and tracheostomy) can be overestimated, as these interventions are rarely considered in the care pathways of patients with Kennedy's Disease and Primary Lateral Sclerosis (PLS)<sup>52,53</sup>. Although the low incidence of these conditions may mitigate their impact on the results, this potential inclusion remains a significant limitation of the study.

Moreover, the decision to group patients with an unestimated onset site with spinal onset site is a limitation motivated by improved result interpretability and supported by similar survival curves, appropriate proportion of spinal onset patients compared to the prevalence reported in literature along with few impacts on the differences in acceleration coefficients (data not shown).

Finally, patients are considered as lost to follow-up at the discharge date of the last detected available hospital stay. Therefore, along with rare clinical events, lack of out-of-hospital activity data, mainly out-of-hospital deaths, and profile stratification, already affecting statistical power, heavy censoring further results in wider confidence intervals and limited detection of potential significant differences.

Future care pathway investigations leveraging real world data in more extensive medico-administrative databases, or a combination of multiple registries, can further extend data

availability (e.g. Riluzole use, earlier detection of diagnosis, vital status and supportive care data) and improve our understanding of disease progression. However, careful consideration and characterization of the sources of bias (e.g. selection bias, confounding, missing data, decision-making processes) introduced in the studies is paramount to assess the validity of the results and often challenging. Consequently, further research and rigorous analyses are needed to improve result interpretability and allow for comparison of results with randomized controlled trials.

Overall, care pathway strategy analysis is crucial, especially in the context of low-incidence diseases restricted to life-support care management. Description and investigation of differences is pivotal to anticipate patient needs, provide enlightened information for informed decisions and foresee healthcare strategies. Health claims databases are powerful resources which, at the expense of rigorous data extraction methodology, offer a large sample size, growing temporal coverage and can be applied to such analyses.

#### Statement of Ethics

Study approval statement: This retrospective cohort study, leveraging healthcare system data, was conducted according to national recommendations and current legislation. Access was granted through the affiliation of the research team with the National Institute for Research in Digital Science and Technology (INRIA), and contributes to a public interest project approved by the delegated general Directorate for science and permitted upon completing training on the database's appropriate use.

Consent to participate statement: In line with French governmental regulations and the National Ethics Committee, no patient consent was required and only de-identified patient information was accessible.

#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

#### Funding Sources

The research leading to these results has received funding from the program "Investissements d'avenir" ANR-10-IAIHU-06.

## Author Contributions

MD, STM and JO participated in conceptualization, supervision and methodology. Investigation was conducted by all co-authors (MD, STM, JO, AH, FS). The original draft was written by MD and all co-authors participated in reviews and editing (MD, STM, JO, AH, FS).

## REFERENCES

1. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. *Eur J Neurol*. 2020;27(10):1918-1929. doi:10.1111/ene.14393
2. Kjældgaard AL, Pilely K, Olsen KS, et al. Prediction of survival in amyotrophic lateral sclerosis: a nationwide, Danish cohort study. *BMC Neurol*. 2021;21(1):164. doi:10.1186/s12883-021-02187-8
3. Millul A, Beghi E, Logroscino G, Micheli A, Vitelli E, Zardi A. Survival of patients with amyotrophic lateral sclerosis in a population-based registry. *Neuroepidemiology*. 2005;25(3):114-119. doi:10.1159/000086353
4. Marin B, Fontana A, Arcuti S, et al. Age-specific ALS incidence: a dose–response meta-analysis. *Eur J Epidemiol*. 2018;33(7):621-634. doi:10.1007/s10654-018-0392-x
5. Arthur KC, Calvo A, Price TR, Geiger JT, Chiò A, Traynor BJ. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. *Nat Commun*. 2016;7(1):12408. doi:10.1038/ncomms12408
6. Ravits JM, La Spada AR. ALS motor phenotype heterogeneity, focality, and spread. *Neurology*. 2009;73(10):805-811. doi:10.1212/WNL.0b013e3181b6bbbd
7. Grad LI, Rouleau GA, Ravits J, Cashman NR. Clinical Spectrum of Amyotrophic Lateral Sclerosis (ALS). *Cold Spring Harb Perspect Med*. 2017;7(8):a024117. doi:10.1101/cshperspect.a024117
8. Chiò A, Moglia C, Canosa A, et al. ALS phenotype is influenced by age, sex, and genetics. *Neurology*. 2020;94(8):e802-e810. doi:10.1212/WNL.0000000000008869
9. Ortholand J, Pradat PF, Tezenas du Montcel S, Durrleman S. Interaction of sex and onset site on the disease trajectory of amyotrophic lateral sclerosis. *J Neurol*. 2023;270(12):5903-5912. doi:10.1007/s00415-023-11932-7

10. Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev*. 2007;(1). doi:10.1002/14651858.CD001447.pub2
11. Bensimon G., Lacomblez L., Meininger V., null null. A Controlled Trial of Riluzole in Amyotrophic Lateral Sclerosis. *N Engl J Med*. 1994;330(9):585-591. doi:10.1056/NEJM199403033300901
12. Soriani MH, Desnuelle C. Care management in amyotrophic lateral sclerosis. *Rev Neurol (Paris)*. 2017;173(5):288-299. doi:10.1016/j.neurol.2017.03.031
13. Norris SP, Likanje MFN, Andrews JA. Amyotrophic lateral sclerosis: update on clinical management. *Curr Opin Neurol*. 2020;33(5):641. doi:10.1097/WCO.0000000000000864
14. Mathis S, Couratier P, Julian A, Vallat JM, Corcia P, Le Masson G. Management and therapeutic perspectives in amyotrophic lateral sclerosis. *Expert Rev Neurother*. 2017;17(3):263-276. doi:10.1080/14737175.2016.1227705
15. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol*. 2006;5(2):140-147. doi:10.1016/S1474-4422(05)70326-4
16. Vianello A, Arcaro G, Palmieri A, et al. Survival and quality of life after tracheostomy for acute respiratory failure in patients with amyotrophic lateral sclerosis. *J Crit Care*. 2011;26(3):329.e7-329.e14. doi:10.1016/j.jcrc.2010.06.003
17. Körner S, Hendricks M, Kollwe K, et al. Weight loss, dysphagia and supplement intake in patients with amyotrophic lateral sclerosis (ALS): impact on quality of life and therapeutic options. *BMC Neurol*. 2013;13(1):84. doi:10.1186/1471-2377-13-84
18. Mitsumoto H, Davidson M, Moore D, et al. Percutaneous endoscopic gastrostomy (PEG) in patients with ALS and bulbar dysfunction. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2003;4(3):177-185. doi:10.1080/14660820310011728
19. Kak M, Issa NP, Roos RP, et al. Gastrostomy tube placement is safe in advanced amyotrophic lateral sclerosis. *Neurol Res*. 2017;39(1):16-22. doi:10.1080/01616412.2016.1259028
20. Bond L, Ganguly P, Khamankar N, et al. A Comprehensive Examination of Percutaneous Endoscopic Gastrostomy and Its Association with Amyotrophic Lateral Sclerosis Patient Outcomes. *Brain Sci*. 2019;9(9):223. doi:10.3390/brainsci9090223
21. Cui F, Sun L, Xiong J, Li J, Zhao Y, Huang X. Therapeutic effects of percutaneous endoscopic gastrostomy on survival in patients with amyotrophic lateral sclerosis: A meta-analysis. *PLOS ONE*. 2018;13(2):e0192243. doi:10.1371/journal.pone.0192243

22. Spataro R, Bono V, Marchese S, La Bella V. Tracheostomy mechanical ventilation in patients with amyotrophic lateral sclerosis: Clinical features and survival analysis. *J Neurol Sci.* 2012;323(1):66-70. doi:10.1016/j.jns.2012.08.011
23. Spittel S, Maier A, Kettemann D, et al. Non-invasive and tracheostomy invasive ventilation in amyotrophic lateral sclerosis: Utilization and survival rates in a cohort study over 12 years in Germany. *Eur J Neurol.* 2021;28(4):1160-1171. doi:10.1111/ene.14647
24. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol.* 2006;5(2):140-147. doi:10.1016/S1474-4422(05)70326-4
25. Hirose T, Kimura F, Tani H, et al. Clinical characteristics of long-term survival with noninvasive ventilation and factors affecting the transition to invasive ventilation in amyotrophic lateral sclerosis. *Muscle Nerve.* 2018;58(6):770-776. doi:10.1002/mus.26149
26. Kleopa KA, Sherman M, Neal B, Romano GJ, Heiman-Patterson T. Bipap improves survival and rate of pulmonary function decline in patients with ALS. *J Neurol Sci.* 1999;164(1):82-88. doi:10.1016/S0022-510X(99)00045-3
27. Segura T, Medrano IH, Collazo S, et al. Symptoms timeline and outcomes in amyotrophic lateral sclerosis using artificial intelligence. *Sci Rep.* 2023;13(1):702. doi:10.1038/s41598-023-27863-2
28. Goldberg M, Jouglu E, Fassa M, Padieu R, Quantin C. The French health information system. *Stat J IAOS.* 2012;28(1-2):31-41. doi:10.3233/SJI-2012-0747
29. Recommendations for clinical practice - Practical modalities of long-term non-invasive positive pressure ventilation at home in neuromuscular diseases. has-sante.fr. May 2006. Accessed July 11, 2024. [https://www.has-sante.fr/upload/docs/application/pdf/ventilation\\_\\_non\\_invasive\\_recos.pdf](https://www.has-sante.fr/upload/docs/application/pdf/ventilation__non_invasive_recos.pdf)
30. Crowther MJ, Lambert PC. Parametric multistate survival models: Flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. *Stat Med.* 2017;36(29):4719-4742. doi:10.1002/sim.7448
31. Ramchandani R, Finkelstein DM, Schoenfeld DA. Estimation for an accelerated failure time model with intermediate states as auxiliary information. *Lifetime Data Anal.* 2020;26(1):1-20. doi:10.1007/s10985-018-9452-5
32. Putter H, Wreede LC de, Fiocco M, Geskus RB, Bonneville EF, Manevski D. mstate: Data Preparation, Estimation and Prediction in Multi-State Models. Published online November 8, 2021. Accessed April 30, 2024. <https://cran.r-project.org/web/packages/mstate/index.html>

33. Jackson C, Metcalfe P, Amdahl J, Warkentin MT, Sweeting M, Kunzmann K. flexsurv: Flexible Parametric Survival and Multi-State Models. Published online April 21, 2024. Accessed April 30, 2024. <https://cran.r-project.org/web/packages/flexsurv/index.html>
34. Grassano M, Moglia C, Palumbo F, et al. Sex Differences in Amyotrophic Lateral Sclerosis Survival and Progression: A Multidimensional Analysis. *Ann Neurol*. n/a(n/a). doi:10.1002/ana.26933
35. Gautier G, Verschueren A, Monnier A, Attarian S, Salort-Campana E, Pouget J. ALS with respiratory onset: Clinical features and effects of non-invasive ventilation on the prognosis. *Amyotroph Lateral Scler*. 2010;11(4):379-382. doi:10.3109/17482960903426543
36. Dupuis L, Pradat PF, Ludolph AC, Loeffler JP. Energy metabolism in amyotrophic lateral sclerosis. *Lancet Neurol*. 2011;10(1):75-82. doi:10.1016/S1474-4422(10)70224-6
37. Martin NH, Lawrence V, Murray J, et al. Decision Making About Gastrostomy and Noninvasive Ventilation in Amyotrophic Lateral Sclerosis. *Qual Health Res*. 2016;26(10):1366-1381. doi:10.1177/1049732315583661
38. Wong AD, Phillips SP. Gender Disparities in End of Life Care: A Scoping Review. *J Palliat Care*. 2023;38(1):78-96. doi:10.1177/08258597221120707
39. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*. 2012;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2
40. Saito J, Kondo N, Saito M, et al. Exploring 2.5-Year Trajectories of Functional Decline in Older Adults by Applying a Growth Mixture Model and Frequency of Outings as a Predictor: A 2010–2013 JAGES Longitudinal Study. *J Epidemiol*. 2019;29(2):65-72. doi:10.2188/jea.JE20170230
41. Dombrowsky T. Trajectories of Functional Decline in Older Adults: A Latent Class Growth Curve Analysis. *West J Nurs Res*. 2023;45(8):715-725. doi:10.1177/01939459231180365
42. Hickson M. Malnutrition and ageing: This article is part of a series on ageing edited by Professor Chris Bulpitt. *Postgrad Med J*. 2006;82(963):2-8. doi:10.1136/pgmj.2005.037564
43. Schneider JL, Rowe JH, Garcia-de-Alba C, Kim CF, Sharpe AH, Haigis MC. The aging lung: Physiology, disease, and immunity. *Cell*. 2021;184(8):1990-2019. doi:10.1016/j.cell.2021.03.005
44. Dent E, Wright ORL, Woo J, Hoogendijk EO. Malnutrition in older adults. *The Lancet*. 2023;401(10380):951-966. doi:10.1016/S0140-6736(22)02612-5

45. Heritier-Barras AC, Adler D, Ferfaglia RI, et al. Is tracheostomy still an option in amyotrophic lateral sclerosis? *Swiss Med Wkly*. 2013;143(3132):w13830-w13830. doi:10.4414/smw.2013.13830
46. Marin B, Hamidou B, Couratier P, et al. Population-based epidemiology of amyotrophic lateral sclerosis (ALS) in an ageing Europe – the French register of ALS in Limousin (FRALim register). *Eur J Neurol*. 2014;21(10):1292-e79. doi:10.1111/ene.12474
47. Logroscino G, Traynor BJ, Hardiman O, et al. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatry*. 2010;81(4):385-390. doi:10.1136/jnnp.2009.183525
48. Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. *The Lancet*. 2011;377(9769):942-955. doi:10.1016/S0140-6736(10)61156-7
49. Rosenbohm A, Liu M, Nagel G, et al. Phenotypic differences of amyotrophic lateral sclerosis (ALS) in China and Germany. *J Neurol*. 2018;265(4):774-782. doi:10.1007/s00415-018-8735-9
50. Chiò A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: A critical review. *Amyotroph Lateral Scler*. 2009;10(5-6):310-323. doi:10.3109/17482960802566824
51. Larson TC, Kaye W, Mehta P, Horton DK. Amyotrophic Lateral Sclerosis Mortality in the United States, 2011–2014. *Neuroepidemiology*. 2018;51(1-2):96-103. doi:10.1159/000488891
52. Turner MR, Talbot K. Primary lateral sclerosis: diagnosis and management. *Pract Neurol*. 2020;20(4):262-269. doi:10.1136/practneurol-2019-002300
53. Protocole National de Diagnostic et de Soins (PNDS) - Maladie de Kennedy. Published online June 2017. Accessed July 11, 2024. [https://www.has-sante.fr/upload/docs/application/pdf/2017-06/dir128/pnds\\_-\\_maladie\\_de\\_kennedy.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2017-06/dir128/pnds_-_maladie_de_kennedy.pdf)

*Table 1: Study population description.*

*Age at first G12.2 detected code refers to the patient age at the day of admission in the first detected stay characterized by a G12.2 diagnosis code (referring to “motor neuron diseases” in the ICD-10). The onset site was defined based on investigation of diagnosis codes indicative of onset site one year prior and one year after the first detected G12.2 diagnosis code.*

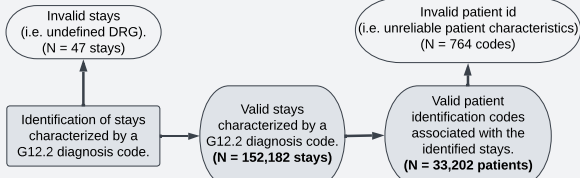
<b>Characteristics</b>	<b>Class</b>	<b>Overall</b>	<b>Men</b>	<b>Women</b>
Number	Patients	21,153	11,608 (54.9)	9,545 (45.1)
Age at first detected G12.2 code	[18,64) (%)	6,800 (32.2)	4,045 (59.2)	2,755 (40.8)
	[64,74) (%)	6,878 (32.5)	3,844 (55.8)	3,034 (44.2)
	[74,103] (%)	7,475 (35.3)	3,719 (49.2)	3,756 (50.8)
	Mean (SD)	67.7 (13.1)	66.7 (13.0)	68.8 (13.3)
Estimated onset	Spinal (%)	13,880 (65.6)	8,120 (58.5)	5,760 (41.5)
	Bulbar (%)	7,273 (34.4)	3,488 (48.0)	3,785 (52.0)

*Figure 1: Patient selection and data extraction flowchart.*

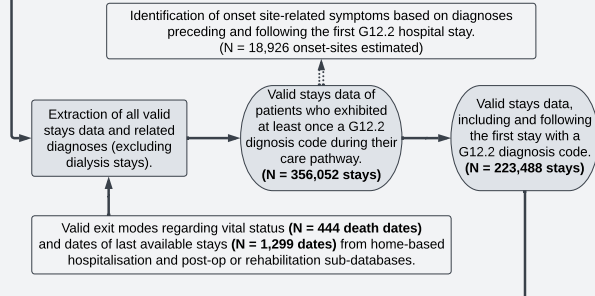
*Multiple steps are required to identify ALS patients and extract the relevant data in the Programme de Médicalisation des Systèmes d'Information. First, we identified all patients who were assigned a "motor neuron disease" diagnosis code (G12.2) during a stay which started between 2013 and 2022. Second, we extracted the entire hospitalization history which was available in the database. We assessed the presence of symptoms indicative of onset site one year prior and one year after the first detected G12.2 diagnosis code. Additionally, we retrieved death dates and last available stays available in the home-based hospitalization and rehabilitation sub-databases. Third, we assessed the eligibility criteria designed to keep newly diagnosed adult patients who are likely affected by ALS. Finally, we retrieved the information regarding the clinical interventions patients underwent and consolidated them with relevant diagnosis codes. (DRG: Diagnosis Related Groups, NIV: Non-invasive ventilation)*

## Patient Identification

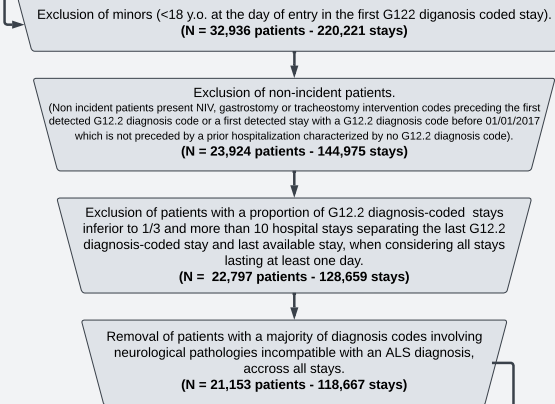
**Step 1**  
Identification of patients who were assigned at least one G12.2 diagnosis code in their hospitalization record between 2013 and 2022.



**Step 2**  
Extraction of all available valid stays associated with the previously identified patients.

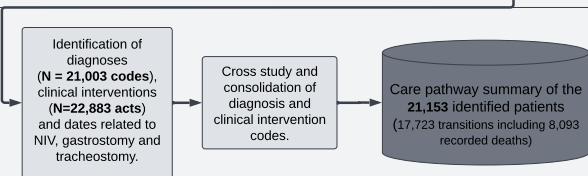


**Step 3**  
Identification of adult incident ALS patients.



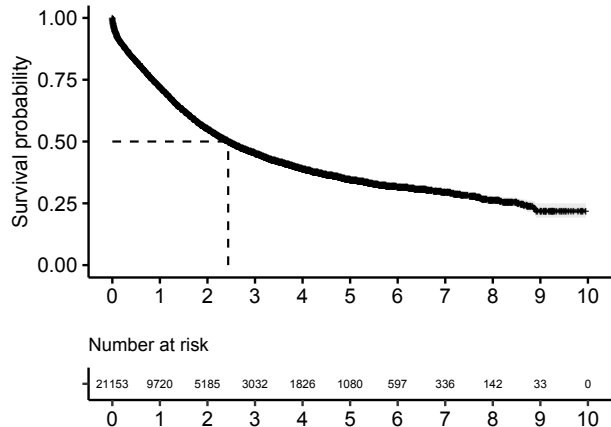
## Data Extraction

**Step 4**  
Extraction of data of interest regarding care pathway of the identified ALS patients.

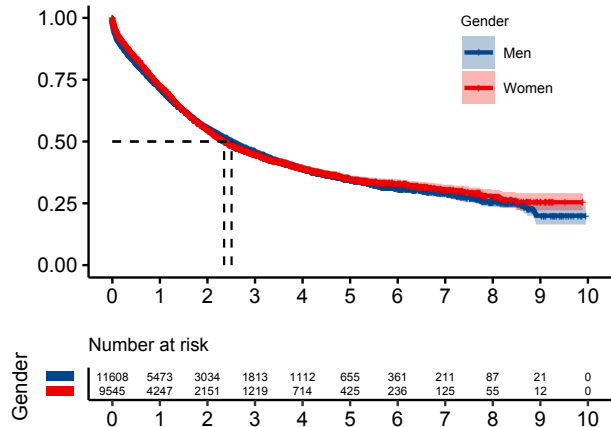


*Figure 2: Overall in-hospital survival and stratified by gender, age class and onset site. Kaplan-Meier plots describing estimated survival functions and their corresponding confidence intervals. Time at  $t = 0$  corresponds to the day the first G12.2 coded hospitalization was detected. Overall survival (A), survival stratified on gender (B), age class at first detected G12.2 diagnosis (C) and onset site (D) are represented. Survival medians are represented through dotted lines.*

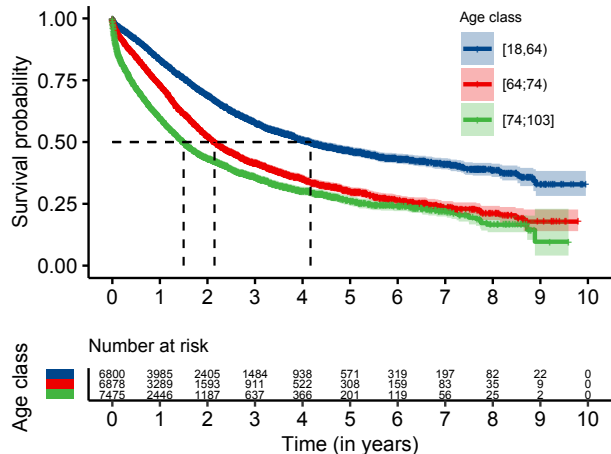
(A) Overall Survival



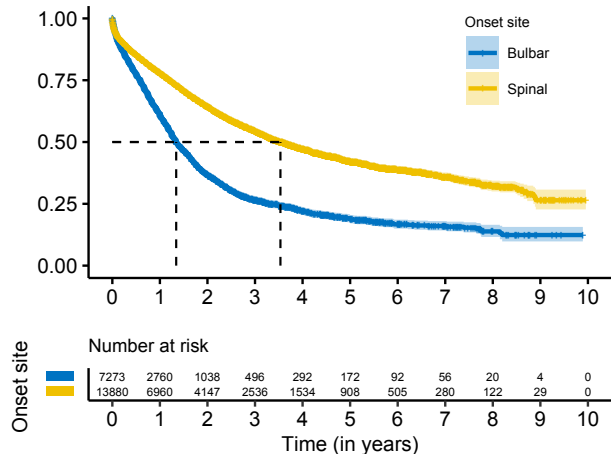
(B) Gender



(C) Age class at first detected G12.2-coded hospitalisation

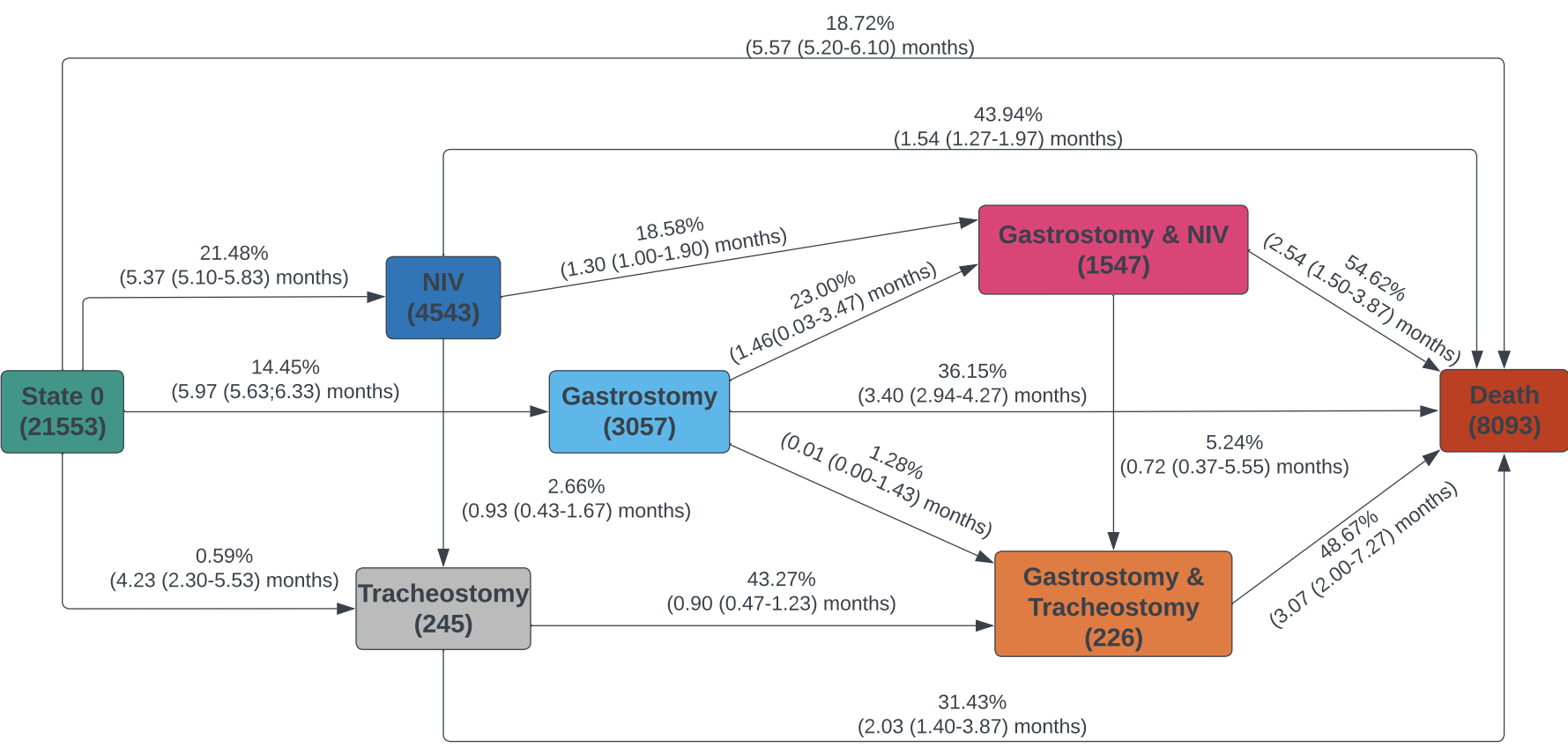


(D) Onset site



*Figure 3: Observed care pathway summary*

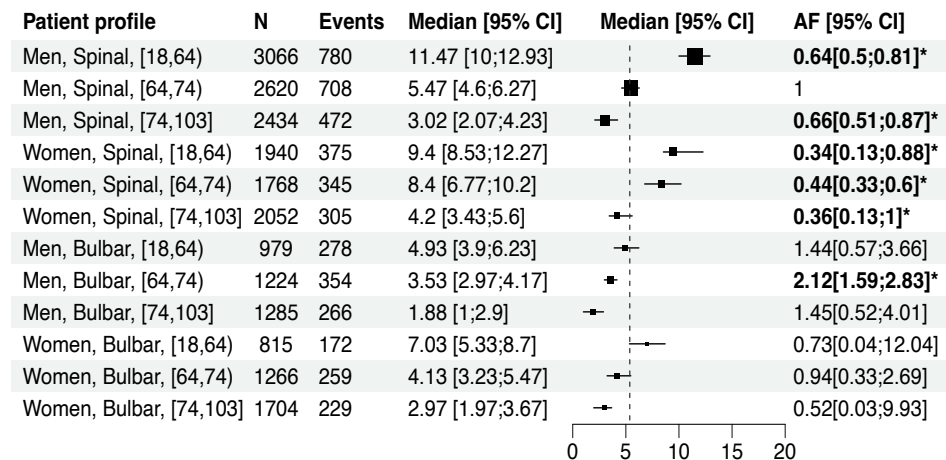
*Median length of stay in each state, along with their confidence interval, preceding the transition to the next state is enclosed in parentheses above the transition. The absolute number of patients who visited the state is supplied under the name of the state and the percentage of transitions associated with this sub-population is found above the transition. The percentage of patients censored for each transition can be computed by subtracting the sum of all transition percentages. (NIV: Non-invasive ventilation)*



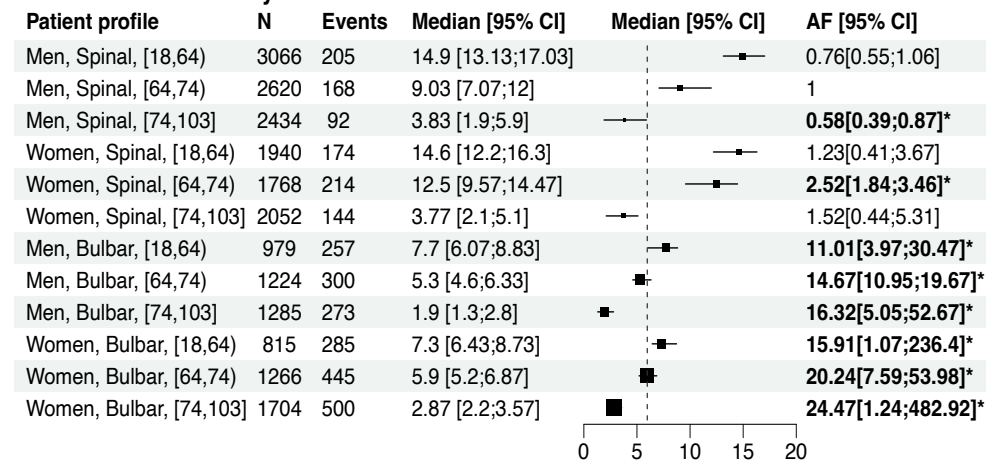
*Figure 4: Patient profile specific time-to-event medians and acceleration factors (AF) for transitions excluding tracheostomy and death.*

*Medians are reported in months and AF were computed relatively to the reference class (men aged [64;74) with spinal onset). Dotted lines represent the overall median times presented in (Figure 3). Significant differences in AF are presented in bold and marked with an asterisk. Inestimable medians and confidence interval values are reported as "NA".*

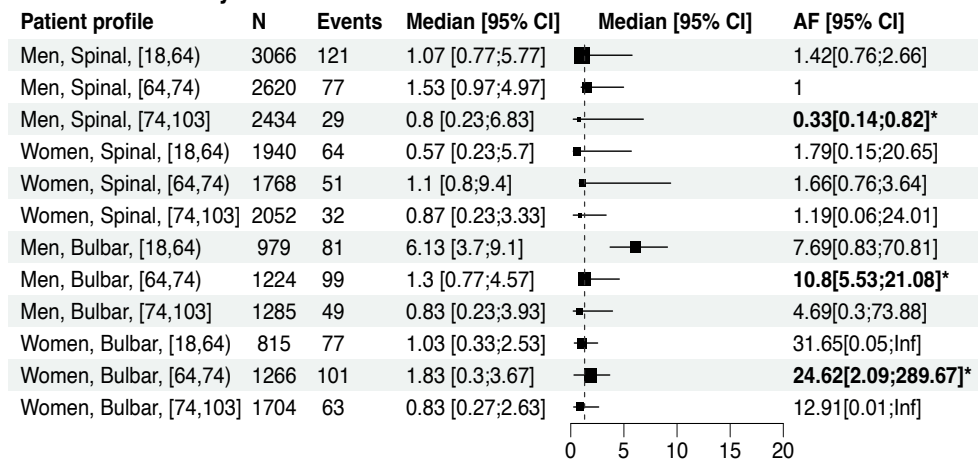
### State 0 -> NIV



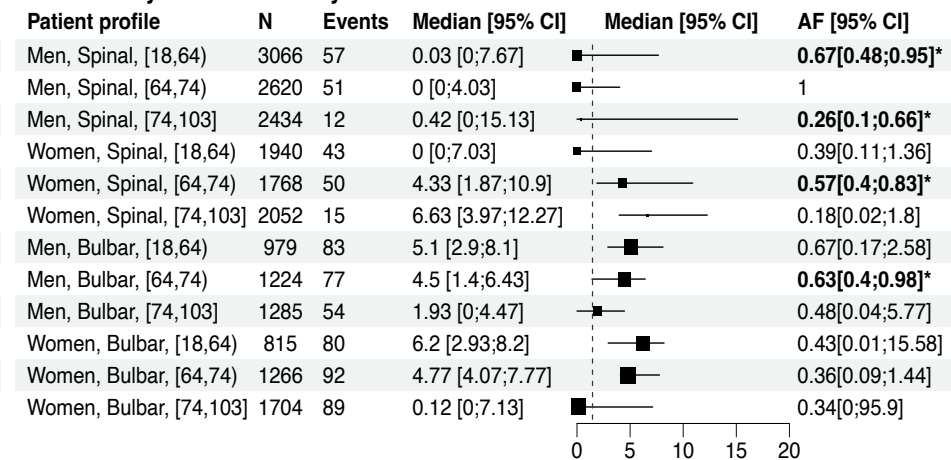
### State 0 -> Gastrostomy



### NIV -> Gastrostomy and NIV



### Gastrostomy -> Gastrostomy and NIV

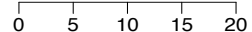


*Figure 5: Patient profile specific time-to-event medians and acceleration factors (AF) for transitions involving death.*

*Medians are reported in months and AF were computed relatively to the reference class (men aged [64;74) with spinal onset). Dotted lines represent the overall median times presented in (Figure 3). Significant differences in AF are presented in bold and marked with an asterisk. Inestimable medians and confidence interval values are reported as "NA".*

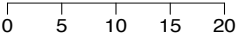
### State 0 -> Death

Patient profile	N	Events	Median [95% CI]	Median [95% CI]	AF [95% CI]
Men, Spinal, [18,64]	3066	346	12 [9.97;13.5]	12 [9.97;13.5]	<b>0.37[0.3;0.46]*</b>
Men, Spinal, [64,74]	2620	474	8.6 [7.3;10.93]	8.6 [7.3;10.93]	1
Men, Spinal, [74,103]	2434	664	3.24 [2.54;4.23]	3.24 [2.54;4.23]	<b>2.85[2.33;3.49]*</b>
Women, Spinal, [18,64]	1940	200	12.47 [10.93;16.1]	12.47 [10.93;16.1]	<b>0.34[0.16;0.76]*</b>
Women, Spinal, [64,74]	1768	304	8.53 [6.3;10.47]	8.53 [6.3;10.47]	0.89[0.71;1.12]
Women, Spinal, [74,103]	2052	482	4.07 [3.1;5.33]	4.07 [3.1;5.33]	<b>2.21[1.07;4.58]*</b>
Men, Bulbar, [18,64]	979	153	7.6 [6.17;9.67]	7.6 [6.17;9.67]	1.13[0.49;2.59]
Men, Bulbar, [64,74]	1224	251	5.4 [4.2;6.53]	5.4 [4.2;6.53]	<b>2.22[1.75;2.82]*</b>
Men, Bulbar, [74,103]	1285	372	2.1 [1.74;2.54]	2.1 [1.74;2.54]	<b>5.96[2.77;12.79]*</b>
Women, Bulbar, [18,64]	815	104	9.07 [7.27;11.5]	9.07 [7.27;11.5]	0.81[0.08;8.31]
Women, Bulbar, [64,74]	1266	210	7.33 [5.67;9]	7.33 [5.67;9]	1.57[0.69;3.57]
Women, Bulbar, [74,103]	1704	400	3.14 [2.4;3.63]	3.14 [2.4;3.63]	4.16[0.5;34.43]



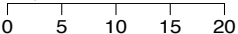
### Gastrostomy -> Death

Patient profile	N	Events	Median [95% CI]	Median [95% CI]	AF [95% CI]
Men, Spinal, [18,64]	3066	94	4.13 [0.6;10.1]	4.13 [0.6;10.1]	<b>0.6[0.43;0.82]*</b>
Men, Spinal, [64,74]	2620	95	2.6 [1.24;6.37]	2.6 [1.24;6.37]	1
Men, Spinal, [74,103]	2434	43	1.77 [1.07;6.67]	1.77 [1.07;6.67]	0.88[0.59;1.3]
Women, Spinal, [18,64]	1940	85	4.53 [0.07;8.83]	4.53 [0.07;8.83]	0.49[0.15;1.57]
Women, Spinal, [64,74]	1768	100	0.2 [0.04;6.03]	0.2 [0.04;6.03]	0.78[0.54;1.12]
Women, Spinal, [74,103]	2052	66	3.27 [1.3;8.2]	3.27 [1.3;8.2]	0.89[0.25;3.22]
Men, Bulbar, [18,64]	979	144	6.23 [3.3;9.1]	6.23 [3.3;9.1]	0.67[0.23;1.96]
Men, Bulbar, [64,74]	1224	165	3.1 [2.07;5.67]	3.1 [2.07;5.67]	1[0.73;1.38]
Men, Bulbar, [74,103]	1285	155	2.67 [1.3;4.13]	2.67 [1.3;4.13]	1.46[0.44;4.85]
Women, Bulbar, [18,64]	815	139	7.43 [4.9;9.3]	7.43 [4.9;9.3]	0.47[0.02;9.88]
Women, Bulbar, [64,74]	1266	221	6.17 [4.5;8.37]	6.17 [4.5;8.37]	0.69[0.22;2.18]
Women, Bulbar, [74,103]	1704	252	3.17 [1.84;5.03]	3.17 [1.84;5.03]	0.99[0.04;24.44]



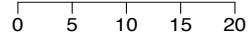
### Gastrostomy and NIV -> Death

Patient profile	N	Events	Median [95% CI]	Median [95% CI]	AF [95% CI]
Men, Spinal, [18,64]	3066	95	9.43 [6.17;13.27]	9.43 [6.17;13.27]	0.6[0.31;1.16]
Men, Spinal, [64,74]	2620	66	5.47 [2.4;11.8]	5.47 [2.4;11.8]	1
Men, Spinal, [74,103]	2434	20	3.07 [1.07;18.97]	3.07 [1.07;18.97]	1.9[0.84;4.33]
Women, Spinal, [18,64]	1940	60	4.67 [4.1;15.5]	4.67 [4.1;15.5]	0.91[0.1;8.53]
Women, Spinal, [64,74]	1768	51	4.33 [4.03;11.33]	4.33 [4.03;11.33]	1.16[0.61;2.22]
Women, Spinal, [74,103]	2052	25	0.7 [0.67;7.6]	0.7 [0.67;7.6]	2.94[0.21;40.24]
Men, Bulbar, [18,64]	979	101	1.85 [1.1;7.3]	1.85 [1.1;7.3]	1.51[0.2;11.22]
Men, Bulbar, [64,74]	1224	108	1.74 [0.7;6.73]	1.74 [0.7;6.73]	<b>1.73[1.01;2.95]*</b>
Men, Bulbar, [74,103]	1285	57	0.77 [0.64;2.67]	0.77 [0.64;2.67]	2.68[0.25;28.16]
Women, Bulbar, [18,64]	815	99	5.4 [3.17;8.27]	5.4 [3.17;8.27]	1.5[0.01;384.81]
Women, Bulbar, [64,74]	1266	122	5.33 [3.3;9.2]	5.33 [3.3;9.2]	1.68[0.23;12.23]
Women, Bulbar, [74,103]	1704	79	1.64 [1.17;5.1]	1.64 [1.17;5.1]	1.59[0;Inf]



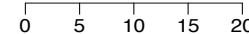
### NIV -> Death

Patient profile	N	Events	Median [95% CI]	Median [95% CI]	AF [95% CI]
Men, Spinal, [18,64]	3066	389	1.74 [0.9;3.63]	1.74 [0.9;3.63]	<b>0.43[0.3;0.64]*</b>
Men, Spinal, [64,74]	2620	389	1.2 [0.64;2.04]	1.2 [0.64;2.04]	1
Men, Spinal, [74,103]	2434	277	0.9 [0.57;1.9]	0.9 [0.57;1.9]	<b>1.61[1.07;2.42]*</b>
Women, Spinal, [18,64]	1940	177	0.97 [0.47;5.17]	0.97 [0.47;5.17]	0.38[0.08;1.7]
Women, Spinal, [64,74]	1768	193	3 [1.2;6.03]	3 [1.2;6.03]	0.88[0.55;1.4]
Women, Spinal, [74,103]	2052	154	0.64 [0.34;1.44]	0.64 [0.34;1.44]	1.18[0.25;5.65]
Men, Bulbar, [18,64]	979	172	6.27 [4.17;8.97]	6.27 [4.17;8.97]	0.58[0.12;2.69]
Men, Bulbar, [64,74]	1224	222	2.5 [1.4;5.03]	2.5 [1.4;5.03]	1.08[0.68;1.72]
Men, Bulbar, [74,103]	1285	168	0.9 [0.64;1.54]	0.9 [0.64;1.54]	1.69[0.35;8.19]
Women, Bulbar, [18,64]	815	98	4.77 [1.34;8.1]	4.77 [1.34;8.1]	0.31[0;32.2]
Women, Bulbar, [64,74]	1266	143	2.87 [1.17;7.17]	2.87 [1.17;7.17]	0.55[0.1;3.02]
Women, Bulbar, [74,103]	1704	123	1.7 [1.3;3.63]	1.7 [1.3;3.63]	1.09[0.01;113.69]



### Tracheostomy -> Death

Patient profile	N	Events	Median [95% CI]	Median [95% CI]	AF [95% CI]
Men, Spinal, [18,64]	3066	25	3.37 [1.37;12.97]	3.37 [1.37;12.97]	<b>0.32[0.13;0.78]*</b>
Men, Spinal, [64,74]	2620	22	1.94 [0.1;4.57]	1.94 [0.1;4.57]	1
Men, Spinal, [74,103]	2434	18	0.67 [0.37;4.7]	0.67 [0.37;4.7]	<b>2.36[1.09;5.13]*</b>
Women, Spinal, [18,64]	1940	9	3.2 [2.27;NA]	3.2 [2.27;NA]	0.21[0;Inf]
Women, Spinal, [64,74]	1768	5	4.13 [3.9;NA]	4.13 [3.9;NA]	0.05[0;1.3]
Women, Spinal, [74,103]	2052	8	1.54 [0.4;NA]	1.54 [0.4;NA]	2.76[0;Inf]
Men, Bulbar, [18,64]	979	14	8.13 [2.54;19.83]	8.13 [2.54;19.83]	0.88[0;300.88]
Men, Bulbar, [64,74]	1224	8	0.7 [0.3;NA]	0.7 [0.3;NA]	1.13[0.13;9.96]
Men, Bulbar, [74,103]	1285	5	5.73 [2.3;NA]	5.73 [2.3;NA]	2.18[0;Inf]
Women, Bulbar, [18,64]	815	7	9.63 [6.57;NA]	9.63 [6.57;NA]	0[0;Inf]
Women, Bulbar, [64,74]	1266	5	4.27 [0.8;NA]	4.27 [0.8;NA]	0.89[0;Inf]
Women, Bulbar, [74,103]	1704	3	1.29 [1.24;NA]	1.29 [1.24;NA]	1.12[0;Inf]



### Gastrostomy and Tracheostomy -> Death

Patient profile	N	Events	Median [95% CI]	Median [95% CI]	AF [95% CI]
Men, Spinal, [18,64]	3066	21	1.17 [0.3;28]	1.17 [0.3;28]	<b>4.63[2.23;9.6]*</b>
Men, Spinal, [64,74]	2620	14	2.3 [1.24;4.57]	2.3 [1.24;4.57]	1
Men, Spinal, [74,103]	2434	4	6.6 [5.47;NA]	6.6 [5.47;NA]	1.19[0.39;3.62]
Women, Spinal, [18,64]	1940	12	3.2 [2.27;NA]	3.2 [2.27;NA]	2.69[0.13;57.06]
Women, Spinal, [64,74]	1768	5	6.8 [4.37;NA]	6.8 [4.37;NA]	0.9[0.32;2.5]
Women, Spinal, [74,103]	2052	2	16.1 [12.5;NA]	16.1 [12.5;NA]	2.13[0.03;131.29]
Men, Bulbar, [18,64]	979	19	13.37 [9.43;25.4]	13.37 [9.43;25.4]	1.98[0.14;27.19]
Men, Bulbar, [64,74]	1224	10	9.73 [2.9;NA]	9.73 [2.9;NA]	1.45[0.64;3.28]
Men, Bulbar, [74,103]	1285	2	12.03 [11.5;NA]	12.03 [11.5;NA]	1.2[0.03;54.03]
Women, Bulbar, [18,64]	815	14	9.3 [6.57;25.17]	9.3 [6.57;25.17]	1.88[0;9846.87]
Women, Bulbar, [64,74]	1266	3	7.27 [NA;NA]	7.27 [NA;NA]	0.86[0.03;28.06]
Women, Bulbar, [74,103]	1704	4	1.34 [NA;NA]	1.34 [NA;NA]	0.53[0;45899.8]

