ORIGINAL RESEARCH

Registration of Amyotrophic Lateral Sclerosis: Validity in the Danish National Patient Registry

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Purpose: Health care databases are a valuable source for epidemiological research on amyotrophic lateral sclerosis (ALS) if diagnosis codes are valid. We evaluated the validity of the diagnostic codes for ALS in the Danish National Patient Registry (DNPR).

Patients and Methods: We obtained data from the DNPR for all adult (>17 years) patients registered with ALS in Denmark between 1987 and 2022 (median population of 4.2 million during the study period). We randomly selected adult patients living in the North Denmark Region and Central Denmark Region (median population 1.4 million), with a primary discharge diagnosis code of ALS, diagnosed at three departments of neurology. We retrieved and reviewed medical records and estimated the positive predictive value (PPV) of the ALS diagnosis.

Results: Over 36 years, we identified 5679 patients. From the validation cohort of 300 patients, we were able to retrieve 240 (80%) medical records, and 215 ALS diagnoses were confirmed. The overall positive predictive value was 89.6% (95% confidence interval (CI): 85.1–92.8). The highest PPV was achieved for diagnoses registered for patients aged \geq 70 years (93.8; 95% CI: 86.2–97.3) compared to patients <60 years (83.4; 95% CI: 73.3–90.7).

Conclusion: We found a high PPV of primary diagnostic codes for ALS from Danish departments of neurology, demonstrating high validity. Thus, the DNPR is a well–suited data source for large-scale epidemiological research on ALS.

Keywords: registries, positive predictive value, international classification of disease codes, epidemiology, amyotrophic lateral sclerosis

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare disease characterized by progressive motor neuron degeneration, with a reported incidence rate between 2.1 and 3.8 per 100,000 persons per year in Europe.¹ Death from ALS is usually due to respiratory failure and occurs within one to four years from diagnosis.² Advances have been made in understanding the genetic background for ALS; however, only up to 10% of cases are genetically inherited.^{2,3} The underlying etiology of sporadic ALS remains poorly understood, and identification of risk factors for ALS has proven difficult.^{1,4} Yet suspicion has been raised, that environmental factors may contribute to ALS risk.^{3,5} Many studies addressing ALS risk factors rely on hospital discharge diagnosis codes recorded in administrative health care databases.^{2,6} Use of these databases for epidemiological research can be a cost-efficient way of collecting data on ALS.^{1,7} National databases in Denmark may provide exact estimates of effect and enable studying of rare exposures or outcomes. The risks of recall bias and non-response are reduced; however, the usability of these databases relies heavily on the validity of the registered data.^{7,8} Thus, to draw valid inferences from database studies on ALS, the validity of the diagnosis needs to be determined.^{1,7,8}

In our study, we examined the quality of ALS discharge diagnosis in the population-based Danish National Patient Registry (DNPR) by estimating the positive predictive value (PPV) using medical record data as a reference standard. Furthermore, we determined whether the validity of the ALS diagnosis varied by year of diagnosis, sex, and patient age.

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Materials and Methods

Setting and Data Sources

Denmark has 5.9 million citizens, and the country is divided into five regions.⁹ The Danish National Health Service provides all inhabitants with tax–supported health care. Since 1968, all Danish citizens have been registered in the Danish Civil Registration System and given a unique 10–digit civil registry number (CPR number).⁸ This number contains information on birth date and sex and enables unique identification and matching of registry data at the individual level. The DNPR was established in 1977 and contains data on all hospital admissions, including CPR number, admission and discharge dates, hospital department, primary discharge diagnosis code (the primary reason for hospitalization), and secondary diagnosis codes.⁷ All neurological hospital care is provided by 14 neurological departments located at five university hospitals and nine general hospitals in the five Danish regions. Hospital data are recorded prospectively for administrative purposes, independent of specific research questions. Data from both private and public hospitals and clinics are recorded in the DNPR. Medical diagnoses have been registered in the DNPR using the International Classification of Disease, version 8 (ICD–8) from 1977 through 1993 and the International Classification of Disease, version 10 (ICD–10) from 1994 onwards.⁷ The ALS disease modifying treatment, riluzole, was approved in Denmark on June 10, 1996.¹⁰

Identification of Coded ALS Cases

Using the DNPR, we identified all patients with discharge diagnoses consistent with ALS:

- ICD-8 from 1980 to 1993: 348.0: sclerosis lateralis amyotrophica (17.6% of all ALS diagnoses).
- ICD-10 from 1994 to 2022: DG122: motor neuron disease including DG122 subcodes: DG122C: atrophia musculorum Duchenne-Aran, DG122F: paralysis spinalis progressiva, and DG122G: amyotrophic lateral sclerosis (82.4% of all ALS diagnoses).

To ensure the highest quality of data for the ALS diagnosis, we included only cases that fulfilled the following criteria: 1) the ALS diagnosis code must be the first primary discharge diagnosis code, given after evaluation at an inpatient and outpatient clinic; and 2) the ALS diagnosis code must be given at a department of neurology, since according to the Danish National Board of Health evaluation and treatment of adult ALS can only be performed by departments of neurology.¹¹ Thus, other departments will not have the expertise to diagnose ALS. In Denmark, even all patients admitted to an ICU must have a local referring department,¹² which in these cases would always be a neurological department. This study was based on data from patients aged >17 years from 1980 to 2022.

From the study population described above (N = 6135), we aimed to create a representative sample of the entire Danish population for validation purpose.¹³ We included ALS cases from two different regions, including both regional and university hospital representative for the nationwide population with regard to sociodemographic and health-related characteristics.¹⁴ We randomly selected 300 cases from the North and Central Denmark Regions, including 200 from Aarhus University Hospital and 50 from each of the general hospital and the additional university hospital. Due to destruction of paper archives, it was impossible to find 56 paper medical records. All missing medical records originated from the period prior to the digitalization of medical records (2011), with approximately 80% being older records from the period before 2005. Furthermore, we excluded four patients with suspected ALS who died during the diagnostic workup.

Medical Record Validation

Validation was performed using medical record data as reference standard. Medical records were manually reviewed by a trained medical student under the supervision of the study neurologist (LL). Neurophysiological examinations were manually reviewed and classified according to the Airlie House criteria.¹⁵ Cases were categorized as ALS or non-ALS according to the revised El-Escorial criteria with inclusion of progressive muscle atrophy (PMA) according to the latest diagnostic criteria,^{16–18} relying on a combination of clinical features, findings on neurophysiological examinations, results from MRI of brain and spine, blood tests, genetic tests, and examinations of cerebrospinal fluid including

neurofilament light chain levels (NFL) obtained within the first year of diagnostic workup. We classified patients according to phenotypes: classic ALS, progressive bulbar palsy, PMA, and ALS with frontotemporal dementia (FTD). Moreover, we retrieved demographic data and data on the hospital where the diagnostic workup was performed, familial predisposition to ALS, and treatment with riluzole since 1996.

Statistical Analysis

PPV was used as a measure of diagnostic validity and was estimated as the proportion of ALS cases identified in the validation cohort who had ALS according to their medical records. We calculated the PPV with 95% confidence intervals (CI) using the exact method for binominal proportions. The analyses were stratified by decade of diagnosis, sex, and age at diagnosis (18–59, 60–69, and \geq 70 years) to evaluate any difference in PPV.

We analyzed the data using Stata Software (version 18; Stata Corp., College Station, TX, USA). The study was registered in the internal list of research projects in Central Jutland Region and approved by The Central Jutland Regional Committee on Health Research Ethics (record number 1–45–70–63–21). We confirm that the data accessed complied with relevant data protection and privacy regulations.

Sensitivity Analyses

Two sensitivity analyses were performed to assess the robustness of our findings. First, we re-categorized patients diagnosed with clinically possible ALS as non-ALS patients. In the second analysis, the identification of patients with ALS in the DNPR was restricted, including only patients with ALS discharge diagnoses who were treated with riluzole, according to medical record data. This ALS definition was validated as the main analysis, using medical record data as reference standard.

Results

In the final validation sample of 240 patients with ALS, the median age at diagnosis was 66 years (interquartile rage: 59–73 years; range 20–92 years), 57.9% were male, and patients were diagnosed with ALS discharge codes 34,809, DG122 and DG122G from 1987 to 2022. ALS diagnosis was correct in 215 of the 240 cases. Of the confirmed cases, 44.2% were classified as definite ALS cases, and 39.5% as probable ALS cases. Fifteen patients (7%) did not meet the criteria for definite or probable ALS and were classified as having possible ALS (Table 1). Among the possible ALS cases, however, 13 cases were treated with riluzole, and 9 cases were categorized as progressive bulbar palsy. Twenty patients (9.3%) presented with only lower motor neuron affection and were classified as having progressive muscle atrophy and were accepted as correctly coded ALS cases. Among the confirmed ALS cases, 57.7% (n = 124) were male, and the mean age at diagnosis was 66 years (range, 34–92 years); however, only two cases were younger than 40 years of age. Additional characteristics of the patients with confirmed ALS are presented in Table 1 and Table 2.

Among the remaining 25 patients whose ALS diagnosis was rejected, all except one was diagnosed with DG122, 13 had central nervous system disorders including primary lateral sclerosis, Parkinson's disease, and structural lesions (eg, stroke and spinal stenosis). Peripheral nervous system disorders and muscle diseases accounted for 10 of the 25 non-ALS cases and included polyneuropathy (including CMT, alcohol-associated polyneuropathy, and polio sequelae), polymyositis, and radiculopathy. Two non-ALS cases had unspecified neurological disorders.

Positive Predictive Values

The overall PPV was 215/240 = 89.6% (95% CI: 85.1–92.8). Stratifying for sex, year of diagnosis, and age at diagnosis, the PPV remained high (Table 2). The highest PPV was achieved for diagnoses registered for patients aged \geq 70 years (PPV = 93.8; 95% CI: 86.2–97.3) and the lowest for patients aged <60 years (PPV = 83.4; 95% CI: 73.3–90.7).

Sensitivity Analyses

In our additional analysis, re-categorizing clinically possible ALS cases as non-ALS cases resulted in a lower PPV compared to the main analysis (PPV = 83.3; 95% CI: 78.1–87.5 vs PPV = 89.6; 95% CI: 85.1–92.8). In contrast, re-definition of ALS cases (ALS diagnosis code and riluzole-treatment) resulted in an increase in the PPV to 98.7 (95% CI: 95.5–99.6).

Variable	Value
Total (N)	215
Age (Y), median	66 (IQR, 60–73)
Age (Y), range	34–92
Hospital of ALS diagnosis	
Aarhus University Hospital	154 (71.6%)
Aalborg University Hospital	20 (9.3%)
Gødstrup Hospital	41 (19.1%)
CSF-data	126 (58.6%)
CSF cell count <10 per mm ³	126 (58.6%)
CSF NFL-data ^a	27 (12.6%)
Increased CSF NFL (n=19) (ng/L), median	6774.5 (IQR, 4,558.5–10,000.0)
MRI of CNS-data	170 (79.1%)
Neurophysiological examination	187 (87.0%)
ALS defined be the revised El Escorial criteria ^b	
Clinically definite ALS	95 (44.2%)
Clinically probable ALS	85 (39.5%)
Clinically possible ALS	15 (7.0%)
ALS phenotype	
Classic ALS	181 (84.2%)
Progressive bulbar palsy	≤10 (≤4.7%)
ALS with FTD	≤5 (≤2.3%)
Progressive muscle atrophy	20 (9.3%)
Genetically verified ALS	≤5 (≤2.3%)
First or second-degree relatives with ALS	5 (2.3%)
Riluzole treatment ^c	157 (73.0%)

Notes: ^aNFL analysis was introduced in Denmark in 2018. ^bProgressive muscle atrophy (n=20) do not fulfill the revised El Escorial criteria, however, is included as an ALS variant. ^cRiluzole approved in Denmark from June 1996.

Abbreviations: ALS, amyotrophic lateral sclerosis; CNS, central Nervous system; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; IQR, interquartile range; MRI, magnetic resonance imaging; N, number of cases; NFL, neurofilament light chain; PPV, positive predictive value; Y, years.

Variable	Total (N)	ALS (N)	Non-ALS (N)	PPV (%)	95% CI
All	240	215	25	89.6	85.1-92.8
Males	139	124	15	89.2	83.0–93.4
Females	101	91	10	90.1	82.7–94.5
Year of diagnosis					
1987–1999	52	47	5	90.4	79.4–95.8
2000–2009	83	75	8	90.4	82.1–95.0
2010-2022	105	93	12	88.6	81.1–93.3
Age at diagnosis					
(years)					
<60	68	57	11	83.4	73.3–90.7
60–69	92	83	9	90.2	82.4–94.8
≥70	80	75	5	93.8	86.2–97.3

Table 2 Validity of ICD-Codes for Amyotrophic Lateral Sclerosis in the DNPR

Abbreviations: ALS, Amyotrophic lateral sclerosis; Cl, confidence interval; N, number of cases; PPV, positive predictive value.

Discussion

We observed that 90% of the primary ALS diagnoses given at departments of neurology were confirmed by review of medical records, and this high PPV persisted across all strata (year of diagnosis, sex, and age groups). Re-categorization of clinically possible ALS cases as non-ALS cases lowered the PPV, whereas restriction of ALS case definition to ALS discharge diagnosis and riluzole treatment increased the PPV considerably compared to the main analysis.

The estimated PPV from our study is comparable with those of other published studies.^{19–22} In Denmark, the validity of the ALS discharge diagnosis was previously examined in 173 subjects during the period from 1982 to 2009 in the DNPR.¹⁹ The PPV for a less restrictive ALS case definition (ICD–8: 348.0, ICD–10 DG122, all hospital departments) compared with medical record review was 77.5% (95% CI: 70.5–83.5%), using the El-Escorial criteria on medical record review as gold standard. However, if patients with clinically suspected ALS on medical record review were categorized as confirmed ALS, the estimated PPV for hospital discharge data was 92.5% (95% CI: 87.5–95.9%).¹⁹ Similar to our results, no differences were observed across sexes, and the PPVs varied by age with a lower PPV among the youngest patients compared to the middle-aged patients; PPV = 77.8% (95% CI: 57.7–91.4%) among patients aged <55 years compared to a PPV of 81.9% (95% CI: 73.2–88.7%) among patients aged 55–74 years. In contrast to our results, they found the lowest PPV (PPV = 67.6%; 95% CI: 50.2–82.0%) for patients older than 75 years. This difference may be explained by the higher number of clinically suspected ALS and PMA patients in the oldest age group compared to the other two age groups.¹⁹

The similar overall PPVs found in the population of patients diagnosed in all hospital departments (PPV = 92.5%) compared to the population diagnosed at a department of neurology (PPV = 89.6%) may be caused by a large overlap of patients diagnosed at a department of neurology.¹⁹ Between 1980 and 2022, patients diagnosed with ALS at a department of neurology represented 91.4% (6135/6713) of patients with primary ALS codes diagnosed at all Danish hospital departments. Still, in future analytical epidemiological studies on ALS risk and prognostic factors, the validity of the diagnosis is of high importance, and a patient population with primary ALS diagnoses from neurological departments may be well suited.²³

Although we examined only a part of the Danish national population (median background population of 1.4 million during the study period), we consider the PPV to be representative of the entire nation due to the uniform structure of record-keeping and the homogenous health care system in Denmark. Moreover, all Danish residents have free tax–funded access to medical care, including hospital admission and treatment. All medical care is registered in one nationwide system, which minimizes the risk of selection problems. Data in the registries are recorded by the treating physicians and collected mainly for administrative use and therefore unrelated to research purposes. Clinicians have no financial incentive to use the ALS code over other codes; therefore, the risk of information bias is low.

Limitations

Our study had several limitations. First, we examined only one dimension of validity: the predictive value of a positive registration of ALS. Because we did not include data on undiagnosed patients with ALS in this study, we were unable to estimate the negative predictive value, sensitivity, and specificity of the ALS diagnosis.²⁴ However, due to the severe symptoms, clinical signs, and progressive nature of ALS, we believe that only few of the most severely affected patients was undiagnosed. Second, 19% of potential cases were excluded from validation in our study because many medical records from before 2011 were missing due to destruction of paper archives. However, we have no reason to suspect that this was related to their accuracy. Third, our validation study was performed using data from only two of the five regions in Denmark. Regional differences in diagnostic practice could affect the PPV, however owing to the uniform nature of the Danish health care system, the structure of record keeping, and the inclusion of neurological departments at both general and university hospitals, we consider our findings to be generalizable for the entire country. Fourth, in our study, the medical records were evaluated without blinding to the registered discharge diagnosis codes.²⁵ However, since the result of the "test under study" (=the register diagnosis) was given by definition for all the examined patients (as only patients who had a diagnosis were included); it is unlikely that lack of blinding of the reviewer would have influenced the PPV.

Finally, we acknowledge that hospital discharge data cannot be considered the gold standard. To address this limitation, we conducted a sensitivity analysis that included only patients with ALS discharge diagnoses who were

treated with riluzole. In this analysis, the estimated PPV was considerably higher than in the main analysis (99% and 90%, respectively).

If the DNRP is used to assess changes in the incidence of ALS over time, the PPV must remain stable over time to obtain valid estimates.²⁶ We found no variation in PPV by study period over the 36–year period of our study.

Conclusion

We showed that primary ALS discharge diagnosis codes from neurological departments in Denmark have high validity, useful for both future descriptive and analytical epidemiological research on ALS.

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Disclosure

The authors report no conflicts of interest in this work.

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