Edinburgh Research Explorer

Improved survival and 30-day mortality after gastrostomy in Scottish motor neurone disease patients: evidence from a national retrospective cohort study using STROBE criteria

Improved survival and 30-day mortality after gastrostomy in Scottish motor neurone disease patients: evidence from a national retrospective cohort study using STROBE criteria

George H. Gorrie, Siddharthan Chandran, Shuna Colville, Judith Newton, Danielle Leighton, Menai Mcdonald, Suvankar Pal, Raeburn Forbes, Mario Hair & Robert Swingler

Taylor & Francis
Taylor & Francis Group

Check for updates

RESEARCH ARTICLE

Improved survival and 30-day mortality after gastrostomy in Scottish motor neurone disease patients: evidence from a national retrospective cohort study using STROBE criteria

GEORGE H. GORRIE[1], SIDDHARTHAN CHANDRAN[2], SHUNA COLVILLE[3], JUDITH NEWTON[3], DANIELLE LEIGHTON[2], MENAI MCDONALD[1], SUVANKAR PAL[2], RAEBURN FORBES[4], MARIO HAIR[1]* & ROBERT SWINGLER[5]

[1]Department of Neurology, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, UK, [2]Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, UK, [3]Anne Rowling Regenerative Neurology Clinic, The University of Edinburgh, Edinburgh, UK, [4]Department of Neurology, Southern HSC Trust, Craigavon Area Hospital, Craigavon, UK, and [5]Department of Neurology, Ealing Hospital, Southall, UK

Abstract

Objectives: Defining historical changes and outcomes in the use of gastrostomy in the management of Scottish MND patients. *Methods*: The 1989–1998 and 2015–2016 Scottish national MND cohorts were used to examine the frequency, timing, and survival related to gastrostomy. The cohorts were censored for survival analysis. *Results*: There were 261 cases, 119 (46%) from the new register (2015–2016) and 142 (54%) from the old register (1989–1999). Percutaneous endoscopic gastrostomy (PEG) tubes were used exclusively in the old register *vs.* the new register where PEG (45%), Radiologically inserted gastrostomy (RIG) (44%) and a small number of peroral image-guided gastrostomy (PIGG) tubes (11%), $p < 0.01$ were used. Odds of 30-d mortality in the old register were 2.8 times that in the new register, $p < 0.01$. Median survival time from gastrostomy was significantly higher in the new register, 2.7 months, $p < 0.05$. Median survival time from onset was also higher in the new register but non-significant, 3.2 months, $p = 0.30$. Multivariate analysis identified age at onset (hazard ratio [HR] 1.02 $p = 0.01$), time from onset to diagnosis (HR 0.74 $p < 0.01$), subtype of onset (HR 1.52 $p = 0.01$), with gastrostomy and Riluzole interacting as variables that predict risk of death. *Conclusions*: Gastrostomy use has increased with techniques changing over time. It is safer and survival time has increased post gastrostomy. Being older and diagnosed more quickly increases risk of death whilst taking Riluzole combined with gastrostomy reduced risk of death. Survival from onset has not significantly changed in Scottish MND patients having gastrostomy.

KEYWORDS: *Amyotrophic lateral sclerosis, motor neurone disease, gastrostomy, survival, therapy, epidemiology, nutrition*

Introduction

Motor neurone disease (MND) or more specifically amyotrophic lateral sclerosis (ALS) is one of the neurodegenerative disorders (1). What sets MND apart is that it is a disorder whose impact is rapidly profound with the median survival from onset being less than three years in many healthcare systems across the world (2). Effective therapeutics have been difficult to develop despite a multitude of trials over three decades (3). Only one drug, Riluzole has been licensed (4) for this

disease until recently with a second drug Edaravone gaining recent Food and Drug Administration (FDA) approval (5). Much of the management of MND is, and has necessarily focused on symptom management. Significant advances in this domain include the use of non-invasive ventilation (NIV) (6), with an improved survival and a positive impact on quality of life. MND can present in around a third of patients initially affecting speech and swallowing, so-called bulbar onset patients. Many of these patients develop early difficulties with swallowing which

can impact on their quality of life and nutritional status. It is not surprising that physicians and healthcare professionals wish to help such individuals by providing them with alternative routes by which they can receive nutrition and hydration. Chief among them is the gastrostomy and to a lesser degree the nasogastric tube.

There has been much debate regarding the when, who and how over gastrostomy insertion in the MND/ALS population (7). Recent studies have highlighted the potential deleterious nature of this procedure (8). Indeed there was concern regarding the role of gastrostomy in the Scottish MND population in the early 2000s, where a one-month mortality after gastrostomy of 25% in MND patients was identified (9). There have been no randomized trials of this intervention to guide clinicians and such studies are unlikely to take place because of ethical difficulties with regard to withholding hydration and nutrition. In the light of the potential hazardous role of gastrostomy in MND patient care, a study of artificial enteral nutrition using the Scottish MND register was undertaken using a national MND register. Comparisons over time were made using historical data form the first national MND register based here in Scotland between 1989 and 1998 to identify if there had been any changes in practice and outcome (10).

Methods

Study population

We used the recently relaunched Scottish MND register and Scottish government statistics to compare the frequency and timing of gastrostomy during the two year period 2015–2016 with that of the original Scottish MND register cohort 1989–1998. Strengthening the reporting of observational studies in epidemiology (STROBE) reporting principles were adhered to in the preparation of the manuscript (11). Both cohorts were censored to enable a comparison of survival. The MND register in Scotland identifies patients from multiple sources, including adult Neurologists, MND care specialists and a platform that enables self-identification *via* the Clinical Audit Research Evaluation MND (CARE MND) website for patients themselves. Ethical approvals were obtained for the SMNDR/CARE-MND *via* the Scotland A Research Ethics Committee. Access to Information Services Division data was approved by the Public Benefit and Privacy Panel for Health and Social Care Scotland. To enhance the accuracy and quality of the data gastrostomy interventions and mortality data were also captured by examining Scottish Government national records from the Information Service Division (ISD). Using this capture-recapture technique ascertainment in the Scottish MND register has been

identified at 99% (12). MND was defined by the revised El Escorial criteria (13). Patients were defined as having, Limb, Bulbar, Respiratory and Behavioral/frontotemporal dementia subtypes at onset. The incident cases diagnosed from the beginning of 2015 to the end of 2016 were evaluated in this study with a censoring date of the 19 March 2018. Dates of disease onset, diagnosis and gastrostomy were collected. Survival is from gastrostomy to either death or census date. Data on potential confounders was collected for gender, age, onset site, tube type, NIV, and Riluzole use.

Missing data

There were no missing data for covariates. We excluded sixteen cases from the survival analysis including nine patients with gastrostomy before diagnosis (7 new and 2 old), six patients with missing onset date (all old register) and one patient with gastrostomy before onset and diagnosis (new register). These 16 cases were excluded from the survival analysis but will be included wherever possible to maximize data use.

Statistical analysis

Univariate analysis was performed using chi-square test for categorical variables, t-test for comparison of mean times and Mann–Whitney for comparison of median times. Time from onset to gastrostomy, survival time from onset and gastrostomy were all heavily skewed with a number of outliers. For these variables, medians are shown in Table 2 and either non-parametric tests (Mann–Whitney) or Kaplan–Meier with log-rank test were used to compare the two registers. Correlation between skewed variables was assessed by calculating Pearson's correlation on natural log transforms. Survival analysis was performed using Cox regression with survival time (in months) from gastrostomy to either death or census date. Covariates were "age at diagnosis (years)", "time between onset and diagnosis (in years)", sex, "time between diagnosis and gastrostomy (months)", "site of onset", tube type and use of Riluzole, NIV status and Register. Reference categories were "female" for gender, "bulbar" for site of onset, "PEG and no use of Riluzole" for tube type and use of Riluzole, no NIV and "old register" for register.

The old register covered a longer time period and this may affect the survival analysis. To adjust for this any patients in the old register with survival longer than the longest in the new register (825 d) were reset as alive and censored at 825 d. This affected nine patients, five of whom had died; this is referred to as the "adjusted old register". Statistical analysis was performed using SPSS version 24 (SPSS Inc., Chicago, IL) and R using R commander (Vienna, Austria) (14).

Table 1. Sample characteristics by register.

	Overall (n = 261)	New register (2015–16) (n = 119)	Old register (1989–98) (n = 142)	p*; OR (95% CI)
Gender (n, % male)	128 (49%)	74 (62%)	54 (38%)	p < 0.01; OR 2.7 (1.6, 4.4)
Onset (n, % bulbar)	151 (60%)	64 (57%)	87 (62%)	p = 0.46 NS
NIV (n, %)	49 (19%)	49 (41%)	0	p < 0.01
Mortality (n, %)	233 (89%)	97 (82%)	136 (96%)	p < 0.01; OR 0.20 (0.08, 0.50)
Adjusted[a] mortality (n, %)	233 (89%)	97 (82%)	131 (92%)	p < 0.01; OR 0.37 (0.17, 0.80)
30-d mortality rate (n, %)	46 (18%)	12 (10%)	34 (25%)	p < 0.01; OR 0.36 (0.18, 0.73)
Tube type & use of Riluzole				
PEG & no Riluzole	148 (57%)	23 (19%)	125 (88%)	p < 0.01
PEG & Riluzole	48 (18%)	31 (26%)	17 (12%)	
RIG & no Riluzole	21 (8%)	21 (18%)	0	
RIG & Riluzole	31 (12%)	31 (26%)	0	
PIGG & no Riluzole	4 (2%)	4 (3%)	0	
PIGG & Riluzole	9 (3%)	9 (8%)	0	
Gastrostomy		n = 111	n = 140	
<3 months from diagnosis	57 (23%)	20 (18%)	37 (26%)	p < 0.05
3–6 months from diagnosis	52 (21%)	28 (25%)	24 (17%)	
6–12 months from diagnosis	61 (24%)	34 (31%)	27 (19%)	
Over 12 months from diagnosis	81 (32%)	29 (26%)	52 (37%)	
Chronological data by register	Overall	New register	Old register	Difference, p**
Mean (±SD) age at Onset (years)	63.5 ± 12.0	62.6 ± 12.7	64.3 ± 11.4	−1.7; p = 0.26 NS
Mean (±SD) age at Diagnosis (years)	64.7 ± 12.0	63.6 ± 12.5	65.6 ± 11.5	−1.9; p = 0.19 NS
Mean (±SD) age at gastrostomy (years)	65.6 ± 11.7	64.2 ± 12.3	66.8 ± 11.0	−2.6; p = 0.07 NS
Median (±IQR) time onset to diagnosis (months)	9.7 ± 8	10 ± 7.6	9.0 ± 4.0	1.0; p = 0.09 NS
Median (±IQR) time onset to gastrostomy (months)	17.7 ± 15.1	16.8 ± 13.9	18.4 ± 16.3	−1.6; p = 0.64 NS
Median survival time from onset (months)[b]	26.6 ± 2.3	28.4 ± 3.7	25.2 ± 3.9	3.2, p = 0.30 NS
Median (±IQR) survival time from gastrostomy (months)[b]	7.2 ± 1.1	8.1 ± 1.7	5.4 ± 1.8	2.7; p = 0.04

*p is from chi-square test, OR: odds ratio. **p from two-sample t-test for means and Mann–Whitney tests for medians and log-rank test for survival.
[a]On adjusted old register. [b]Results are the same using adjusted old register.

Table 2. HR (95% CI) for stepwise Cox regression of survival time from gastrostomy.

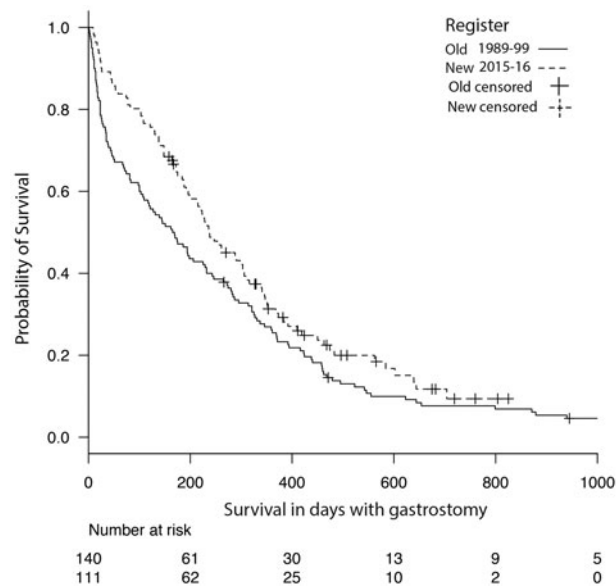|	p	HR (95% CI)
Age at onset (years)	0.01	1.02 (1.01, 1.03)
Time (years) onset to diagnosis	<0.01	0.75 (0.62, 0.90)
Subtype onset site (spinal)	0.01	1.52 (1.10, 2.11)
Gastrostomy (reference PEG with no Riluzole)	0.049	
PEG tube & Riluzole	0.036	0.66 (0.45, 0.97)
RIG tube (no Riluzole)	0.081	0.61 (0.35, 1.06)
RIG tube & Riluzole	0.042	0.63 (0.41, 0.98)

Cox & Snell R squared = 0.12.

Figure 1. Kaplan–Meier survival analysis of old and new registers post gastrostomy, log-rank test $p = 0.04$.

Results

Sample characteristics

As can be seen from Table 1 there were a total of 261 cases with 119 (46%) from the new register (2015–2016) and 142 (54%) from the old register (1989–1998). There were significant differences in the sex distribution between the two registers. The majority of cases in the new register (62%) were male but they formed the minority in the old register (38%), the change was statistically significant $p < 0.01$; odds ratio 2.7 (confidence interval [CI], 1.6–4.4). In both registers, patients who had gastrostomy tubes inserted were predominantly bulbar in onset (60%) with no significant difference between the two groups. There were significant changes in the types of gastrostomy tubes used, the use of Riluzole and NIV. No patients in the old register received NIV but this had been used in 41% of patients in the new register by the time of censorship. Mean age at onset and gastrostomy were lower in the new register although the difference only approached significance for age at gastrostomy. Median time between onset and gastrostomy was lower in the new register but the difference was not significant.

Survival and mortality

Median time between onset and death and from gastrostomy to death was higher in the new register, however, only survival from gastrostomy was statistically significant (Kaplan–Meier analysis, log-rank test $p = 0.04$, Figure 1). There was a statistically significant difference in both overall and 30-d mortality, odds of both overall and 30-d mortality in the old register was around 2.8 times that in the new register. The distribution of time from diagnosis to gastrostomy between registers was different.

In the new register, there were roughly equal numbers "<3 mths", "3–6 mths", "6–12 mths", and ">12 mths" from diagnosis. In the old register, there were more in the two extreme categories, "<3 mths" and ">12 mths". This was not however linked to greater 30-d mortality, with the mortality rate of 25% consistent across the time categories (Table 1). In the old register, there was a weak positive correlation between time from onset to diagnosis and time from diagnosis to gastrostomy ($r = 0.22$, $p = 0.01$). Those in whom the disease progression was slower tended to wait longer for gastrostomy. There was no such correlation in the new register ($r = 0.07$, $p = 0.49$) the timing of gastrostomy was not related to disease progression.

Cox regression model

A backward stepwise Cox regression was run with survival time (in months) from gastrostomy to either death or census date and all other factors as covariates. There were 239 cases in the model with 22 (8%) missing. There were 214 (90%) deaths. The model fit was poor (R squared = 0.12). In the final model age at onset, time between onset and diagnosis, subtype, Riluzole use, and gastrostomy tube were significant predictors (Table 2). The use of Riluzole and type of tube differed significantly between the two registers (Table 1). Both RIG tubes and Riluzole were more widely used in the new register. The findings were not materially different when using the adjusted old register. There is a potential bias in the use of Riluzole in that it may not be given to individuals who were deteriorating quickly. However, the median time from onset to diagnosis was similar for those with and without Riluzole

(median ± IQR; no Riluzole 9.99 ± 9.07 months; Riluzole 9.25 ± 7.18 months; $p = 0.84$).

Discussion

Gastrostomy is widely used to improve nutrition and hydration in people with MND, its efficacy, however, has not been evaluated in a clinical trial. Our earlier study highlighted the potentially deleterious nature of the procedure because at a time when the intervention was being introduced from 1989 to 1998 the 30-d mortality was 25%. Since then patient selection, treatments, and operative techniques have changed. With the relaunch the Scottish MND register we have been able to compare the frequency, timing, and survival in the new register with historical data.

We have collected information on a national basis with a high level of case ascertainment. This has limited but not eliminated bias by recall, case selection, or that produced by a particular center and its procedures. For example a center may only have access to one particular gastrostomy insertion technique. In addition a unique historical perspective was possible given access to original data from one of the first national MND registers in the world, based in Scotland between 1989 and 1998 (12,15). However, there are limitations in this study, with possible ascertainment bias produced by retrospective data collection. It is not a randomized study so causation cannot be inferred only association. Bias due to lack of inclusion will be reduced by the use of a national register with near complete case identification. The time period for follow up after the 2015–2016 cohort was different from the 1989–1998 cohort. This was adjusted as part of the statistical approach. No nutritional data such as body mass index (BMI) were collected in the original register that limited its use as a variable in the analysis. There is evidence that weight loss of 10% or more prior to gastrostomy can predict a poorer outcome (16). Quality of life data on the impact of gastrostomy was not collected in the original register and this is an additional limitation of this work. In the original register, data on cognition was not collected nor was their identification of the presence or absence of multidisciplinary care. Multidisciplinary care has been identified to improve survival in MND patients (17). It is increasingly recognized that patients with MND can have significant cognitive deficits and this is associated with a poorer prognosis (18,19). One further limitation of this work relates to complications post procedure. These were not examined and the cause of death in those dying within the 30-d period post gastrostomy was not identified either in the old register or the new register.

There are significant differences between the two registers with regard to sex, use of Riluzole, use of NIV, types of gastrostomy, and 30-d mortality. Some of the differences reflect evolution of clinical practice, for example Riluzole was not widely available for patients with MND in Scotland during the time of the old register and NIV was not yet identified as an effective treatment for MND patients until 2006. Radiological insertion of gastrostomy is also a more recent development. The reason for the change in sex distribution is unknown. It was of interest to examine how these new variables and the passage of time may have impacted on the use and outcomes of gastrostomy in the Scottish MND population.

We have observed a significant increase in the number of gastrostomies in our population, 119 in a two year period *vs.* 142 from 1989 to 1998. It is safer now with a lower 30-d mortality of 10%. This is higher than the PROGAS study figure of 4% (16), however, our ascertainment technique was population-based so was less likely to be subject to inclusion bias. Reassuringly, the 10% 30-d mortality is similar to that reported in a recent meta-analysis of gastrostomy in MND (20). This analysis did incorporate studies that were relatively small in number and related to historical practice. More men are having the procedure performed 62 *vs.* 38% and the median survival from gastrostomy was significantly increased (8.1 *vs.* 5.4 months, (2.7, $p < 0.05$)) while overall survival from onset was also increased but not significantly (28.4 *vs.* 25.2 months (3.2, $p = 0.30$, NS)). The cause of these changes is likely to be complex.

There are clearly increasing number of gastrostomies occurring in this patient population. Decision making surrounding gastrostomy is complex (21). More people could be undergoing gastrostomy because of the increasing amounts of readily accessible information *via* social media and the internet for example https://mytube.mymnd.org.uk/. There may also be an increasing availability of the procedure. Radiological Insertion of Gastrostomy is now more routine and can be performed on more advanced patients with respiratory compromise (22). Other factors that may be contributory could include a more interventional approach to palliative care and an increasing involvement of patients in decision making with regard to their care.

Many factors are likely to contribute to risk when it comes to survival after a gastrostomy. It is interesting to observe that in the new register, there were fewer gastrostomies being performed within three months of diagnosis or after 12 months from diagnosis. Performing gastrostomies at the two extremes my select out patients who are deteriorating faster and who are at the end stages of their condition and could contribute to the

differences seen in the study. The results of the multivariate analysis indicate that Riluzole and gastrostomy interact and are significant variables that are contributing to the observed change in survival after gastrostomy in the new register. When these are controlled for, the variable of "register" loses its significance in the multivariate analysis. Radiological insertion of gastrostomy was not performed during the time of the old register. It can be conducted with the use of less sedation. This may contribute to an improved safety profile of the technique in patients who have respiratory compromise. RIG without Riluzole, when compared to PEG without Riluzole, was not significant suggesting an important contribution of Riluzole in the interaction. Riluzole was given infrequently in the old register. There is evidence that it slows disease in randomized trials and reduces risk of death in disease registers (23). There was no suggestion that Riluzole use was skewed to individuals who were progressing less quickly. The PROGAS study did identify that RIG tubes were associated with more complications post procedure but did not identify an increased mortality pattern with their use compared with PEG tubes. The PROGAS study, however, did not collect data on Riluzole and it was not factored into the analysis.

It is interesting to note that the use of NIV did not appear to be a significant variable with regard to survival after a gastrostomy in the Cox model. It should be noted that the timing of NIV was not specified in this analysis (that is before or after the procedure). The timing of the introduction of NIV may reduce risk of sedation during interventional procedures, such as gastrostomy. NIV use in patients with bulbar onset disease can be challenging and its benefit is less in terms of its impact on survival (6). This may be one factor that contributes to the lack of effect on survival from diagnosis between the two cohorts despite the introduction of NIV over time (24). This is an area that requires further study.

Age at diagnosis and speed of diagnosis were contributory variables that influence survival after gastrostomy. They have been observed by others in MND registers as variables which predict prognosis (25). Every year of age at onset increased HR by 2%, which should be noted when considering gastrostomy in the very old (50 years HR 2 *vs.* 85 years HR 2.7). Every year between onset and diagnosis reduced HR by 26% while spinal onset increased HR by 53%. The increased hazard associated with spinal onset is likely to reflect the tendency to perform gastrostomy in spinal onset patients later on in the disease course compared to bulbar onset patients. None of the other variables were significant, in particular time from diagnosis to gastrostomy made no difference to survival in the populations under study.

Conclusions

These observations may help guide decision making with regard to gastrostomy in MND patients. This study is not designed to advocate one particular approach but provides a historical analysis of gastrostomy in Scottish MND patients. It supports an individualized and holistic approach rather than a time-pressured or prophylactic approach to the use of gastrostomy in patients with MND. The use of Riluzole combined with gastrostomy in the management of MND patients is supported by this research. Despite the advances of NIV and Riluzole in the intervening 20 years it was disappointing not to see a significant improvement in survival from onset. This may reflect the predominant bulbar onset pattern in the population that was studied (60%) double that seen in an unselected MND population. The difference in survival between the two registers form gastrostomy was small and its impact on survival from onset was lost in the variation over the longer time period. This variation reflects a complex reality involving a large number of variables that can affect MND patient's survival many of which were not captured in this work. The lack of significant change in survival from onset over a 20-year interval emphasizes the importance of developing new effective therapeutics to treat this devastating condition. Given the limited impact on survival, it will be important for future work to define the impact of gastrostomy on the quality of life of MND patients who have this procedure performed. One approach would be to prospectively collect data on survival and quality of life in those who have and who do not have gastrostomies inserted. An alternative approach would be to perform a randomized trial on those where the decision to intervene is not clear cut and collect such data.

Declaration of interest

The authors report no conflict of interest.

Funding

References

1. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. N Engl J Med. 2017;377:162–72.
2. Beghi E, Logroscino G, Chiò A, Hardiman O, Mitchell D, Swingler R, et al. The epidemiology of ALS and the role of population-based registries. Biochim Biophys Acta. 2006;1762:1150–7.
3. Petrov D, Mansfield C, Moussy A, Hermine O. ALS clinical trials review: 20 years of failure. Are we any closer to registering a new treatment? Front Aging Neurosci. 2017;9:68.

4. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/riluzole study group. N Engl J Med. 1994;330:585–91.

5. Writing Group and Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16:505–12.

6. 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;5:140–7.

7. Katzberg HD, Benatar M. Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev.* 2011;1:CD004030.

8. McDonnell E, Schoenfeld D, Paganoni S, Atassi N. Causal inference methods to study gastric tube use in amyotrophic lateral sclerosis. Neurology. 2017;89:1483–9.

9. Forbes RB, Colville S, Swingler RJ, Scottish Motor Neurone Disease Research Group. Frequency, timing and outcome of gastrostomy tubes for amyotrophic lateral sclerosis/motor neurone disease–a record linkage study from the Scottish Motor Neurone Disease Register. J Neurol. 2004;251:813–7.

10. The Scottish Motor Neuron Research Group. The Scottish Motor Neuron Disease Register: a prospective study of adult onset motor neuron disease in Scotland. Methodology, demography and clinical features of incident cases in 1989. J Neurol Neurosurg Psychiatry. 1992;55:536–41.

11. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12:1500–24.

12. Forbes RB, Colville S, Parratt J, Swingler RJ. The incidence of motor nueron disease in Scotland. J Neurol. 2007;254:866–9.

13. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1:293–9.

14. Fox J. Using the R commander: a point-and-click interface for R. Boca Raton, FL: CRC Press; 2016.

15. Davenport RJ, Swingler RJ, Chancellor AM, Warlow CP. Avoiding false positive diagnoses of motor neuron disease: lessons from the Scottish Motor Neuron Disease Register. J Neurol Neurosurg Psychiatry. 1996;60:147–51.

16. ProGas Study Group. Gastrostomy in patients with amyotrophic lateral sclerosis (ProGas): a prospective cohort study. Lancet Neurol. 2015;14:702–9.

17. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000. J Neurol Neurosurg Psychiatry. 2003;74:1258–61.

18. Elamin M, Bede P, Montuschi A, Pender N, Chio A, Hardiman O. Predicting prognosis in amyotrophic lateral sclerosis: a simple algorithm. J Neurol. 2015;262:1447–54.

19. Wolf J, Safer A, Wohrle JC, Palm F, Nix WA, Maschke M, et al. Factors predicting survival in ALS patients–data from a population-based registry in Rhineland-palatinate, Germany. Neuroepidemiology. 2015;44:149–55.

20. Stavroulakis T, Walsh T, Shaw PJ, McDermott CJ, Progas Study. Gastrostomy use in motor neurone disease (MND): a review, meta-analysis and survey of current practice. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14:96–104.

21. Martin NH, Landau S, Janssen A, Lyall R, Higginson I, Burman R, et al. Psychological as well as illness factors influence acceptance of non-invasive ventilation (NIV) and gastrostomy in amyotrophic lateral sclerosis (ALS): a prospective population study. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:376–87.

22. Allen JA, Chen R, Ajroud-Driss S, Sufit RL, Heller S, Siddique T, et al. Gastrostomy tube placement by endoscopy *versus* radiologic methods in patients with ALS: a retrospective study of complications and outcome. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14:308–14.

23. Mandrioli J, Malerba SA, Beghi E, Fini N, Fasano A, Zucchi E, et al. Riluzole and other prognostic factors in ALS: a population-based registry study in Italy. J Neurol. 2018;265:817–27.

24. Banfi P, Volpato E, Valota C, D'Ascenzo S, Alunno CB, Lax A, et al. Use of noninvasive ventilation during feeding tube placement. Respir Care. 2017;62:1474–84.

25. Rooney J, Byrne S, Heverin M, Corr B, Elamin M, Staines A, et al. Survival analysis of Irish amyotrophic lateral sclerosis patients diagnosed from 1995–2010. PLoS One. 2013;8:e74733.