The prevalence of multimorbidity and its impact on survival in people with motor neuron disease

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Abstract

Objectives: To determine the prevalence of multimorbidity in people with motor neuron disease (MND) and to identify whether specific patterns of multimorbidity impact survival beyond age alone.

Methods: We performed a retrospective analysis of the Scottish national MND register 01/01/2015-29/10/2019. People with amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy or progressive bulbar palsy were included. We fitted latent class regression models incorporating comorbidities (class indicators), age, sex and bulbar onset (covariates), and survival (distal outcome) with multimorbidity as a hypothesised latent variable. We also investigated the association between the Charlson Comorbidity Index and survival in Cox regression and compared its discrimination and calibration to age alone.

Results: 937 people with MND were identified (median age 67, 60.2% male); 64.8% (515) had two or more comorbidities. We identified a subpopulation with high prevalence of cardiovascular disease but, when accounting for the relationship between age and individual comorbidities, there was no difference in survival. Both Charlson Comorbidity Index (hazard ratio [HR] per unit increase 1.11 95%CI 1.07, 1.15; P<0.0001) and age (HR per year increase 1.04 95% CI 1.03, 1.05; P < 0.0001) were significantly associated with survival but discrimination was higher for age compared to Charlson Comorbidity Index (C-index 0.63 vs 0.59).

Conclusions: Multimorbidity is common in MND necessitating holistic inter-disciplinary management but age is the dominant predictor of prognosis in people with MND. Excluding people with MND and multimorbidity from trial participation may do little to homogenise the cohort in terms of survival potential and could harm generalisability.

Introduction

Motor neuron disease (MND) is a relentlessly progressive neurodegenerative disease; prognosis is typically short, but variable. A proportion of people with MND (pwMND) have comorbid disease,[1-6] which could contribute to differential survival. If so, understanding this may allow for better personalised prognostic estimates, a more holistic approach to care, and refine pragmatic analyses of real-world disease cohorts and inclusive clinical trials. Previous studies investigating the impact of specific comorbidities on MND survival have yielded conflicting results, ranging from negative[1,3] to neutral[2,7,8] and beneficial effects[9,10]. Discordant results may have arisen due to differences between study populations, classification of comorbidities or complexity in the impact of different patterns of individual comorbidities and multimorbidity.

Multimorbidity, defined as the co-existence of multiple health conditions, is an evolving concept that acknowledges the interaction of comorbidities with one another in ways that create clinical complexity[11]. In the general population, multimorbidity is associated with greater disability than expected based on the additive disability attributable to each disease in isolation[12]. Given the age distribution of MND and the prevalence of comorbidities previously reported, multimorbidity, and related polypharmacy, are likely to be a frequent occurrence. However, to our knowledge, their prevalence has not been systematically investigated in pwMND and no studies have attempted to determine the effects of specific patterns of multimorbidity in any neurodegenerative disease. The few studies published examining multimorbidity in neurodegenerative diseases[3,13-16] have mainly assessed impact on outcomes other than survival.

The only examination to address survival impact, from a multicentre Italian study, indicated that the Charlson Comorbidity index (CCI), a weighted index of comorbidities, was significantly associated with survival in pwMND in univariate, but not multivariable, analysis, after adjusting for age, cardiovascular disease and other variables[3]. However, the non-significant adjusted result may have occurred due to duplicate adjustment for age in the calculation of CCI itself or conditioning arbitrarily on cardiovascular disease in multivariable analysis. Therefore, additional research is required to determine whether multimorbidity impacts survival beyond the effect of age alone, a known predictor of survival[17]. Furthermore, it is possible that particular patterns or clusters of comorbidities exist that interact with one another and MND to determine survival, hereafter termed multimorbidity patterns. For example, concomitant lung disease and heart failure may worsen MND-related respiratory failure and cardiovascular disease is associated with mortality, as suggested by previous literature[1,3].

Against this background, our objectives were: 1) To investigate the prevalence and patterns of multimorbidity and polypharmacy in pwMND 2) To determine if specific multimorbidity patterns differentially impact on survival beyond age alone.

Methods

Patient selection

Patients were drawn from the Scottish Clinical Audit Research Evaluation for Motor Neurone Disease (CARE-MND) platform[18], a prospectively maintained national population-based register which achieves longitudinal deep clinical phenotyping. People with ALS (pwALS), primary lateral sclerosis, progressive bulbar palsy or progressive muscular atrophy registered on CARE-MND 01/01/2015-29/10/2019 were included. The STROBE criteria[19] and the PROBAST tool[20] were used for preparation of the manuscript.

Ascertainment of multimorbidity

We extracted data on comorbidities present at diagnosis as listed in medical records; comorbidities are recorded in free text and were deemed to be absent if not recorded. We also used medication data to complement the comorbidity data where reasonable inferences about the likely comorbidities could be made. For participants with missing data who attended our centre we also searched hospital records. Conditions were grouped into 19 candidate comorbidities [21] using clinical judgement (Table 1 for candidate conditions, Supplementary Table 1 for grouping). Cognitive impairment was measured using the Edinburgh Cognitive and Behavioural Screen (ECAS) for a subset of participants. We did not incorporate cognitive impairment as a comorbidity into latent class analysis because it was not possible to establish whether these were early manifestation of frontotemporal dementia associated with MND or independent comorbidities. However, cognitive impairment forms an integral part of the Charlson Comorbidity Index (see below) and was thus included in its calculation.

Explanation of analysis strategy

To discriminate multimorbidity patterns we used latent class regression, a statistical approach which classifies individuals into mutually exclusive subgroups (latent classes) based on an unobservable construct. Here, the construct of interest is multimorbidity, which is measured by multiple observed variables, the comorbidities (latent class indicators). As such, we aimed to categorise and sort pwMND into "multimorbidity classes" based on having similar profiles of comorbidities. To investigate if latent class membership differentially impacts on survival, we combined latent class analysis with Cox regression in a "one-step" approach where we regress survival on multimorbidity class. Furthermore, to avoid confounding of relationships between multimorbidity and survival we included age at symptom onset and sex as covariates in the model. Survival was also adjusted for bulbar onset, a known predictor of survival, which was judged to be independent of other covariates and latent class membership. In this model not only the comorbidities but also age, sex and survival could determine which class a person with MND is assigned to[22], and these variables were examined for their ability to predict survival. Additionally, we investigated the predictive ability of the CCI, a weighted multimorbidity index[23]. We compared the "age-weighted" CCI (0-4 points for age groups <50 years to >80 years) to the "non-age-weighted" CCI (excluding points for age group) and to age alone. We subsequently performed sensitivity analysis including only pwALS.

Latent class regression

Continuous-time survival mixture Cox-regression models, a form of latent class analysis, were fitted by maximum likelihood estimation with robust standard errors for which up to 5000 random starts with up to 1250 final stage optimisations were specified. We fitted these models using class indicators (comorbidities) to inform the measurement part of the model, and distal time-to-event censored outcome (survival) with covariates (age, sex, bulbar onset) and latent class as the structural part of the model. We extended this by examining direct interactions between age and comorbidities. Hereby, we regressed individual comorbidities on age in univariate logistic regression and included the significant regression relationships ($P<0.05$) in the model statement (Supplementary Table 2). To decide on the optimal number of latent classes, we considered the Bayesian information criterion (BIC, lower value indicates better fitting model), the parametric bootstrap likelihood test and the Vuong-Lo-Mendell-Rubin test alongside the substantive interpretability of the model. To evaluate classification quality, we reported the entropy measure and the mean posterior probability of class membership. The logrank test was used to determine whether survival differed significantly between latent classes and the effect of class membership on survival was examined in Kaplan-Meier analysis. All P-values are two-tailed and P-values < 0.05 were considered significant. The linearity of age in relation to survival was confirmed using martingale residual plots; age was mean centered for ease of interpretation. To aid convergence of the latent class regression models, only comorbidities deemed of prognostic importance were included in latent class regression.

Application of the age-adjusted Charlson Comorbidity Index (CCI)

In addition to counts of conditions, we calculated the CCI to align with previous research on multimorbidity in MND[3]. We adapted the CCI by removing the hemiplegia criterion and, due to the data availability in our cohort, we scored all liver disease as "mild". Survival was regressed on CCI in a Cox proportional hazards model and results are displayed as hazard ratios (HR) per unit increase (CCI) or year/10-year increase (age) and 95% confidence intervals. Kaplan-Meier curves were visually inspected for violation of the proportional hazards assumption. Model discrimination was assessed using Harrell's C-index and calibration using the Grønnesby and Borgan test; larger P-values indicate better calibration.

Missing data were handled using full information maximum likelihood estimation in latent class regression and multiple imputation by chained equations with predictive mean matching when calculating hazards by CCI. Latent class regression was performed in MPlus version 8.4 and all other analyses were performed and figures generated in R version 4.0.0 using the packages mice[24] and MplusAutomation[25] and UpSetR[26] and base R.

Results

Demographics

Between 01/01/2015 and 29/10/2019, 937 pwMND were identified of whom 57 (6.1%) had missing survival data ,143 (15.2%) had missing comorbidity data (where data were not recorded in initial data capture) and 418 (44.6%) had missing data on cognitive testing. 564 (60.2%) pwMND were male and the median age at symptom onset was 67 years (IQR 16, range 22-96). The population comprised people with amyotrophic lateral sclerosis (649, 69.3%), progressive bulbar palsy (80, 8.5%), primary lateral sclerosis (27, 2.9%) and progressive muscular atrophy (25, 2.7%), and unrecorded subtype (remainder, most likely ALS). Site of onset included spinal (503, 58.3%), bulbar (281, 32.6%) mixed (70, 8.1%) and pure respiratory (9, 1.0%). Median survival from symptom onset was 29 months (95% CI 27, 31).

Prevalence of comorbidities, multimorbidity, medication use and polypharmacy

Overall, 86.5% (685) had one or more comorbidity and 25.4% (202) had four or more comorbidities.

The most common comorbidities were hypertension (318, 39.4%), psychiatric disorders/depression/anxiety (243, 29.3%), hyperlipidaemia (178, 22.3%), ischaemic heart disease/arrythmia (147, 18.4%), osteoarthritis (142, 17.2%) and cancer (101, 12.5%; most commonly prostate and breast). 52.9% (285) used one or more medication during their disease course (excluding medications prescribed for MND management). The most frequently used medications were analgesics (300, 42.8%), proton pump inhibitors (240, 34.2%) and statins (195, 27.8%). The distribution of comorbidities and medication usage was similar between the entire cohort and pwALS (Table 1). Intersection analysis shows that there were no specific combinations of comorbidities that occurred particularly frequently, but that the most common co-occurring comorbidities were psychiatric disorders and hypertension, diabetes and hypertension, and hyperlipidaemia and hypertension (Fig 1).

Multimorbidity patterns and impact of multimorbidity on survival

Socioeconomic class, measured using the Scottish Index of Multiple Deprivation 2016[27], was not related to survival in univariate analysis and therefore not included in the analysis. We initially fitted latent regression models comprising comorbidities, survival, age, sex and bulbar onset but not direct relationships between age and individual comorbidities (Fig 2, solid lines). Models with 1-5 latent classes were fitted; a 6-class solution did not converge. The 2-class model had the best fit. It yielded a "multimorbidity" class (n=336) with very high prevalence of cardiovascular disease and heart failure, and mildly elevated prevalence of all other conditions except asthma and autoimmune disease compared to the "healthy class" (n=504). Members of the "multimorbidity class" were considerably older compared to the "healthy class" and had significantly worse survival (Fig 3a).

In view of the substantial age difference in this class and the higher prevalence of many comorbidities with age, we sought to determine whether comorbidities were in fact acting as surrogates for age by incorporating direct effects between class indicators (comorbidities) and covariate (age) in the model when adjusting for age (Fig 2, dashed lines). We fitted models with 1-3 classes; a 4-class solution did not

converge. The BIC and parametric bootstrap likelihood test results favoured the 1-class (null) model whilst the Vuong-Lo-Mendell-Rubin likelihood ratio test favoured a 2-class solution (Supplementary table 3). The 2-class model yielded a "heart disease" class (n=80) with, again, a high prevalence of cardiovascular disease and heart failure, and moderately elevated prevalence of chronic lung disease (except asthma), neurological disease, urinary problems and chronic renal disease compared to the other class (n=760), (Supplementary Fig 1). There was no difference in survival between classes (Fig 3b; see Supplementary Table 4 for details of structural model). The entropy was 0.81, indicating good classification quality (entropy range 0-1 ,1 indicates perfect classification). The 2-class model with direct effects was fitted in sensitivity analysis including only pwALS. The class composition and survival differences were similar to the model fitted in all pwMND.

Application of the CCI

Age-weighted CCI, non-age-weighted CCI and age alone were all significantly associated with survival, but discrimination was higher for age alone. The median age-weighted CCI was 3 (IQR 3, range 0-12). Sensitivity analysis including only pwALS yielded similar results. We attempted sensitivity modifications to the CCI; however, none resulted in better predictive performance. Because data on cognitive testing were frequently missing, we conducted a "best-case" analysis that assumed that all pwMND with missing cognitive data did not have cognitive impairment and a "worst-case" analysis where all pwMND with missing cognitive data were recorded as having cognitive impairment. In the "worst-case" analysis the age-weighted and non-age-weighted CCIs performed better although their performance remained worse compared to age at symptom onset alone (Table 2). Lastly, we found that smoking was not related to survival in pwMND (HR 1.002 95%CIs 0.83, 1.21).

Discussion

In keeping with previous literature, our work indicates that hypertension, heart disease, psychiatric disorders and cancer are the commonest comorbidities in pwMND[1,3]. The prevalence of these and other comorbidities was higher in our study compared to prior research; which is likely explained by the higher mean age of our cohort but may also speak to the relatively high ascertainment of these conditions given the strong primary care in Scotland's universal healthcare system[1,3,5]. Interestingly, there is growing evidence that ALS, the most common MND subtype, differentially affects individuals with lower prevalence of cardiovascular disease[2,28-30]. One possible explanation may be that people with severe cardiovascular disease are less likely to live long enough to develop MND.

The high prevalence of multimorbidity and polypharmacy in our study has implications for clinical care. For the overwhelming majority of pwMND, attention will need to be paid to the optimal management of other medical conditions. Multimorbid pwMND, whose MND is generally managed in specialist neurological settings, are likely to benefit from a holistic approach with inter-disciplinary team involvement with

emphasis on coordination of care across specialties, in line with clinical guidelines[31]. The impact of polypharmacy and potential side effects of treatments on MND also needs consideration.

We hypothesised that pwMND can be categorised into multimorbidity patterns that differentially impact on prognosis using latent class regression, a method to identify unobservable subgroups of a population based on the similarity of their characteristics. This approach allowed us to frame the analysis in terms of multimorbidity patterns, acknowledging the interrelatedness of comorbidities[11]. Our unbiased approach identified a class dominated by cardiovascular disease and heart failure, which was associated with a modestly reduced survival in the initial analysis, replicating previous findings [1,3].

However, as cardiovascular disease is a composite endpoint of numerous pathophysiological processes that are individually strongly associated with age, it is possible that this grouping and modest survival effect was a reflection of the complex relationship with age and individual components for cardiovascular disease. Consistent with this observation, we noted that when extending the analysis to examine not only the effect of age on multimorbidity and survival, but also the direct relationships between age and individual comorbidities, we found that survival effects were conditioned away. In addition, the size of the multimorbid disease class (which was dominated by cardiovascular disease) was much reduced (n = 80 vs n = 336) when comparing the adjusted to unadjusted two-class model. In summary, our findings suggest that an association of cardiovascular disease and survival exists but that it is primarily a mediator for the dominant effects of age. Similarly, comparing the HR per unit increase of the non-age-weighted CCI (1.06) to that of the age-weighted CCI (1.11) and the HR for age per 10-year increase (1.45) suggests that the effect of age on survival is larger than any effect of comorbidities on survival. It is possible that the statistical significance of the non-age-weighted CCI could have arisen due to uncontrolled confounding by age.

Our results indicate that age rather than multimorbidity may be best used for prognostication. The ascertainment of age has practical advantages, since data are readily available in clinical practice whereas no standardised measurement exists for multimorbidity[32]. Age is likely to be a proxy for numerous metabolic and cellular factors; it is thought that the putative pathogenic mechanisms of ALS closely resemble those involved in the normal ageing process[33].

Further, our findings suggest that, rather than there being a shared mechanistic impact of multimorbidity patterns and MND, a comorbidity would need to exert an even more devastating effect on MND survival to influence prognosis. In contrast to MND, multimorbidity is highly predictive of mortality in general medical and oncology patients[34-36]. Notably, few diseases are as relentlessly progressive as MND and for many conditions, effective management strategies are available whereas existing interventions for MND only confer a survival gain of several months[37]. In oncology patients, vulnerability to the side effects of chemotherapy and/or eligibility for the latter may, in part, explain why multimorbidity impacts on mortality.

Previous research has identified that clinical trials exclude a median of 77% of participants due to comorbidities[38] and several recent seminal MND trials have imposed strict exclusion criteria based on multimorbidity and polypharmacy. However, our findings support widening participation as excluding multimorbid pwMND from participation would seem to do little to homogenise the study population with respect to survival potential; rather, it may deprive pwMND of opportunities to engage in clinical research, slow recruitment, and harm generalisability.

Strengths and limitations

A strength of our study is its high representativeness of the Scottish MND population as shown by the high case ascertainment (99%) of our registry database[39]. Our analysis strategy, latent class regression and application of the CCI, is associated with a lower risk of inflated type 1 errors compared with testing multiple potential predictors using stepwise procedures[40].

Whilst our MND registry collects data prospectively, our analysis and design for this study was retrospective, with attendant limitations. We assumed unrecorded comorbidities to be absent; however, some comorbidities may have been undiagnosed and/or unrecorded. Data on cancer metastasis, diabetic complications and severity of liver disease may not have been consistently reported, which could have affected calculation of the CCI. Nonetheless, it is likely that missing data on complications of cancer, diabetes and liver disease only affect a relatively small proportion of individuals. Misclassification of comorbidities could have led to violation of the conditional independence assumption of latent class analysis. Data on cognitive testing were likely missing not at random where pwMND with poor cognition are less likely to have been tested. For this reason, we conducted a "best case" and "worst case" analysis, which showed no major differences between the two cases. Furthermore, our results may be subject to unmeasured confounders such as diet and nutrition, for which data were unavailable. Lastly, we were unable to take into account the relative severity of comorbidities; to do this, future prospective research is required.

Conclusion

In this population-based analysis of 937 pwMND, multimorbidity and polypharmacy were common, necessitating holistic inter-disciplinary management. We identified a subpopulation with high prevalence of cardiovascular disease; however, after accounting for the relationship between age and individual comorbidities in the model, there was no difference in survival. This suggests that age is the dominant predictor of prognosis in people with MND and that the previously identified association between cardiovascular disease and survival is mediated by age. Excluding people with MND and multimorbidity from trial participation may do little to homogenise the cohort in terms of survival potential and could harm generalisability.

Declarations

Contributor statement: Conception and design: SAG, PKAK, SP. Data acquisition: SAG, JL, CARE-MND consortium. Statistical analysis: SAG, PKAK. Drafting the manuscript, revising the manuscript for important intellectual content and interpretation of the data: all authors. Supervision of the project: SP.

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Ethics approval: Participants consented to inclusion in the CARE-MND register. Ethics approval for CARE-MND was provided by the Scotland A Research Ethics Committee (Approval: 15/SS/0126). Consent from participants was obtained at the time of their registration with the CARE-MND register.

Patient consent to publication: Not required.

Data availability: Data available upon request from the authors.

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Table 1. Comorbidities and polypharmacy in pwMND

a) Denotes comorbidities included in latent class regression b) Cognitive impairment not included in total number of comorbidities, presented here due to being part of CCI c) excluding medications commonly used for MND symptom management. Cardiovascular disease includes ischaemic heart disease, arrhythmias, peripheral vascular disease; COPD = Chronic obstructive pulmonary disorder; TIA: Transient ischaemic attack.

Fig 1. Intersection plot of comorbidities. Autoimm = Autoimmune condition, COPD.ILD.OSA = Chronic obstructive pulmonary disorder/interstitial lung disease/obstructive sleep apnea, CVS = Cardiovascular disease, DM = Diabetes mellitus, HF = Heart failure

Fig 2. Hypothesised relationships between comorbidities (class indicators), multimorbidity (latent variable), survival (distal outcome), and age, bulbar onset and sex (covariates) in pwMND. Grey shade - measurement model; white shade - structural model. Solid line: initial analysis, dashed lines: extended analysis including direct effects between age and individual comorbidities.

Fig 3a. Kaplan-Meier curve displaying survival according to latent class for the 2-class model not including direct relationships between comorbidities and age. Class 1 is the “healthy class" and class 2 is the “multimorbid class".

Fig 3b. Kaplan Meier curve for survival according to class membership for the 2-class model with direct relationships between age and individual comorbidities. Class 1 is the "healthy class” and class 2 is the “heart disease” class.

Table 2. Association between CCI, age and survival

Association between CCI and age alone and survival in pwMND. CCI: Charlson's comorbidity index; HR: Hazard ratio per unit increase (CCI) or 1-year/10-year increase (age); 95%CI: 95% confidence interval. Age-weighted CCI range: 0-12; median 3. Non-age-weighted CCI range: 0-10; median 1.

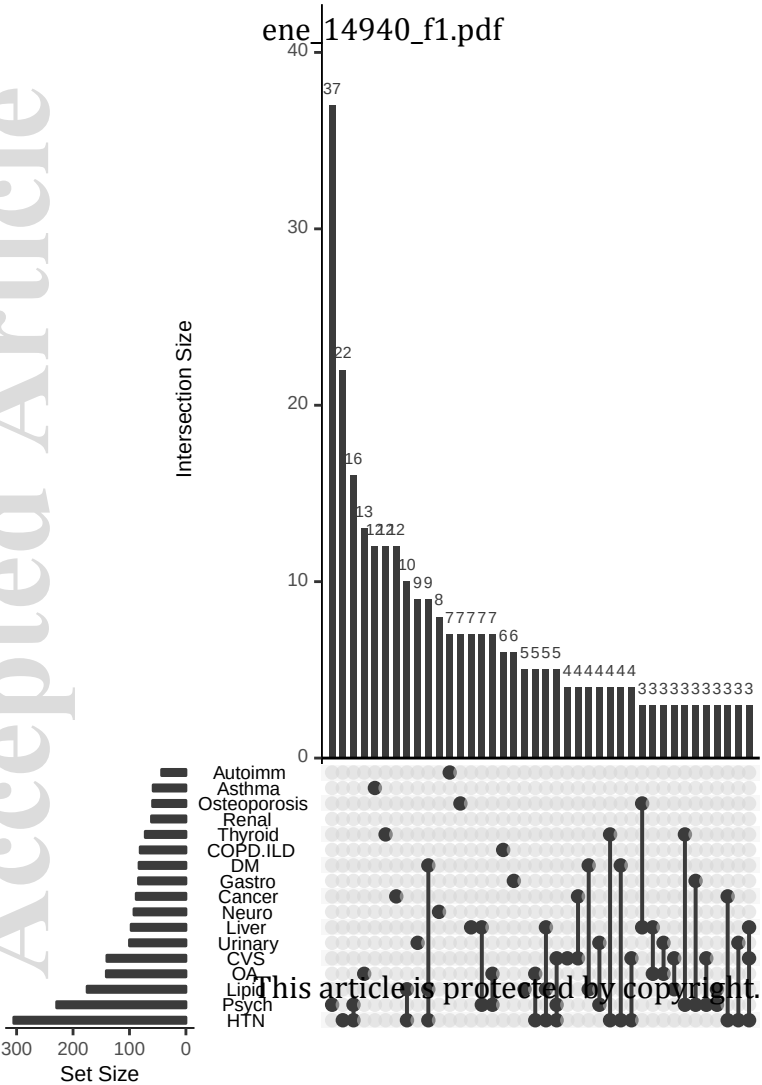
Table 1. Comorbidities and polypharmacy in pwMND

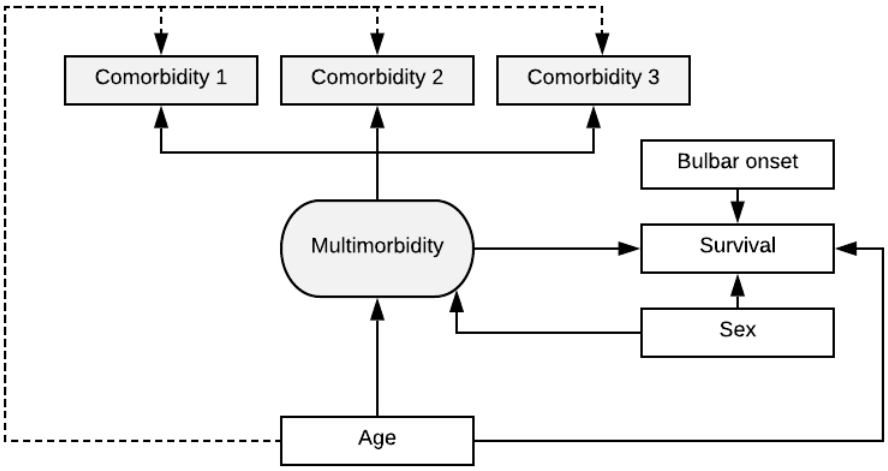
Characteristic	Measure	All MND number (%)	ALS number (%)
Number of comorbidities*	0	109 (13.7)	80 (10.1)
	1	170 (21.4)	132 (16.6)
	2	167 (21.0)	127 (16.0)
	3	146 (18.4)	105 (13.2)
	≥ 4	202 (25.4)	142 (17.9)
Types of comorbidities	Cardiovascular disease[a]	147 (18.4)	102 (17.4)
	Heart failure or cardiomyopathy[a]	43 (5.4)	29 (4.9)
	Hypertension	318 (39.4)	219 (37.1)
	Hyperlipidaemia	178 (22.3)	138 (21.8)
	COPD/Interstitial lung disease/obstructive sleep apnea[a]	84 (10.5)	56 (9.5)
	Asthma[a]	59 (7.4)	37 (6.3)
	Gastroenterological disease[a]	84 (10.6)	60 (10.2)
	Liver disease[a] and alcohol excess	104 (13)	77 (13)
	Neurological disease/Stroke/TIA[a]	99 (12.4)	65 (11.1)
	Osteoarthritis	142 (17.9)	111 (18.9)
	Osteoporosis	60 (7.5)	43 (7.3)
	Autoimmune disease[a]	46 (5.8)	27 (4.6)
	Thyroid disease	74 (9.3)	53 (9.0)
	Diabetes mellitus (type 1 and 2)[a]	85 (10.7)	65 (11.1)
	Cancer[a]	101 (12.5)	70 (11.8)
	Psychiatric disorder (including Depression/Anxiety)	234 (29.3)	166 (28.3)
	Urinary disorder[a]	103 (12.9)	70 (11.9)
	Chronic renal condition[a]	63 (7.9)	40 (6.8)
	Cognitive impairment*(abnormal ECAS)[b]	225 (43.4)	121 (40.1)
Number of medications[c]	0	72 (9.1)	54 (9.2)
	1-2	214 (27.0)	166 (28.3)
	3-6	325 (40.9)	244 (41.6)
	≥ 7	90 (11.3)	63 (10.8)
Common medication types	Analgesia	300 (42.8)	222 (42.1)
	Anti-anginals/anti-arrythmics	65 (9.3)	46 (8.7)
	Antiplatelets	165 (23.5)	116 (22)
	Anti-diabetic	41 (5.8)	33 (6.3)
	Beta-blocker	112 (16.0)	81 (15.4)
	Diuretic	52 (7.4)	39 (7.4)

	Inhaler	94 (13.4)	66 (12.5)
	Proton pump inhibitor	240 (34.2)	177 (33.6)
	Serotonin re-uptake inhibitor	171 (24.4)	128 (24.3)

Table 2. Association between CCI, age and survival

Sample	Measure	Age-weighted CCI	Non-age-weighted CCI	Age alone (per 1-year increase)	Age alone (per 10-year increase)
All MND "best case"	HR (95% CIs)	1.11 (1.07, 1.15)	1.06 (1.00, 1.13)	1.04 (1.03, 1.05)	1.45 (1.34, 1.57)
	P-value	P < 0.0001	P=0.034	P < 0.0001	P < 0.0001
	C-index	0.59	0.53	0.63	0.63
All MND "worst case"	HR (95% CIs)	1.12 (1.09, 1.16)	1.09 (1.03, 1.15)	NA	NA
	P-value	P < 0.0001	P=0.003	NA	NA
	C-index	0.61	0.57	NA	NA
ALS only "best case"	HR (95% CIs)	1.12 (1.07, 1.17)	1.07 (1.01, 1.14)	1.04 (1.03, 1.05)	1.42 (1.31, 1.54)
	P-value	P < 0.0001	P=0.015	P < 0.0001	P < 0.0001





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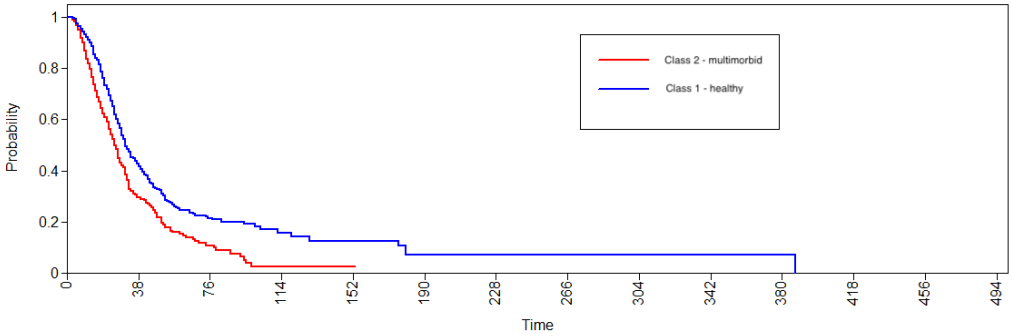

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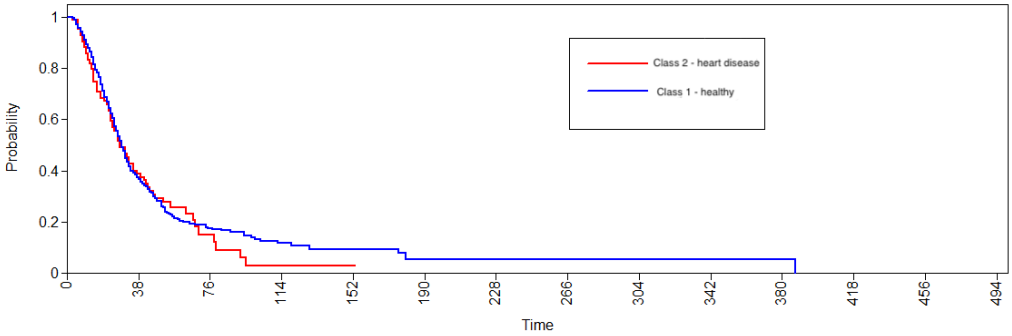

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