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ORIGINAL ARTICLE

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

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Abstract

Background and purpose: This study was undertaken 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 from 1 January 2015 to 29 October 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: A total of 937 people with MND were identified (median age = 67 years, 60.2% male); 64.8% (n = 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% confidence interval [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 interdisciplinary 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.

KEYWORDS
amyotrophic lateral sclerosis, clusters, comorbidity, motor neuron disease, multimorbidity, prognosis, survival

CARE-MND Consortium members are listed in the Acknowledgements section.

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 refinement of 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 coexistence 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 multivariate analysis, after adjusting for age, cardiovascular disease, and other variables [3]. However, the nonsignificant adjusted result may have occurred due to duplicate adjustment for age in the calculation of CCI itself or conditioning arbitrarily on cardiovascular disease in multivariate 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 (i) to investigate the prevalence and patterns of multimorbidity and polypharmacy in pwMND and (ii) to determine whether 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 that achieves longitudinal deep clinical phenotyping. People with amyotrophic lateral sclerosis (pwALS), primary lateral sclerosis, progressive bulbar palsy, or progressive muscular atrophy registered on CARE-MND from 1 January 2015 to 29 October 2019 were included. The STROBE criteria [19] and the PROBAST tool [20] were used in 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, Table S1 for grouping). Cognitive impairment was measured using the Edinburgh Cognitive and Behavioural Screen 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 this was an early manifestation of frontotemporal dementia associated with MND or an independent comorbidity. However, cognitive impairment forms an integral part of the CCI (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 that 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 whether 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

TABLE 1 Comorbidities and polypharmacy in people with MND

Characteristic	Measure	All MND, *n* (%)	ALS, *n* (%)
Comorbidities, *n*	0	109 (13.7)	80 (13.7)
	1	170 (21.4)	132 (22.5)
	2	167 (21.0)	127 (21.7)
	3	146 (18.4)	105 (17.9)
	≥4	202 (25.4)	142 (24.2)
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 apnoea[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 (Types 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 (10.3)	54 (10.2)
	1–2	214 (30.5)	166 (31.5)
	3–6	325 (46.4)	244 (46.3)
	≥7	90 (12.8)	63 (12.0)
Common medication types	Analgesic	300 (42.8)	222 (42.1)
	Antianginal/antiarrhythmic	65 (9.3)	46 (8.7)
	Antiplatelet	165 (23.5)	116 (22)
	Antidiabetic	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 reuptake inhibitor	171 (24.4)	128 (24.3)
	Statin	195 (27.8)	151 (28.7)

Note: Cardiovascular disease includes ischaemic heart disease, arrhythmias, and peripheral vascular disease.

Abbreviations: ALS, amyotrophic lateral sclerosis; COPD, chronic obstructive pulmonary disorder; ECAS, Edinburgh Cognitive and Behavioural Screen; MND, motor neuron disease; TIA, transient ischaemic attack.

[a]Denotes comorbidities included in latent class regression.

[b]Cognitive impairment was not included in the total number of comorbidities, but is presented here due to being part of the Charlson Comorbidity Index.

[c]Excluding medications commonly used for MND symptom management.

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 (Table S2). 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 log-rank 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 less than 0.05 were considered significant. The linearity of age in relation to survival was confirmed using martingale residual plots; age was mean centred 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 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 ratio (HR) per unit increase (CCI) or year/10-year increase (age) and 95% confidence intervals (CIs). Kaplan–Meier curves were visually inspected for violation of the proportional hazards assumption. Model discrimination was assessed using Harrell 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], MplusAutomation [25], UpSetR [26], and base R.

RESULTS

Demographics

Between 1 January 2015 and 29 October 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 at initial data capture), and 418 (44.6%) had missing data on cognitive testing. A total of 564 (60.2%) pwMND were male, and the median age at symptom onset was 67 years (interquartile range [IQR] = 58–74, range 22–96). The population comprised pwALS (*n* = 649, 69.3%), progressive bulbar palsy (*n* = 80, 8.5%), primary lateral sclerosis (*n* = 27, 2.9%), progressive muscular atrophy (*n* = 25, 2.7%), and unrecorded subtype (the remainder, most likely ALS). Site of onset included spinal (*n* = 503, 58.3%), bulbar (*n* = 281, 32.6%) mixed (*n* = 70, 8.1%), and pure respiratory (*n* = 9, 1.0%). Median survival from symptom onset was 29 months (95% CI = 27–31).

Prevalence of comorbidities, multimorbidity, medication use, and polypharmacy

Overall, 86.3% (*n* = 685) had one or more comorbidity, and 25.4% (*n* = 202) had four or more comorbidities. The most common comorbidities were hypertension (*n* = 318, 39.4%), psychiatric disorders/depression/anxiety (*n* = 243, 29.3%), hyperlipidaemia (*n* = 178, 22.3%), ischaemic heart disease/arrhythmia (*n* = 147, 18.4%), osteoarthritis (*n* = 142, 17.2%), and cancer (*n* = 101, 12.5%; most commonly prostate and breast). A total of 59.2% (*n* = 415) used more than two medications during their disease course (excluding medications prescribed for MND management). The most frequently used medications were analgesics (*n* = 300, 42.8%), proton pump inhibitors (*n* = 240, 34.2%), and statins (*n* = 195, 27.8%). The distribution of comorbidities and medication usage was similar between the entire cohort and pwALS (Table 1). Intersectional analysis shows that there were no specific combinations of comorbidities that occurred particularly frequently, but that the most commonly co-occurring comorbidities were psychiatric disorders and hypertension, diabetes and hypertension, and hyperlipidaemia and hypertension (Figure 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,

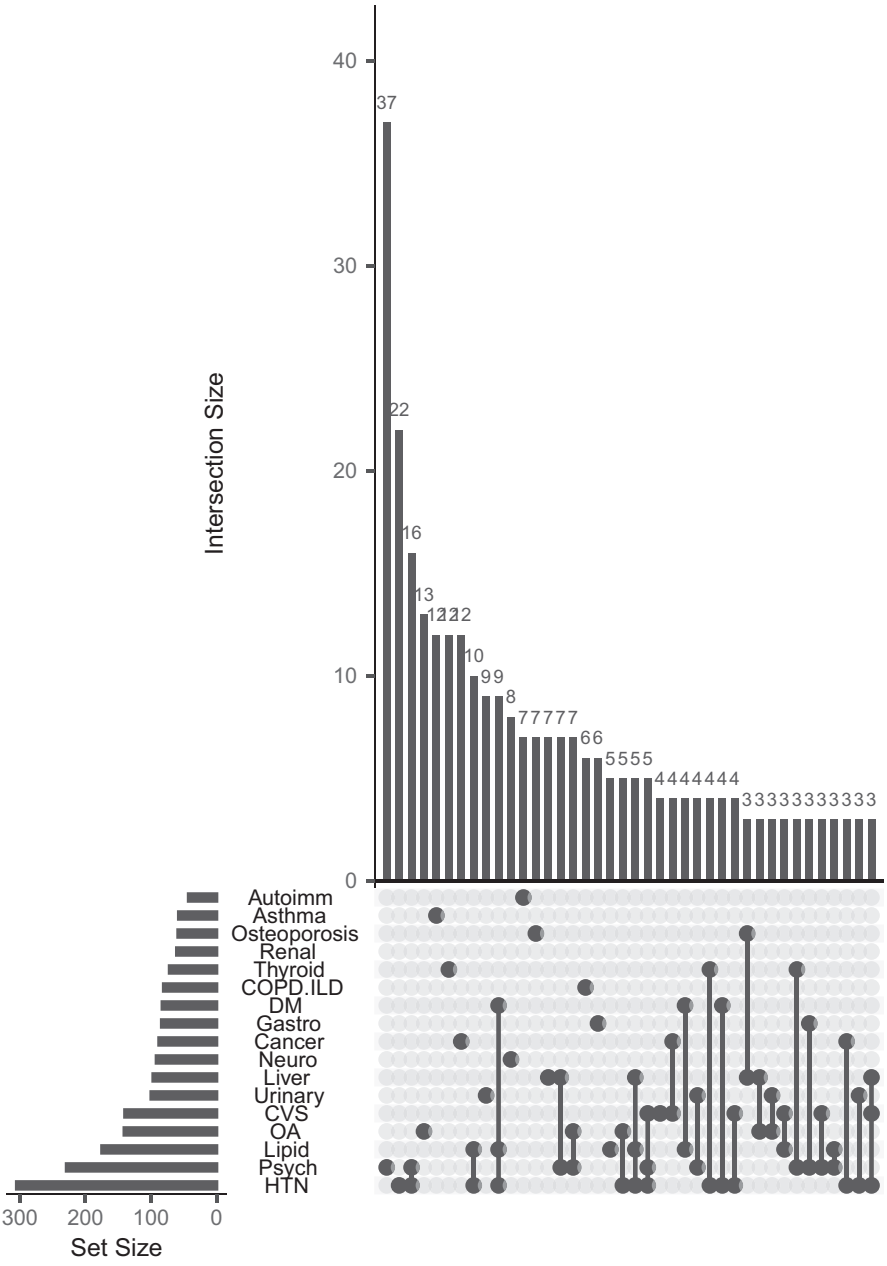

FIGURE 1 Intersection plot of comorbidities. Autoimm, autoimmune condition; COPD.ILD, chronic obstructive pulmonary disorder/interstitial lung disease; CVS, cardiovascular disease; DM, diabetes mellitus, HTN, hypertension; OA, obstructive sleep apnoea

age, sex, and bulbar onset but not direct relationships between age and individual comorbidities (Figure 2, solid lines). Models with one to five latent classes were fitted; a six-class solution did not converge. The two-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 (Figure 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 acting as surrogates for age by incorporating direct effects between class indicators (comorbidities) and covariate (age) in the model when adjusting for age (Figure 2, dashed lines). We fitted models with one to three classes; a four-class solution did not converge. The BIC and parametric bootstrap likelihood test results favoured the one-class (null) model, whereas the Vuong–Lo–Mendell–Rubin likelihood ratio test favoured a two-class solution (Table S3). The two-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; Figure S1). There was no difference in survival between classes (Figure 3b; see Table S4 for details of structural model). The entropy was 0.81, indicating good classification quality (entropy range = 0–1; 1 indicates perfect classification). The two-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.

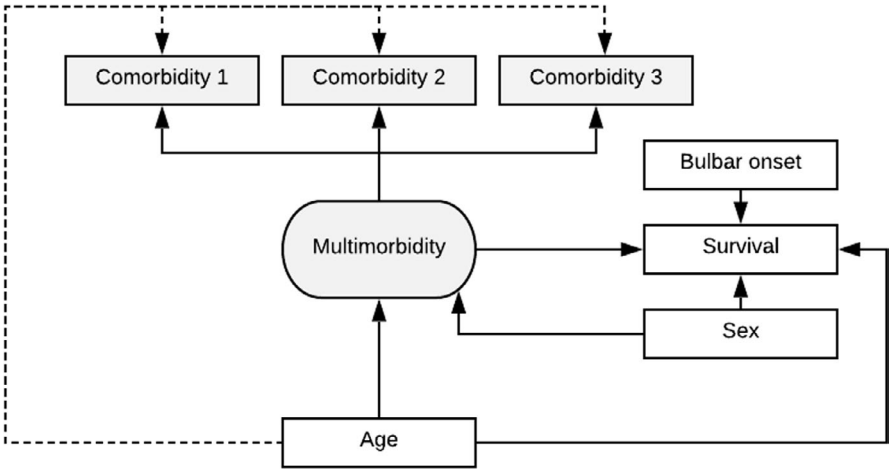

FIGURE 2 Hypothesised relationships between comorbidities (class indicators), multimorbidity (latent variable), survival (distal outcome), and age, bulbar onset, and sex (covariates) in people with motor neuron disease. Grey indicates measurement model; white indicates structural model. Solid lines indicate initial analysis; dashed lines indicate extended analysis, including direct effects between age and individual comorbidities

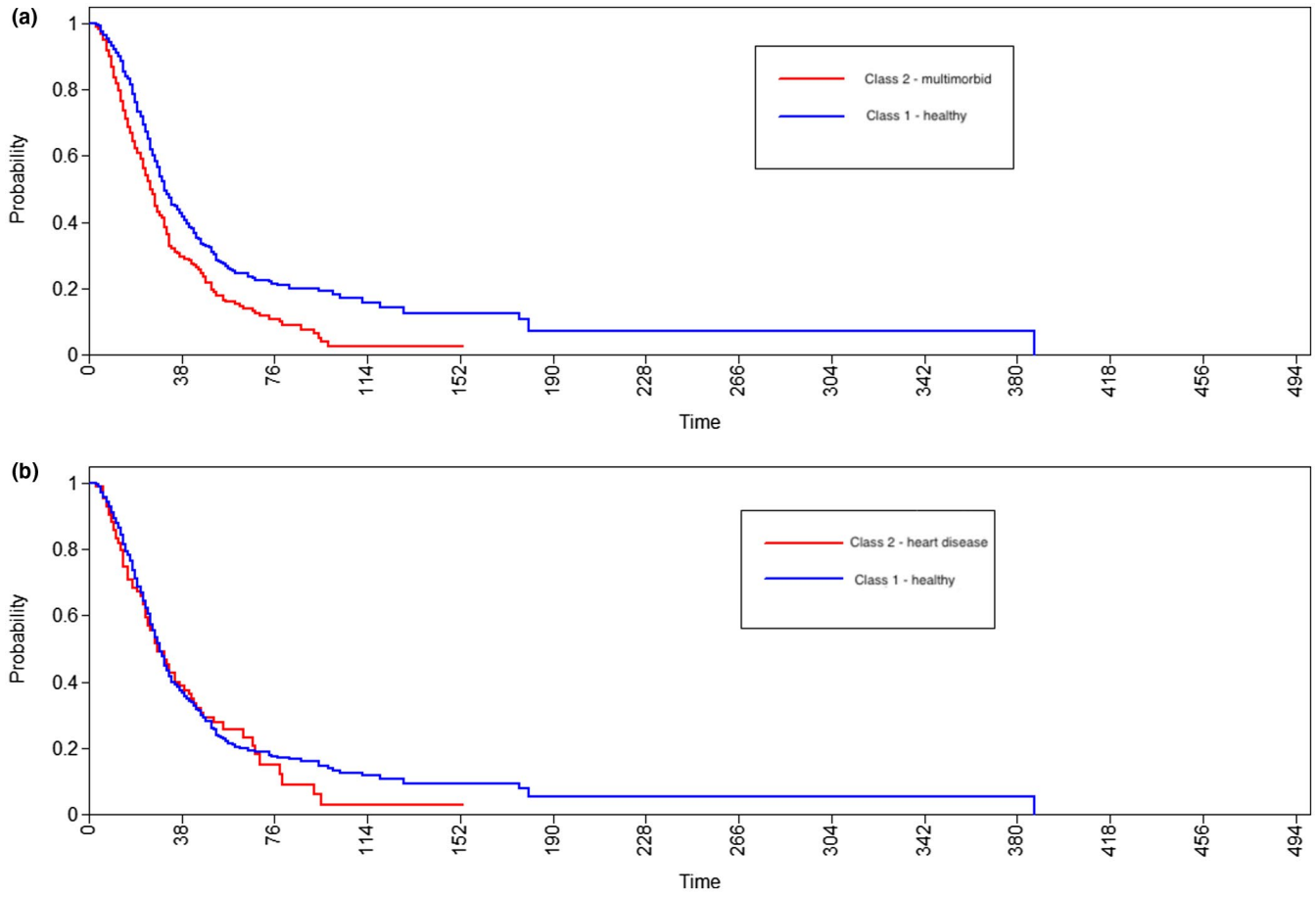

FIGURE 3 (a) Kaplan–Meier curve displaying survival according to latent class for the two-class model not including direct relationships between comorbidities and age. Class 1 is the "healthy class" and Class 2 is the "multimorbid class." (b) Kaplan–Meier curve for survival according to class membership for the two-class model with direct relationships between age and individual comorbidities. Class 1 is the "healthy class" and Class 2 is the "heart disease" class [Colour figure can be viewed at wileyonlinelibrary.com]

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 = 2–5, 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

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% CI)	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	<0.0001	0.034	<0.0001	<0.0001
	C-index	0.59	0.53	0.63	0.63
All MND, "worst case"	HR (95% CI)	1.12 (1.09–1.16)	1.09 (1.03–1.15)	NA	NA
	p	<0.0001	0.003	NA	NA
	C-index	0.61	0.57	NA	NA
ALS only, "best case"	HR (95% CI)	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	<0.0001	0.015	<0.0001	<0.0001
	C-index	0.59	0.54	0.63	0.63

Note:: Association between CCI and age alone and survival in people with MND. Age-weighted CCI range = 0–12, median = 3. Non-age-weighted CCI range = 0–10, median = 1.

Abbreviations: ALS, amyotrophic lateral sclerosis; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio per unit increase (CCI) or 1-year/10-year increase (age); MND, motor neuron disease; NA, not applicable.

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% CI = 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 health care 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 interdisciplinary 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, because 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].

Furthermore, 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 indicated 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].

Whereas our MND registry collects data prospectively, our analysis and design for this study were 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, because 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.

CONCLUSIONS

In this population-based analysis of 937 pwMND, multimorbidity and polypharmacy were common, necessitating holistic interdisciplinary 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 pwMND and that the previously identified association between cardiovascular disease and survival is mediated by age. Excluding pwMND and multimorbidity from trial participation may do little to homogenise the cohort in terms of survival potential and could harm generalisability.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

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ETHICAL 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.

DATA AVAILABILITY STATEMENT

Data available upon request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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