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Frailty and Quality of Life for People With Alzheimer's Dementia and Mild Cognitive Impairment

Aine M. Ní Mhaoláin, MB, MRCPsych[1], Damien Gallagher, MB, MRCPsych[1], Lisa Crosby, SRN[1], Deirdre Ryan, MSc[1], Loretto Lacey, PhD[2], Robert F. Coen, PhD[1], Davis Coakley, MD, FRCPI, FRCP[1,3], J. Bernard Walsh, FRCPI, FRCP[1,3], Conal Cunningham, MD, FRCPI[1,3], and Brian Lawlor, MD, FRCPI, FRCPsych[1]

Abstract

Background: Our aim was to investigate the relationship between frailty and health-related quality of life (HR-QOL) in cognitively impaired elderly individuals. Methods: A cross-sectional observational study of a convenience sample of 115 patients with a diagnosis of Alzheimer's dementia or mild cognitive impairment. Frailty was measured using the biological syndrome model and HR-QOL was measured using the DEMQOL-Proxy. Regression models were constructed to establish the factors associated with HR-QOL. Results: Frailty and neuropsychiatric symptoms were associated with HR-QOL, with Mini-Mental State Examination (MMSE) scores $\geq$21 ($P = .037$, $P \leq .001$, and $R^2 = .362$). Functional limitation was associated with HR-QOL, with MMSE scores $\leq$20 ($P = .017$ and $R^2 = .377$). Conclusion: Frailty and neuropsychiatric symptoms were the determinants of HR-QOL in the earlier stages of cognitive impairment. Functional limitation predicted HR-QOL in the later stages of cognitive impairment. Frailty may represent a novel modifiable target in early dementia to improve HR-QOL for patients.

Keywords

frailty, quality of life, Alzheimer's disease, mild cognitive impairment

Introduction

Dementia currently affects 24.3 million people worldwide, Alzheimer's disease (AD), occurring in middle or late life, accounts for 50% to 60% of all cases.[1] Cognitive impairment profoundly affects the lives of patients and their families. Without a cure, the main question in care is how to promote well-being and maintain an optimal quality of life (QOL). Addressing life quality is increasingly included as part of clinical guidelines for treating cognitively impaired patients.[2] Alzheimer's disease is a complex illness with considerable heterogeneity in abnormalities of behavior, cognition, insight, and judgment. Given this complexity, there has been discussion about how best to measure the impact of cognitive impairment on individuals and their families in terms of life quality. The measurement of health-related QOL (HR-QOL) which evaluates broad patient-related outcomes is now considered to be an important concept in the evaluation of QOL in those with cognitive impairment.

Quality of life and HR-QOL are often used interchangeably, with little distinction between the two concepts. However, HR-QOL represents health-related well-being and so can be measured as a disease-specific entity in connection with illnesses such as AD. Key dimensions of HR-QOL are physical functions, sensations, self-care/dexterity, cognition, pain/discomfort, and emotional/psychological well-being. Understanding what contributes to HR-QOL in the context of specific disease processes has repeatedly shown to work for improvement in patient management. Health-related QOL is now recognized as an important end point in disease management, perhaps equal in importance to survival and only treatments which improve HR-QOL are regarded as effective intervention even without survival benefit.[3] Expanding our knowledge of key factors that may be associated with HR-QOL in cognitively impaired patients may improve our ability to intervene with preventative or supportive strategies to minimize the burden of illness in dementia.

With this in mind, our focus in this study has been on the area of frailty in the cognitively impaired. Frailty is an emerging geriatric syndrome that infers increased risk of poor health outcomes and may represent an important physical health-related variable that to date has not been fully evaluated in

[1] Mercer's Institute for Research on Ageing, St James's Hospital, Dublin, Ireland
[2] Janssen Alzheimer Immunotherapy, Dublin, Ireland
[3] Department of Medicine for the Elderly, St James's Hospital, Dublin, Ireland

Corresponding Author:
Aine M. Ní Mhaoláin, TRIL Clinic, St James's Hospital, Dublin 8, Ireland
Email: ainemullen@gmail.com

those with cognitive deficits. It is a multidimensional construct of age-related reduction in physiologic reserve and resistance to stressors, both intrinsic and environmental. Frailty can be delineated from comorbidity and infers an increased risk of health decline, disability, and mortality regardless of concurrent illnesses.[4] Intervention in the early stages of frailty may lead to reversal of the syndrome and minimize if not prevent some of its associated adverse outcomes.[5]

Although the clinical hallmark of AD is progressive loss of memory and other cognitive abilities, several studies have shown persons may also exhibit changes in mobility and body composition suggesting frailty.[6,7] The frailty syndrome has been associated with both incident mild cognitive impairment (MCI) and AD and can be easily measured in this population.[8-10] If frailty is associated with HR-QOL in vulnerable elderly individuals who are cognitively impaired then it may represent a key target for intervention, given its potential reversibility.This study enables a consideration of the relationship, if any, between frailty and HR-QOL in dementia and MCI while accounting for other domains of clinical importance such as cognition, activity limitation, behavioral disorder, carergiver burden, and caregiver depression. Our hypothesis being that the frailty syndrome may represent an important modifiable factor associated with HR-QOL as measured in older adults with a diagnosis of AD or MCI.

Methods

Sample

Participants were recruited as a convenience sample in the course of the Enhancing Care in Alzheimer's Disease (ECAD) Study which was cross-sectional in design and conducted in 2009. They were identified from referrals to the memory clinic of a university teaching hospital in Dublin. All participants received verbal and written communication about the details of the study and informed written consent was obtained from each participant. If on assessment a participant with cognitive impairment was deemed not to have the capacity to consent to inclusion in the study, written consent by proxy was obtained from the primary caregiver. All participants provided verbal assent for inclusion in the study. Inclusion criteria required patients to have received a diagnosis of probable AD or amnestic MCI and to be a community dweller of age >50 years. Patients were excluded if they had comorbid illness, which was a significant independent cause of disability (eg, Parkinson's disease or dense hemiplegia), or if they did not have a caregiver who was willing and able to complete the required assessments. Local ethics approval was obtained for the study.

Assessment

Probable or possible AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and MCI according to international consensus criteria.[11,12] Assessments were completed by a trained nurse and doctor in the patient's home. Sociodemographic and medical details were collected as part of a structured questionnaire. Diagnoses were reviewed and Mini-Mental State Examination (MMSE) was conducted on the patient as a measure of cognition at the time of recruitment to the study. Previous work in the area of cognitive impairment and HR-QOL have indicated the importance of assessing it separately for mild, moderate, and more severely impaired patients as predictors vary by cognitive severity.[13] To account for the impact of cognitive impairment on HR-QOL in our sample, patients were divided into 2 groups according to their MMSE scores. Any score on the MMSE greater than or equal to 25 points (out of 30) is effectively normal (intact). Below this, scores can indicate severe ($\leq$9 points), moderate (10-20 points), or mild (21-24 points) cognitive impairment.[14] This division provided 2 groups for evaluation that were clinically meaningful in terms of degree of cognitive impairment (moderate-to-severe impairment: MMSE $\leq$20; milder cognitive impairment MMSE $\geq$21). We identified a number of other factors based on the current literature available on HR-QOL in Alzheimer's dementia and MCI to include in our assessment. Including these factors in our evaluation of HR-QOL ensured we accounted for any confounders in our analysis of the relationship between frailty and HR-QOL. The factors included were age, gender, an assessment of care-recipient cognition (MMSE), caregiver depression (Center for Epidemiologic Studies Depression scale), level of reported carer burden (Zarit Burden Inventory), care-recipient functional limitations (Disability Assessment for Dementia scale), a global assessment of illness severity (Washington University Clinical Dementia Rating scale), and presence of neuropsychiatric symptoms ([NPS] Neuropsychiatric Inventory).[15-19]

Frailty. Frailty was measured using the biological syndrome model which was originally described by Fried using 5 frailty criteria such as weight loss, exhaustion, slowed gait, impaired grip strength, and reduced physical activity.[4] Our only adaptation to these criteria being the definition of weight loss which was assessed objectively as body mass index (BMI) of less than 18.5 kg/m^2, rather than a subjective report of weight loss of more than 10 pounds. This was reflective of similar adaptations for the weight loss criterion from other large population-based studies validating the biological syndrome model of frailty.[20] Exhaustion was determined by 2 questions from the Center for Epidemiologic Studies–Depression scale (CES-D), "I felt that everything I did was an effort," "I could not get going."[21] Slowness was defined in terms of usual pace walking speed and weakness was assessed using grip strength, both dependent on gender, BMI, and using the cut points as per the Cardiovascular Health Study.[4] Low activity was defined by kilocalories expended per week, dependent on responses to selected items from the Minnesota Leisure Time Activity Questionnaire.[22] Primary caregivers of the cognitively impaired participant confirmed all self-report criteria. Frailty scores ranged from 0

indicating robust with no frailty criteria present to 5 representing complete frailty. Categorization of these scores determines those with 0 to 1 criterion present as nonfrail and those with 2 frailty criteria to be intermediately or prefrail and those with 3 or more criteria to be fully frail.[4]

Patient function. Patient function was assessed with the Disability Assessment for Dementia (DAD) scale, a well-validated, multi-item instrument that assesses 10 activities of daily living to include 6 instrumental activities of daily living and 4 basic activities of daily living.[23] The DAD is based on an interview with the caregiver rating the patient's actual performance on observed activities of daily living over the preceding 2 weeks.

Neuropsychiatric symptoms. Neuropsychiatric symptoms (NPS) were assessed with the Neuropsychiatric Inventory (NPI) a structured interview completed with the caregiver during which they are questioned regarding the occurrence of delusions, hallucinations, agitation, depression, anxiety, euphoria/ elation, apathy, disinhibition, irritability/ lability, aberrant motor behavior, night time behavior, and appetite change.[24] The frequency and severity of each symptom is recorded and multiplied to give a possible maximum score of 144.

Health related-quality of life. Quality of life was measured using the 31-item DEMQOL-Proxy which is a structured interview completed with the caregiver during which they are questioned regarding 5 domains of HR-QOL.[25] These include daily activities and looking after yourself, health and well-being, cognitive functioning, social relationships, and self-concept. The DEMQOL-Proxy has been shown to be comparable to the best available proxy measure in mild, moderate, and severe dementia. It has been validated in the United Kingdom in a large sample of people with dementia and their carers and demonstrates good acceptability and internal consistency.[25]

Illness severity. Severity of illness was assessed using the Washington University Clinical Dementia Rating scale (CDR) a well-validated, global assessment instrument that yields both global and Sum of Boxes (SOB) scores.[26] The CDR-SOB score is considered a more detailed quantitative general index than the global score and provides more information about patients with mild dementia. The CDR is obtained through semi-structured interviews of patients and informants, on 6 domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale, the CDR-SOB score is obtained by summing each of the domain box scores.

Caregiver burden and depression. Caregiver burden was measured with the Zarit Burden Inventory, which is a 22-item self-report instrument where caregivers rate the frequency with which they experience certain stressful aspects of caregiving on a scale from 0 (*never*) to 4 (*nearly always*).[27] A measure of depressive symptoms in caregivers was based on a shortened form (10-items) of the 20-item CES-D-20 scale.[28]

Sample Size and Statistical Analysis

A priori sample size calculation for multiple regression analysis of the DEMQOL-Proxy showed that to detect a medium effect size (power = 0.8 and $\alpha = .05$) with 7 predictor variables required a minimum sample size of 103. Given our sample size was in excess of this at 115 participants, it is presumed we had more than sufficient power to evaluate the variables of largest effect under investigation. The collected data were analyzed using the SPSS 16.0 statistical package program. Bivariate analysis using the Spearman correlation coefficient was carried out to assess the strength of association between the independent variables and HR-QOL. Sequential multivariate regression analyses were then conducted to determine which variables best predicted HR-QOL.Variables that on bivariate analysis were associated with the DEMQOL-Proxy were entered into the multivariate regression models determined by the strength of their association. We set the critical value for significance in all analyses at $P < .05$.

Results

A total of 115 patients were assessed, 44 men (38%) and 71 women (62%). Ninety-five participants had a diagnosis of AD and 20 a diagnosis of MCI. Mean age was 74 years and mean MMSE score was 20. Using our definition, 51.3% of patients could be classified as robust or not frail, while 48.7% were at an intermediate or complete stage of frailty (29.6% intermediately frail and 19.1% fully frail). There was no significant difference in the presence of frailty dependent on gender (Fisher exact test, $P = .443$). Summary data regarding patient clinical characteristics are outlined in Table 1. Bivariate analysis revealed that neither age nor gender had a significant correlation with HR-QOL scores (Spearman rho, $P = .512$, $P = .147$). Similarly neither caregiver depression scores nor burden scores correlated significantly with HR-QOL (Spearman rho, $P = .399$, $P = .103$). Table 2 shows the explanatory variables that were significantly associated with the DEMQOL-Proxy on bivariate analysis, including NPS ($P < .001$), functional limitations ($P < .001$), illness severity ($P = .001$), and frailty ($P = .001$). Cognition determined by the MMSE showed a trend toward correlation but did not quite reach statistical significance ($P = .058$). To evaluate which patient variables best predicted HR-QOL, NPS (NPI), functional status (DAD), dementia severity (CDR-SOB), and frailty were entered into a stepwise regression model with the DEMQOL-Proxy score as the dependent variable. Total NPI score and frailty score were retained in the optimal model which explained 26.4% of the variance in observed HR-QOL (Table 3). The sample was then split into patients with milder impairment (MMSE $\geq$ 21, n = 71) and moderate-to-severe disease (MMSE $\leq$ 20, n = 44) to determine whether the relationships changed according to the severity of cognitive impairment. The same stepwise linear regression analyses were conducted in both groups. In patients with mild impairment, frailty and NPS were retained as the optimal predictors

Table 1. Summary Data Regarding Patient Clinical Characteristics[a]

Parameter, n (%)		
Gender	Male	Female
	44 (38%)	71 (62%)
Parameter	Mean ± SD	Score (Min-Max)
Age (years)	74.13 (9.14)	
Cognitive function (MMSE)	20.5 (6.5)	(1-30)
Illness severity (CDR-SOB)[b]	6.17 (3.78)	(0.5-18)
Neuropsychiatric symptoms (NPI)	24.38 (26.12)	(0-132)
Activities of daily living (DAD)	12.52 (11.86)	(0-40)
Dependence scale[c]	6 (3)	(0-14)
DEMQOL-Proxy[d]	93 (16)	(31-124)

Abbreviations: MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; SOB, Sum of Boxes; NPI, Neuropsychiatric Inventory; DAD, Disability Assessment for Dementia scale.
[a] n = 115.
[b] Washington University CDR Scale, a global assessment instrument that yields a detailed quantitative general index in the form of a SOB score.
[c] A measure of patient dependency was assessed using the Dependence scale.
[d] Health-related quality of life as measured using the dementia-specific DEMQOL-Proxy report.

Table 2. Bivariate Correlates of HR-QOL in Cognitively Impaired Patients

Variables	Spearman Rho	Significance, *P* Values
Age	−.068	.512
Gender	−.146	.147
Cognition (MMSE)	−.192	.058
Caregiver Depression (CESD-10)[a]	−.090	.399
Caregiver Burden (Zarit)[b]	−.173	.103
Fuctional limitations (DAD score)	−.497	<.0001[e]
Illness severity (CDR-SOB)[c]	−.333	.001[f]
Neuropsychiatric symptoms[d]	−.601	<.0001[e]
Frailty	−.328	.001[f]

Abbreviations: MMSE, Mini-Mental State Examination; CESD, Center for the Epidemiological Studies–Depression; CDR, Clinical Dementia Rating; SOB, Sum of Boxes; NPI, Neuropsychiatric Inventory; DAD, Disability Assessment for Dementia scale.
[a] CESD-10 scale.
[b] Zarit Burden inventory Disability Assessment for Dementia scale.
[c] Washington University Clinical Dementia Rating scale SOB score.
[d] NPI.
[e] Statistically significant: $P < .001$.
[f] Statistically significant: $P < .05$.

($P = .037$ and $P \leq .001$, respectively), which explained 36.2% of the variance in HR-QOL. In patients with moderate-to-severe impairment, functional limitations remained the sole predictor ($P = .017$), explaining 37.7% variance in HR-QOL.

Power Calculation

Our sample was split into patients with milder impairment and moderate-to-severe disease, a post hoc statistical power calculation for multiple regression analysis was completed for each subset. Given an R^2 (.362) for model 2 (MMSE $\geq$ 21), the observed power with 4 predictors, an α of .05, and a sample size of 71 was 0.97. For model 3 (MMSE $\leq$ 20) with an R^2 of .377, 4 predictors, an α of .05 and a sample size of 44, the observed power was calculated to be 0.99.

Table 3. Sequential Multiple Regression Models of Quality of Life in the Total Sample and in Patients With Mild and Moderate-to-Severe Cognitive Impairment

	β	Significance, *P* Values	R^2
Model 1: total sample (n = 115)			
Neuropsychiatric symptoms	−.377	.001[c]	.264
Functional limitations (DAD)	−.118	.446	
Illness severity (CDR-SOB)	.051	.707	
Frailty	−.192	.047[c]	
Model 2: MMSE ≥ 21 (n = 71)			
Neuropsychiatric symptoms[a]	−.505	.0001[d]	.362
Functional limitations (DAD)	.030	.845	
Illness severity (CDR-SOB)[b]	−.070	.595	
Frailty	−.240	.037[c]	
Model 3: MMSE ≤ 20 (n = 44)			
Neuropsychiatric symptoms	−.121	.567	.377
Functional limitations (DAD)	−.798	.017[c]	
Illness severity (CDR-SOB)	.472	.113	
Frailty	−.212	.250	

Abbreviations: MMSE, Mini-Mental State Examination; CESD, Center for the Epidemiological Studies–Depression; CDR, Clinical Dementia Rating; SOB, Sum of Boxes; NPI, Neuropsychiatric Inventory; DAD, Disability Assessment for Dementia scale.
[a] NPI.
[b] Washington University CDR scale SOB score.
[c] Statistically significant: $P < .05$.
[d] Statistically significant: $P < .001$.

Discussion

Over half of our cognitively impaired participants could be classified as robust or not frail and a large proportion almost 30% were at a level of intermediate frailty a stage considered to be potentially reversible. We have identified an important correlation between advancing frailty and HR-QOL. When linear regression models were constructed, increasing NPS and frailty were the key predictors of HR-QOL in the total sample. However, when we assessed the sample according to cognitive status, we found that increasing frailty and NPS were more significant determinants of HR-QOL in the earlier stages of disease while deteriorating functional ability was the most important determinant of HR-QOL as the disease progressed. A key point to note in terms of our findings is that, in contrast with some of the current literature available on proxy-assessed HR-QOL in patients with dementia, neither carer burden nor depression scores correlated with HR-QOL within our cohort. Some previous studies have found that both depression and burden are often associated with lower ratings of HR-QOL in dementia using proxy measures.[13] Our negative finding may suggest lower levels of burden and depression within our carer group reflective perhaps of our sample of mostly mild-to-moderate cognitively impaired

patients. However a recent study has been published, which has also found that caregiver burden and depression are not consistent independent predictors of carer-rated QOL in dementia patients, which reflects our finding also.[29]

Other findings are more consistent with current literature. Similar to previous studies we have found no association between age or gender and HR-QOL.[30,31] Nor did we find a significant correlation between HR-QOL and cognition as measured by the MMSE which is in agreement with work in the area to date.[13,31] Our results continue to reinforce the importance of behavioral and psychological symptoms in determining HR-QOL in the cognitively impaired individuals. Neuropsychiatric symptoms are common manifestations of AD. A consistent pattern is observed in the literature that increasing behavioral disorder is associated with decreased HR-QOL for caregiver ratings.[32] There is a belief that the prevalence of NPS increases as disease progresses; however, recent studies indicate that a high proportion of participants display clinically meaningful NPS as early as the stage of MCI.[33] This is comparable with our finding that the association between NPS and HR-QOL appears to be most important in the milder stages of cognitive impairment compared to more moderate-to-severe disease. The pattern of association between activity limitation and HR-QOL in dementia in the literature to date has been somewhat less clear. It is known to be strongest for proxy ratings and in severe dementia.[31,34] This likely underlies our finding of functional limitations being retained as the optimal predictor of HR-QOL when we evaluated our subset of more severely cognitively impaired with an MMSE of $\leq$20.

In addition to reinforcing findings from the current literature, we introduce novel data suggesting that frailty represents an important predictor of HR-QOL in cognitively impaired patients particularly for those with mild impairment. In the past, the term frailty has often been used interchangeably with disability and chronic disease. However, as our knowledge of frailty grows the importance of defining it as a separate clinical entity is becoming more apparent. Frailty increases the susceptibility to acute illness, falls, and disability, thus caring for frailer cognitively impaired older adults may represent a more challenging process due to their complex medical, psychological, and social needs. This may underlie to some extent the association found between frailty in our cognitively impaired group and HR-QOL as assessed by a proxy measure. A further factor may be that at the earlier stages of cognitive decline increasing frailty could contribute to functional limitations for the patient, thereby affecting HR-QOL. Frailty has previously been identified at the stage of mild cognitive decline.[35] Recent work also indicates that in fact core components of frailty, including impaired grip strength, slowed gait, and low BMI, may actually predict subsequent development of dementia.[36,37] Therefore, it is comprehensible that frailty may significantly influence HR-QOL even at the milder stages of impairment. The importance of identifying frailty as a key determinant of HR-QOL in dementia lies in the reversibility of frailty at an early stage and its potential role as a novel target for intervention.[5]

Limitations for this study include the fact that findings from this population of patients with MCI and mostly mild-to-moderate AD may not be readily extrapolated to patients with more severe cognitive impairment. We may therefore have failed to capture those with a higher level of frailty and so lack the ability to generalize. Despite this, it must be acknowledged that it is only the earlier stages of frailty that have been shown to be reversible and so have potential for interventional targeting. A further limitation is our use of a proxy report to measure HR-QOL. Recent studies indicate meaningful data on HR-QOL in dementia can be obtained using either subjective or proxy measures. Proxy reports, however, only provide us with an evaluation of carer's views about how they believe the person with cognitive impairment would report on their own HR-QOL. In this way, it is likely to reflect a different aspect of outcome than a self-report measure would.[13,38] Yet the affective, cognitive, and reality distortion aspects of dementia can belie a person's perception of their own QOL.[39] Proxy report is not directly influenced by deficits, which may occur in those with cognitive decline.[40] Despite the numerous biases inherent in proxy reporting, it is often considered to be a preferable choice.[41] Also the significance of proxy assessed HR-QOL must not be diminished. At the very least, proxy reports provide complementary views of the same important construct. Moreover, the perspective of family carers regarding HR-QOL is of critical importance when clinical decisions are made on behalf of patients.

We must stress the cross-sectional nature of our study does not allow us to draw any conclusions regarding causality. We do, however, extend prior work on HR-QOL in cognitively impaired patients by identifying frailty as a potential novel target associated with HR-QOL that has not previously been reported. We have also examined the value of this physical syndrome as an independent predictor of HR-QOL in the context of already known determinants. A further strength of our work is the fact we have evaluated predictors of HR-QOL in 2 groups, those with mild impairment and those with moderate-to-severe impairment. Previous studies have indicated the importance of assessing QOL separately for mild, moderate, and more severely impaired patients as predictors vary by cognitive severity.[13]

Conclusion

Alzheimer's disease and cognitive impairment represent a significant public health concern due to increasing prevalence and the serious consequences for patients, their families, and health services. Health-related QOL is an important resource in offering valuable information about the impact of cognitive impairment. Our data suggest that frailty and NPS are the key determinants of HR-QOL in the earlier stages of cognitive impairment. Functional limitations represent the sole predictor of HR-QOL in the later stages of cognitive decline. Frailty may be a novel modifiable factor in early dementia that could represent a target for intervention to improve HR-QOL for patients and their caregivers.

Authors' Notes

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Declaration of Conflicting Interests

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