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Original Study

# The Impact of Frailty and Comorbidity on Institutionalization and Mortality in Persons With Dementia: A Prospective Cohort Study

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A B S T R A C T

*Objectives:* The predictive value of frailty and comorbidity, in addition to more readily available information, is not widely studied. We determined the incremental predictive value of frailty and comorbidity for mortality and institutionalization across both short and long prediction periods in persons with dementia.
*Design:* Longitudinal clinical cohort study with a follow-up of institutionalization and mortality occurrence across 7 years after baseline.
*Setting and Participants:* 331 newly diagnosed dementia patients, originating from 3 Alzheimer centers (Amsterdam, Maastricht, and Nijmegen) in the Netherlands, contributed to the Clinical Course of Cognition and Comorbidity (4C) Study.
*Measures:* We measured comorbidity burden using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and constructed a Frailty Index (FI) based on 35 items. Time-to-death and time-to-institutionalization from dementia diagnosis onward were verified through linkage to the Dutch population registry.
*Results:* After 7 years, 131 patients were institutionalized and 160 patients had died. Compared with a previously developed prediction model for survival in dementia, our Cox regression model showed a significant improvement in model concordance (U) after the addition of baseline CIRS-G or FI when examining mortality across 3 years (FI: U = 0.178, $P = .005$, CIRS-G: U = 0.180, $P = .012$), but not for mortality across 6 years (FI: U = 0.068, $P = .176$, CIRS-G: U = 0.084, $P = .119$). In a competing risk regression model for time-to-institutionalization, baseline CIRS-G and FI did not improve the prediction across any of the periods.
*Conclusions:* Characteristics such as frailty and comorbidity change over time and therefore their predictive value is likely maximized in the short term. These results call for a shift in our approach to prognostic modeling for chronic diseases, focusing on yearly predictions rather than a single prediction across multiple years. Our findings underline the importance of considering possible fluctuations in predictors over time by performing regular longitudinal assessments in future studies as well as in clinical practice.



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Dementia is accompanied by an increase in dependence in daily life activities[1] and premature mortality.[2–6] Increased dependency puts patients at risk of nursing home placement[7]—an outcome known to be associated with anxiety, depression, decreased quality of life,[8,9] and increased rates of mortality.[10] Reducing risk factors for institutionalization and death may delay these adverse outcomes.[11,12] Potentially modifiable risk factors for disease progression[13,14] and mortality[5,15–17] in individuals with dementia are frailty and comorbidity. Frailty is characterized by decreased reserves and diminished resistance to stressors due to the cumulative declines of multiple physiological systems.[18] The Frailty Index (FI) is one of the most commonly used operational definitions of frailty.[19] The FI is a scale based on deficits associated with health status covering multiple bodily systems, with higher scores indicating more frailty. Several studies have shown an increased prevalence of frailty in patients with dementia vs without dementia.[16,20] The presence of multiple chronic diseases is also common among older people,[21] indicating that dementia patients are likely to suffer from concurrent diseases, ie, comorbidity.

Given these associations, frailty and comorbidity indexes may be able to improve predictions of institutionalization and mortality and thereby aid individualized prognosis and advanced care planning for dementia patients. However, the use of frailty and comorbidity indexes in clinical practice requires time for data collection. It is preferable to use prognostic factors that are commonly available in the setting of a memory clinic, such as age, cognitive function, and the type of dementia, if these could provide us with a prediction of similar accuracy. However, if comorbidity and/or frailty contribute to the prediction in addition to these established predictors, their use may be recommended. A critical assessment of the incremental predictive value of frailty and comorbidity, in addition to more readily available factors, is therefore necessary to determine whether clinical implementation of these indexes is useful for the prediction of adverse events.

Thus, the primary aim of the present study was to examine the incremental predictive value of frailty and comorbidity for institutionalization and survival in dementia. Because comorbidity burden and frailty status may change during the follow-up period, the values of these variables collected at baseline may not be representative of the patient's state across the entire study. We therefore hypothesize that the predictive ability of baseline frailty and comorbidity will decrease with longer prediction periods. Hence, the secondary aim of this study was to compare the predictive power of these factors across prediction periods of increasing length.

## Methods

### *Participants*

We used data from the Clinical Course of Cognition and Comorbidity (4C) Study. This cohort study comprises a sample of 331 dementia patients in the Netherlands who were recruited by 3 memory clinics at their time of dementia diagnosis between 2010 and 2011. An elaborate description of the study protocol and characteristics of the 4C dementia cohort can be found elsewhere.[22] Local ethical committees approved the study and written consent was obtained from participants. The diagnosis of dementia was based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria.[23] At baseline and during each yearly follow-up, participants underwent a comprehensive assessment of their cognitive and functional abilities, neuropsychiatric symptoms, and general health status. After 3 years, the active follow-ups ended, after which patients were followed passively by means of registry data for mortality and institutionalization outcomes.

### *Outcomes*

The main outcomes of this study are time-to-institutionalization and time-to-death, measured from date of inclusion in the study, which corresponds to the moment of dementia diagnosis. Dates of death and institutionalization were verified and updated up to February 2017 using the Dutch population registry. This resulted in a maximum follow-up period of 7 years. Being institutionalized was defined as living in a nursing home or a senior home.

### *Independent Variables of Interest*

We used the baseline Cumulative Illness Rating Scale for Geriatrics (CIRS-G) total score (range: 0-56) to measure comorbidity.[24] When stratifying patients into groups with and without significant comorbidities, a CIRS-G score $\geq$2 in 2 or more domains (excluding the psychiatric domain) was used as a cut-off. In addition, we constructed an FI (range: 0-1) based on the accumulation of deficits approach, using a total of 35 items collected at diagnosis, as listed in Appendix 1, Table A1. The FI is calculated by dividing the sum of all deficits present by total amount of deficits counted.[25] The FI was calculated if a patient had answered at least 23 deficits. Patients with an FI $\geq$ 0.25 were considered to be frail.[26]

### *Initial Prognostic Model*

As a reference model, on top of which we wanted to evaluate the prognostic value of frailty and comorbidity, we included demographics and disease characteristics readily available in the memory clinic setting. These variables were shown to be predictive for mortality in a previously published model, based on registry data from 15,209 dementia patients from memory clinics in Sweden.[27] These were age, gender, Mini-Mental State Examination (MMSE) score,[28] institutionalization status (yes or no), coresident (yes or no), and dementia type. This information was collected at the moment of diagnosis. Because of the low numbers of subjects with less prevalent dementia types, we operationalized "dementia type" as a variable with 3 categories: Alzheimer's disease (without a vascular component), any dementia with a vascular component (vascular and mixed type dementia), and other dementia type. Because nearly all subjects who were institutionalized at baseline reported to be living alone (19 of 21), these risk factors were combined into a "residency" variable, which dichotomized the population into "living alone or institutionalized" vs "living at home with a coresident" in the prognostic model for mortality. The large majority (99%) of coresidents consisted of family members.

### *Statistical Analyses*

Differences in survival time between groups were assessed using the log-rank test. Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95% confidence intervals (95% CIs) for mortality. Competing risk regression models were used to calculate subdistribution hazard ratios with 95% CIs for institutionalization. These models take into account the fact that individuals who have died are no longer at risk for institutionalization (ie, these models correct for the competing risk of death).[29] We verified the assumption of proportionality by examining log minus log plots and Schoenfeld residuals of the variables included in the models. The added predictive value of frailty and comorbidity was assessed for 1-, 3-, and 6-year prediction periods by calculating the improvement in concordance using the function *rcorrp.cens* from R package Hmisc.[30] The resulting U-statistic, from here on referred to as the model fit improvement index (U), represents the fraction of all possible pairs of observations for which the extended model (ie, including comorbidity or frailty)

provided more concordant predictions as compared to the original model (ie, without comorbidity or frailty). This statistic can range from −1 (concordance decreased for all pairs) to 1 (concordance improved for all pairs). Overall model performance was assessed by the concordance index (c-index), obtained through bootstrap cross-validation (500). We performed complete case analyses, so subjects with missing values for explanatory variables were excluded from the models (N = 8 and N = 9 for institutionalization and mortality, respectively). Moreover, participants who were already institutionalized at baseline were excluded from the model predicting institutionalization (N = 21). As institutionalization rates appeared to differ across the study centers in our multicenter study, the analyses for institutionalization were corrected for study center. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc, Cary, NC) and R version 3.3.2.

## Results

The main characteristics of the cohort (N = 331) at the baseline assessment are presented in Table 1. The FI in our sample ranged from 0.03 to 0.76, and more than half of the sample (N = 218, 65.9%) was considered to be frail (FI ≥ 0.25). The CIRS-G in our sample ranged from 1 to 27, and 60.4% (N = 200) of the sample suffered from significant comorbidity (CIRS-G score ≥2 in 2 or more domains). An overview of the affected CIRS-G domains is depicted in Appendix 2, Table A2. Among the 331 participants, 131 were institutionalized and 160 had died during the 7 years of follow-up. The log minus log plots and Schoenfeld residuals showed no evidence of violation of the proportional hazard assumption.

### *Mortality*

The median time-to-death among the 331 persons with dementia was 5.3 years. Survival times stratified by age and gender are reported in Appendix 3, Table A3. Univariable analyses showed that patients who suffered from significant comorbidity at baseline had a shorter survival time as compared to patients without significant comorbidity (Δ median survival time = −1.1 years, *P* log rank = .001). Similarly, patients who were frail at baseline survived for significantly shorter times as compared to those who were nonfrail (Δ median survival time = −1.3 years, *P* log rank = .010). The survival curves for frailty and comorbidity status are shown in Figures 1 and 2, respectively.

Table 2 depicts the added value of CIRS-G and FI for the prediction of survival time during 1-, 3-, and 6-year follow-up periods, in addition to the variables from our reference model.[27] The HRs indicate that having a 10% higher CIRS-G is associated with a twofold increase in mortality risk, whereas having a 0.1 higher FI increased mortality risk by 24% to 79% across the first 1 to 3 years of follow-up. The addition of either CIRS-G or FI to the model, including age, gender, MMSE score, residency, and dementia type, significantly improved the predictions of survival time during 1- and 3-year follow-up periods, as indicated by the index of model fit improvement. The fraction of subject pairs for which the model including the FI provided more concordant predictions as compared to the model without frailty is 0.478 (*P* < .001) for 1-year mortality, as indicated by the model fit improvement index. For CIRS-G, this fraction was somewhat smaller and borderline nonsignificant (U = 0.314, *P* = .052). Both the HR and the index of model fit improvement for the FI decreased with longer prediction periods and became nonsignificant at a 6-year follow-up (HR = 1.01, 95% CI: 0.90-1.13). A similar pattern was observed for CIRS-G (Table 2). The models including either CIRS-G or FI showed similar performance across the entire follow-up period, with a c-index of 0.72.

**Table 1**
Baseline Characteristics of the Study Sample (N = 331)

| Characteristics | Median (IQR), or n (%) |
|---|---|
| Age, y | 76.2 (67.4-83.0) |
| Gender—male, n (%) | 150 (45.3) |
| Institutionalized—yes, n (%) | 21 (6.4) |
| Co-resident—none, n (%) | 120 (36.5) |
| Type of dementia: Alzheimer's disease, n (%) | 216 (65.3) |
| Type of dementia: Vascular and mixed type dementia, n (%) | 71 (21.4) |
| Type of dementia: Other, n (%) | 44 (13.3) |
| MMSE score | 22.0 (20.0-24.0) |
| CIRS-G total score | 9.0 (5.0-13.0) |
| Frailty Index | 0.29 (0.20-0.41) |

MMSE range: 0-30; CIRS-G range: 0-56; FI range: 0-1.
Being institutionalized was defined as living in a nursing home or a senior home.

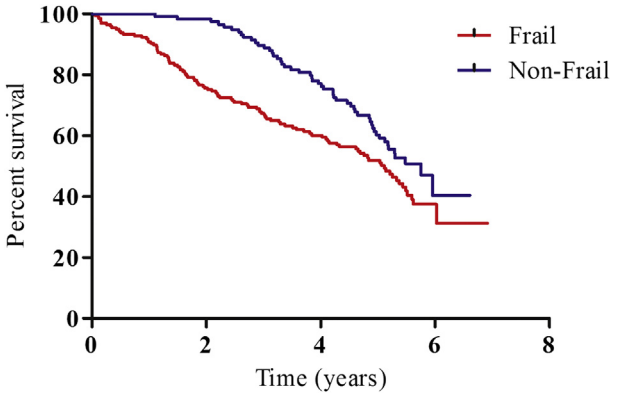


**Fig. 1.** Survival stratified by frailty status, based on the dichotomized frailty index (FI). Frail (red line) = FI ≥ 0.25; nonfrail (blue line) = FI < 0.25.

When stratifying the effect of CIRS-G on 3-year mortality by organ system (Appendix 2, Table A2), it became apparent that the effect of CIRS-G is not the result of disease in a single organ system, but rather the result of accumulation of comorbidity in multiple organ systems.

Adding the FI to a model that already included CIRS-G did not result in significant model fit improvement for any of the prediction periods (results not shown). When adding CIRS-G to the model including FI, only a slight model fit improvement was observed at a prediction period of 3 years (U = 0.148, *P* = .038).

### *Institutionalization*

The median time-to-institutionalization among the 331 persons with dementia was 5.1 years. Observed time-to-institutionalization

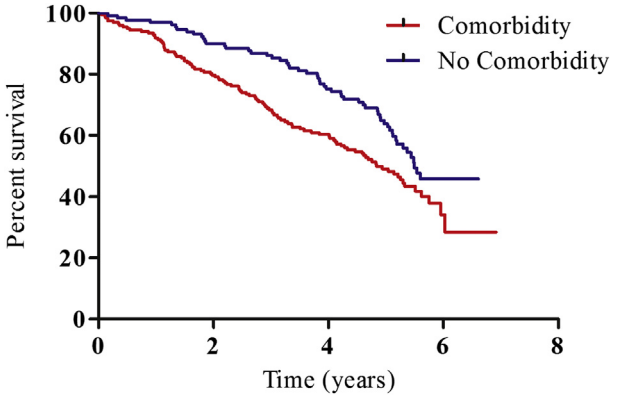


**Fig. 2.** Survival stratified by comorbidity status, based on the dichotomized CIRS-G score. Comorbidity (red line) = 2 or more domains of the CIRS-G have a score ≥2; no comorbidity (blue line) = fewer than 2 domains of the CIRS-G have a score of ≥2.

**Table 2**
Predictive Value of Baseline Frailty and Comorbidity for Mortality Across Different Prediction Periods (N = 322)

| Covariate of Interest | Follow-up, y | No. of Deaths | HR (95% CI) | Index of Model Fit Improvement (U) | *P* Value for U |
|---|---|---|---|---|---|
| Cumulative Illness Rating Scale | 1 | 19 | 2.68 (1.11-6.49) | 0.314 | .052 |
| | 3 | 78 | 2.09 (1.26-3.46) | 0.180 | .012 |
| | 6 | 153 | 1.30 (0.89-1.90) | 0.084 | .119 |
| Frailty Index | 1 | 19 | 1.79 (1.24-2.59) | 0.478 | <.001 |
| | 3 | 78 | 1.24 (1.06-1.47) | 0.178 | .005 |
| | 6 | 153 | 1.01 (0.90-1.13) | 0.068 | .176 |

Models were adjusted for age, gender, MMSE score, residency, and dementia type. The CIRS-G (range: 0-56) was divided by 10 and the frailty index (range: 0-1) was multiplied by 10 in order to enhance interpretability of the estimates. HRs thus represent the effects of a 0.1-point higher frailty index, or a 5.6-point higher CIRS-G on the original scales.

stratified by age and gender is reported in Appendix 3, Table A4. Participants who were institutionalized (N = 131) were more often female, but their baseline age, MMSE score, CIRS-G score, and FI did not differ significantly from those who were not institutionalized during the time they were followed.

Table 3 depicts the added value of CIRS-G and FI for the prediction of 1-, 3-, and 6-year institutionalization, in addition to the variables from our reference model.[27] The predictions of institutionalization within 1, 3, and 6 years did not improve significantly by the addition of either CIRS-G or FI to the model, as indicated by the index of model fit improvement. Similar to the results for mortality, the HR and model fit improvement index for both CIRS-G and FI showed a decreasing pattern across increasing prediction periods (Table 3). The models including either CIRS-G or FI showed similar performance across the entire follow-up period, with a c-index of 0.61.

## Discussion

This study showed that the CIRS-G and FI provide incremental value for the prediction of short-term (1- to 3-year) survival in dementia, in addition to more readily available predictors of mortality from the memory clinic. Baseline CIRS-G and FI showed a higher predictive value for short-term mortality, as compared to long-term mortality. In contrast, time-invariant factors such as gender and dementia type remained significant in the long term, suggesting that the observed discrepancy between long- and short-term results for CIRS-G and FI may be caused by the changing frailty and comorbidity status over time. When comparing the predictive value of the 2 indexes, the FI showed a higher model fit improvement for 1-year mortality as compared to the CIRS-G, but for 3- and 6-year mortality, the model fit improvement was similar for both measures. For the prediction of time-to-institutionalization, neither the CIRS-G nor the FI provided significant model fit improvement across any of the prediction periods. The prediction models for mortality showed a higher predictive performance than the models for institutionalization, as shown by the c-index.

This study has multiple strengths. It includes a representative sample of dementia patients from a clinical setting, as subjects were not excluded based on comorbid conditions.[22] The long follow-up time allowed us to compare predictions across multiple prediction periods, offering valuable insight in the short- and long-term benefit of measuring frailty and comorbidity for the prediction of institutionalization and mortality in dementia. In contrast to many other studies examining institutionalization, we have reduced survivorship bias by taking into account the competing risk of mortality. To enhance applicability, we used the FI, as opposed to alternative frailty operationalizations. Besides its favorable discriminative ability,[26] the FI is also preferred because it may be derived from various sets of variables.[25] This means the FI does not depend on the measurement of specific characteristics, and although it is not a routinely used measure, it can be calculated based on routinely available electronic health record data, for example, from primary care.[31] One of the limitations of this study is its inability to distinguish nursing homes from sheltered housing facilities based on registry data. Possible misclassification of the outcome may therefore, in part, explain the lack of an incremental predictive value of the FI and CIRS-G for institutionalization. It should also be noted that the 1-year models in this study might suffer from overfitting because of the small amount of events. However, we expect the amount of overfitting to be minimal, since our relatively small set of covariates was selected a priori.

The observed median time-to-death in our sample is comparable to that reported previously by a study from the UK.[32] The results of the present study are also in line with previous findings from the ICTUS study—a large European cohort including 1,191 patients with Alzheimer's disease. In this cohort, the FI was predictive of survival time and time-to-hospitalization, but not for time-to-institutionalization, after correction for age and gender.[15] Unfortunately, the follow-up of the ICTUS study was limited to 2 years, which precludes comparison to our long-term results. Moreover, they did not take into account competing risks. An Italian study based on a small sample of dementia patients (N = 75) also showed decreasing HRs of frailty, as defined by the Cardiovascular Health Study criteria, with longer prediction periods. However, the study did not examine the incremental predictive value of frailty

**Table 3**
Predictive Value of Frailty and Comorbidity for Institutionalization Across Different Prediction Periods (N = 302)

| Covariate of Interest | Follow-up, y | No. of Institutionalizations (No. of Competing Events) | SHR (95% CI) | Index of Model Fit Improvement (U) | *P* Value for U |
|---|---|---|---|---|---|
| Cumulative Illness Rating Scale | 1 | 29 (15) | 1.19 (0.56-2.52) | 0.050 | .634 |
| | 3 | 86 (31) | 0.93 (0.57-1.51) | −0.038 | .558 |
| | 6 | 130 (55) | 0.68 (0.45-1.04) | 0.020 | .722 |
| Frailty Index | 1 | 29 (15) | 1.16 (0.85-1.60) | 0.062 | .615 |
| | 3 | 86 (31) | 1.06 (0.89-1.27) | 0.030 | .664 |
| | 6 | 130 (55) | 1.04 (0.89-1.21) | 0.016 | .792 |

SHR, subdistribution hazard ratio.
Models were adjusted for age, gender, MMSE score, coresident, dementia type, and study center. The CIRS-G (range: 0-56) was divided by 10 and the frailty index (range: 0-1) was multiplied by 10 in order to enhance interpretability of the estimates. Hazard ratios thus represent the effects of a 0.1-point higher frailty index, or a 5.6-point higher CIRS-G on the original scales.

in addition to MMSE scores.[33] Our results showed that, like frailty, comorbidity status also appears to be more predictive of short-term than long-term mortality. As with frailty, the comorbidity status may fluctuate over time, rendering baseline CIRS-G unrepresentative of long-term comorbidity status. This notion is supported by the findings of our recent systematic review, suggesting a time-dependent association between comorbidity and dementia progression.[34]

The lack of incremental value of both FI and CIRS-G for the prediction of institutionalization suggests that other factors might play a more important role in the prediction of this outcome. This is supported by the low performance of the models for institutionalization (c-index = 0.61). Given the initial prognostic model used in this study was developed to predict mortality, it is perhaps unsurprising that our models perform better when predicting time-to-death (c-index = 0.72). This low model performance for institutionalization is likely due to the fact that a wide range of factors beyond the examined predictors, such as a patient's family, social and financial situation, as well as the sudden onset of concurrent diseases or symptoms, are influencing an individual's ability to live independently.[35] However, this type of information is often lacking in research data, as is the case in the present study. Additionally, there may be complex interactions between the factors influencing institutionalization, of which we are currently unaware. A previous study suggested that longitudinal assessment of the clinical symptoms of dementia may provide the best way to predict institutionalization.[36] Piccinin et al.[37] describe analytical approaches to make more time-sensitive use of health information, including the use of time-varying covariates, which could guide future research on this topic.

## Conclusions

Shared decision making for the planning of care and end-of-life decisions with caregivers and persons with dementia is becoming increasingly important in today's care systems. Therefore, it is more important than ever for clinicians to be able to provide accurate information on the estimated time-to-institutionalization and time-to-death. To our knowledge, this is the first study addressing the incremental value of comorbidity or frailty for the prediction of adverse outcomes in dementia across different prediction periods. The fact that significant improvement of mortality prediction was only observed for shorter prediction periods suggests that the added predictive value of frailty and comorbidity is dependent on the time frame for which the prediction is made. These findings stress the importance of taking into account the length of the prediction period, as well as the stability of predictors over time, when building prognostic models. These implications are not limited to the field of dementia, because all chronic diseases inherently involve a changing disease, context, and patient status, as they evolve across multiple years. To accurately predict mortality, it is important to take these changing characteristics into account and discriminate between stable predictors (such as gender) and possibly changing predictors (such as frailty, comorbidity, and cognition).[37] Stable predictors are likely to have an enduring prognostic value, whereas changing factors may merely have prognostic value across shorter time periods. Many prognostic models focus on predictions across several years, but for understanding the full impact of stable and changing predictors, short-term predictions are probably more accurate and therefore more valuable in clinical practice. The option to provide multiple short-term predictions across several years is often ignored, even though patients with chronic diseases tend to regularly consult their physician. These results call for a shift in our approach to prognostic modeling for the course of chronic diseases and underline the importance of considering possible fluctuations in predictors over time by performing regular longitudinal assessments in future studies as well as in clinical practice.

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## Appendix 1

**Table A1**
List of the 35 Variables Included in the Frailty Index

| Health Variable | Cut Point |
|---|---|
| Diseases | |
| Cardiovascular disease | Yes = 1, No = 0 |
| Cerebrovascular disease | Yes = 1, No = 0 |
| Psychiatric disorder | Yes = 1, No = 0 |
| Endocrine disease | Yes = 1, No = 0 |
| Somatic disorder | Yes = 1, No = 0 |
| Disabilities | |
| Help bathing | Yes = 1, No = 0 |
| Help dressing | Yes = 1, No = 0 |
| Help brushing teeth | Yes = 1, No = 0 |
| Use walking aid | Yes = 1, No = 0 |
| Help eating | Yes = 1, No = 0 |
| Help correspondence | Yes = 1, No = 0 |
| Help using toilet | Yes = 1, No = 0 |
| Help going out | Yes = 1, No = 0 |
| Help shopping | Yes = 1, No = 0 |
| Help with housework | Yes = 1, No = 0 |
| Help with meal preparations | Yes = 1, No = 0 |
| Help taking medication | Yes = 1, No = 0 |
| Help with finances | Yes = 1, No = 0 |
| Lost more than 10 lb in last year | Yes = 1, No = 0 |
| Self-rating of health by EuroQol 5D VAS | <70 = 1, >70 = 0 |
| How health has changed in last year | Worse = 1, Better/Same = 0 |
| Bedridden | Yes = 1, No = 0 |
| Symptoms | |
| Cut down on activity/interests | Yes = 1, No = 0 |
| Feel everything is an effort | Most of time = 1, Some time = 0.5, Rarely = 0 |
| Feel depressed | Yes = 1, No = 0 |
| Feel happy | Yes = 1, No = 0 |
| Feel lonely | Yes = 1, No = 0 |
| Have trouble getting going | Most of time = 1, Some time = 0.5, Rarely = 0 |
| High blood pressure | Yes = 1, No = 0 |
| Extrapyramidal symptoms | Yes = 1, No = 0 |
| Nonfluent speech | Yes = 1, No = 0 |
| Physical performance | |
| Disrupted physical activity | Yes = 1, No = 0 |
| BMI | <18.5, ≥30 = 1, 25-30 = 0.5, 18.5-25 = 0 |
| Grip strength | Gender and BMI dependent cut-offs[1] |
| Usual walking speed | <2.5 ft/s = 1, ≥2.5 ft/s = 0 |

## Appendix 2

**Table A2**
Organ Systems Affected by Significant Comorbidity (CIRS-G Score ≥ 2) and Their Effects on 3-Year Institutionalization and Mortality

| Organ System | n (%) | Mortality (n = 322) | Institutionalization (n = 302) |
|---|---|---|---|
| | | HR (95% CI)* | SHR (95% CI)† |
| Cardiovascular system | 189 (57) | 1.25 (0.75-2.10) | 1.01 (0.61-1.68) |
| Heart | 90 (27) | | |
| Vascular | 170 (52) | | |
| Hematopoietic | 25 (8) | | |
| Respiratory system | 111 (34) | 0.94 (0.59-1.49) | 1.11 (0.37-3.31) |
| Respiratory | 54 (16) | | |
| Eye, ear, nose larynx, pharynx | 72 (22) | | |
| Gastrointestinal system | 85 (26) | 1.43 (0.89-2.31) | 0.60 (0.26-1.41) |
| Upper digestive tract | 43 (13) | | |
| Lower digestive tract | 35 (11) | | |
| Liver | 21 (6) | | |
| Genitourinary system | 89 (27) | 1.24 (0.76-2.03) | 0.53 (0.24-1.18) |
| Kidney | 19 (6) | | |
| Urogenital | 75 (23) | | |
| Other systems | 137 (41) | 1.55 (0.98-2.47) | 0.90 (0.47-1.73) |
| Neuromuscular system | 70 (21) | | |
| Neurologic | 48 (15) | | |
| Endocrine/metabolic system | 59 (18) | | |

SHR, subdistribution hazard ratio.
*Adjusted for age, gender, MMSE, residency, dementia type, and study center.
†Adjusted for age, gender, MMSE, coresident, dementia type, and study center.

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## Appendix 3. Stratified Survival Times

**Table A3**
Median (IQR) Time-to-Death by Age Category and Gender Based on Kaplan-Meier Estimates

| Age | Men | | Women | |
|---|---|---|---|---|
| | Deaths/N | Median (IQR) | Deaths/N | Median (IQR) |
| <75 | 26/79 | 6.0 (5.0-NA) | 24/72 | NA (4.9-NA) |
| 75-84 | 38/53 | 4.1 (2.5-5.5) | 32/66 | 4.6 (2.9-NA) |
| ≥85 | 15/18 | 2.0 (0.9-3.0) | 25/43 | 4.2 (2.0-6.0) |

IQR, interquartile range; NA, not assessable due to insufficient events in this group.

**Table A4**
Median (IQR) Time-to-Institutionalization by Age Category and Gender Based on Cumulative Incidence Rates, Corrected for Competing Risk of Death

| Age | Men | | Women | |
|---|---|---|---|---|
| | Events*/n | Median (IQR) | Events*/n | Median (IQR) |
| <75 | 26/79 | NA (4.2-NA) | 30/72 | NA (3.0-NA) |
| 75-84 | 19/53 | NA (2.0-NA) | 29/66 | 3.1 (1.6-NA) |
| ≥85 | 4/18 | NA (1.7-NA) | 23/43 | 2.4 (0.8-NA) |

QR, interquartile range; NA, not assessable due to insufficient events in this group.
*Events represent the number of institutionalizations.