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► To cite this version:

Florence Canoui-Poitrine, Claudia Martinez-Tapia, Elena Paillaud, Simone Mathoulin-Pelissier, Frederic Pamoukdjian, et al.. Geriatric impairments were directly and indirectly associated with mortality in older patients with cancer: a structural equation analysis. *Journal of Clinical Epidemiology*, 2022, 148, pp.17-26. 10.1016/j.jclinepi.2022.04.004 . hal-03668837

HAL Id: hal-03668837

<https://hal.science/hal-03668837>

Submitted on 23 Sep 2022

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A comprehensive model of geriatric factors for mortality among older patients with cancer: a structural equation approach.

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Declarations of interest: None

Abstract

Objective: We assessed the direct and indirect effects between six geriatric domains and 6- and 12-month mortality in older cancer patients.

Study Design and Setting: We included cancer patients aged ≥ 70 from the ELCAPA cohort, referred for geriatric assessment between 2007 and 2016. We used structural equation modelling to examine the interrelationships between six geriatric domains (function and mobility, nutrition, cognition, mood, comorbidities and polypharmacy, and social support) and the direct and indirect relationships between these domains, the cancer stage, site, and treatment on one hand and mortality on the other.

Results: The analysis included 1434 patients (mean age: 80 ± 5.6 ; women: 48%; main cancer sites: digestive tract (36.2%), urinary tract and prostate (26.6%), and breast (16.5%); metastatic cancer: 48%). Direct relationships to 6- and 12- month mortality were identified for functional impairment (standardized coefficient (SC): 0.37 ($P < 0.001$) and 0.32 ($P < 0.001$), respectively), poor nutritional status (SC: 0.11 ($P = 0.005$) and 0.14 ($P = 0.001$)), poor social support (SC=0.07 ($P = 0.08$) and 0.09 ($P = 0.02$)), cancer site, stage, and treatment. The effects of comorbidities, cognitive impairment and depression on mortality were mediated by functional and nutritional status.

Conclusion: In older cancer patients, functional and nutritional impairments were the strongest direct prognostic geriatric factors for mortality.

Key words: geriatric assessment, cancer, survival, structural equation modelling

Running title: A comprehensive model of geriatric factors for mortality among older cancer patients

Word count: 3496

What is new

- Functional impairment had the strongest direct association with mortality, followed by nutritional status
- Conversely, the effects of comorbidities, depression, and cognitive impairment were indirect and were mediated by functional and nutritional status
- Our approach enabled us to better characterize the complex relationships between geriatric domains
- Our findings confirm that interrelations between geriatric factors influence the latter's effects on patient outcomes
- Our work's main clinical implication is that a wide-ranging, multidomain approach to geriatric oncology is needed both for clinical evaluation and patient management

Introduction

Older adults represent a growing population of cancer patients; two-thirds of all new cancers are diagnosed in adults aged 70 and over [1]. It has been established that some geriatric variables are prognostic factors in older patients with cancer, independently of oncological factors [2-4]. Most of these factors involve impairments in health- and function-related domains, which are closely related to the concept of frailty. Frailty is defined as a state of increased vulnerability to stressors; it results from a decrease in physiological reserves in multiple organ systems and leads to an elevated risk of adverse health outcomes, such as functional decline, disability, falls, hospitalization, and death [5, 6]. Malnutrition, impaired mobility, impaired functional and cognitive status, comorbidities, and depression have been independently associated with overall mortality in older patients with various types of cancer [2-4, 7-10].

However, there are many correlations between the various geriatric factors, and the causal pathways between these factors and mortality have yet to be characterized. Studies of whether depression, impaired cognitive status and other comorbidities are independent prognostic factors (i.e. after accounting for functional and nutritional status) have provided inconsistent findings. This observation may be due (at least in part) to mediation processes; the factors might exert their effects on mortality through the impairment of functional or nutritional status. Furthermore, a relationship between geriatric factors may be either unidirectional or bidirectional. For example, nutritional impairment may affect functional status, and functional impairment may affect nutritional status [11, 12]. Lastly, oncological factors may moderate or mediate the relationship between certain geriatric factors and mortality. For example, the association between nutritional status and mortality depends on the cancer site [13, 14].

Standard multivariate prognostic models can identify independent factors for predicting mortality but may overlook more complex associations and may fail to capture the complexity of the relationships between geriatric and oncological variables. Structural equation modelling (SEM) can distinguish between direct and indirect effects of geriatric and oncological factors on mortality [15]. We therefore hypothesized that geriatric impairments and individual clinical characteristics (mainly cancer site, metastatic status, and cancer treatment) have both direct effect and indirect (mediated) effects on mortality in older cancer patients.

The objective of the present analysis was therefore to use SEM to assess the direct and indirect effects of six main geriatric domains (function and mobility, nutrition, cognition, mood, comorbidities and polypharmacy, and social support) on 6- and 12-month mortality in a population of older cancer patients, while taking account of the cancer site, metastatic status, and cancer treatment.

Materials and methods

Design and patients

The Elderly Cancer Patients (ELCAPA) study is a prospective, multicentre, open-cohort study of individuals aged 70 and over with a solid or haematological cancer and having been referred for a multidimensional geriatric assessment (GA) at a geriatric oncology clinic in the Paris area of France. The inclusion of patients in this cohort started in January 2007. Informed consent was obtained from all patients prior to inclusion. The protocol was approved by the appropriate independent ethics committee (*CPP Ile-de-France I*, Paris, France). The study is registered at ClinicalTrials.gov (NCT02884375).

For the purposes of the present analysis (ELCAPA-29), we included ELCAPA patients recruited between January 2007 and March 2016 from 10 participating centres. Patients with missing data for metastatic status, cancer site, cancer treatment, Mini Mental State Examination (MMSE) score, and/or follow-up were not included in the main analysis. In a sensitivity analysis, we additionally included some of these patients by imputing missing MMSE data.

Data collection and endpoints

Data on demographic characteristics (age and sex) and clinical characteristics (cancer site, metastatic status, and cancer treatment [curative treatment, palliative treatment, or supportive care alone) were collected prospectively. A senior geriatrician with expertise in oncology assessed the following GA domains at baseline (for details, see below in the conceptual framework section): function and mobility, nutrition, cognition, mood, comorbidities and polypharmacy, and social support. The endpoints were overall survival in the 6 and 12 months following the GA. Vital status was identified from medical records or at the public records office.

Proposed conceptual framework

The conceptual framework for SEM was established after we had searched the literature (**Supplementary Table 1**) [16] for publications on interrelationships between geriatric domains in general and longitudinal studies in particular; the objective was to identify specific, unidirectional, causal trajectories (e.g. variables associated with functional decline or cognitive decline). All 6 domains, in addition to clinical and demographic variables, were hypothesized to potentially affect mortality. SEM allows one to estimate the association between observed or latent variables [17]. Latent variables are unobserved variables that are estimated from two or more observed variables (i.e. indicators).

We considered six latent variables, built with the following geriatric indicators: (i) *function and mobility*: the Activities of Daily Living (ADL) score, the Instrumental ADL (IADL) score, the Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) and the timed up-and-go (TUG) test; (ii) *nutrition*: body mass index (BMI – kg/m²) and weight loss in the last 3 months (in kilograms); (iii) *cognition*: the MMSE score, and a history of cognitive disorders; (iv) *mood*: the mini-Geriatric Depression Scale (mini-GDS) and symptoms of depression; (v) *comorbidities and polypharmacy*: the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) score, and the number of prescription medications taken daily; (vi) *social support*: living alone, having an identified primary caregiver, and having children.

To build each latent variable, two or more indicators were chosen by considering validated clinical tests or other frequently used relevant variables for measuring a specific domain in older patients.

Functional and mobility scores were used to construct a latent variable representing a common health domain, and were chosen in accordance with (i) the International Society of Geriatric Oncology (SIOG) consensus on GA in older cancer patients and (ii) other studies in older adults [4, 18]. In the SIOG consensus, various tools for assessing function and mobility are included in the functional status domain [4]. It has been shown that both, physical impairments and disabilities are related to physical function [18].

For the assessment of nutrition, we chose objective measures related to body weight (such as the BMI and weight loss) rather than tools like the Mini Nutritional Assessment (MNA) which cover a broad, poorly specified spectrum that can encompass domains like general health, cognition, and mood, in addition to nutritional status.

In the absence of a validated scale for social support in the ELCAPA database, variables covering the social domain [19, 20] (mainly living alone, having a primary caregiver, and having children) were used as indicators in this respect.

A Confirmatory Factor Analysis (CFA) was then performed to assess the global goodness of fit of the proposed measurement mode before adding any pathways; results from this assessment were found to be acceptable, as indicated by a CFI of 0.92, with RMSEA of 0.072 and TLI of 0.89. Of note, absolute values of loadings of each item on their respective latent variable were all superior to 0.4 (all P-values <0.001), to the unique exception of the variable “Having children” for which we found an absolute loading value of 0.3. For this latter indicator, we nonetheless decided to keep it into the model considering its clinical relevance.

The conceptual framework used to test the direct and indirect effects of clinical and geriatric variables on mortality is shown in **Figure 1a**.

Statistical analysis

The patients’ characteristics were described as the frequency (percentage) for qualitative variables and the mean \pm standard deviation (SD) or median [interquartile range (IQR)] for quantitative variables. Correlations between geriatric variables were described by building a correlation matrix; a correlation network was then generated to graphically express the interrelationships between these variables. In the main analysis, the k-nearest neighbours algorithm was used to impute missing values for all variables, with the exception of those with a missing data rate of 15% or more (the MMSE score, in the present analysis). Further details of missing data imputation and correlation analyses are given in the **Supplementary Material**.

SEM was performed with mortality as a binary outcome. Separate models were built for 6-month and 12-month mortality. The mean- and variance-adjusted weighted least squares estimator was used; this is a robust estimator that is appropriate for binary or ordered categorical observed variables. The model examined (i) the relationships between the six main latent geriatric domains (function, nutrition, cognition, mood, comorbidities, and social support) and (ii) the influence of the domains, the cancer stage, the cancer site and cancer treatment on overall 6- and 12-month mortality. Each latent construct was measured by two or three observable indicators, which were either binary, ordinal or continuous. The effects of each latent geriatric domain were estimated. The models were adjusted for age, sex, cancer type/metastatic status, and cancer treatment. Relationships with $P \geq 0.05$ were removed from

the hypothetical model. Goodness-of-fit was assessed by calculation of the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the root mean squared error of approximation (RMSEA). CFI and TLI values between 0.90 and 0.95 are considered to be acceptable, and values greater than 0.95 are considered to be good. RMSEA values below 0.06 indicate a good fit [21].

R software [22] (version 3.4.3) was used for the correlation analyses, visualization (with the corplot, psych and qgraph packages), and SEM (with the lavaan package [23]).

Results

Of the 2443 patients included in the ELCAPA cohort between January 2007 and March 2016, 523 (21.4%) had missing data for metastatic status, cancer site or cancer treatment, and 165 others were lost to follow-up (**Figure 2**). Of the 1755 remaining patients, 321 (18%) did not have an MMSE score. The main analysis therefore included 1434 patients. The proportion of missing data for the other 13 geriatric indicators was 4% on average and ranged from 0.07% (living alone) to 13.2% (TUG).

Baseline characteristics of the study population

The patients' demographic, clinical and geriatric characteristics are described in **Table 1**. The mean age was 80.4 ± 5.6 , 48.1% of the patients were women, and 48% had metastases. The most frequent cancer types were digestive tract cancer (36.2%), urinary tract and prostate cancers (26.6%), and breast cancer (16.5%). Curative treatment had been selected for 44.4% of the patients and supportive care alone, for 21.4%. More than half of the study participants had a poor performance status (ECOG-PS ≥ 2). The comorbidity burden was high (median CIRS-G score: 12), and 40% of the participants lived alone at home.

The correlations between the various geriatric variables are described in the **Supplementary data** and are shown in **Figure S1** (a: correlation matrix; b: correlation network).

Structural equation modelling

The final SEM model for 12-month mortality is shown in **Figure 1b** and is detailed in **Supplementary Table 2**, which additionally shows the standardized coefficients applied to 6-month mortality. The coefficients in the SEM measurement model (i.e. the relationships between latent variables and their indicators) are detailed in **Supplementary Table 3**.

The 6- and 12-month overall survival rates [95%CI] were 68.1% [65.6%-70.5%] and 55.5% [52.9%-58.1%], respectively. Significant direct pathways to 12-month mortality were identified for three of the six geriatric domains (functional impairment, nutritional status and poor social support), the combined tumour site/metastatic status variable, and cancer treatment. The model revealed that the effects of comorbidities, cognitive impairment and depression were mediated by other geriatric domains. Several statistically significant relationships were identified: (i) depression and comorbidities were positively associated with cognitive, nutritional and functional impairments; (ii) comorbidities were positively associated with depression; (iii) cognitive impairment was positively associated with nutritional and functional impairment; and (iv) poor social support was negatively associated with cognitive impairment. Nutritional status was strongly correlated with functional impairment and less strongly correlated with social support. The final model's fit was very good, according to the RMSEA (0.036 [90%CI: 0.033-0.039]), CFI (0.955) and TLI (0.941). Similar fit indices were found for the model of 6-month mortality.

After imputing missing MMSE score, the sensitivity analysis on the 1755 patients with full data for metastatic status, cancer site, cancer treatment, and vital status showed very similar results to those described for the sample of 1434 patients (data not shown).

Discussion

Our results are likely to provide a better understanding of the health status relationships that influence mortality among older patients with cancer. By applying SEM, we were able to identify oncological and geriatric prognostic factors, estimating the factors' direct and indirect associations with survival, and thus illustrate the intricate effects of each geriatric domain on mortality. Functional impairment had the strongest direct association with mortality, followed by nutritional status. Interestingly, poor social support was also found to have a direct effect on survival. Conversely, the effects of comorbidities, depression, and cognitive impairment were indirect and were mediated by functional and nutritional status.

Our approach contrasts with earlier modelling studies in which the various geriatric domains were all included in a single model, despite the strong intercorrelations between them. Here, SEM enabled us to better characterize these complex relationships between geriatric domains.

Firstly, functional impairment was affected by comorbidities, cognitive impairment, and depression. Patients with comorbidities, cognitive disorders or depression were more likely to have poorer functional (ADL and IADL) scores, a poorer performance status, and lower mobility than patients with no such impairments. The relationship between function and these three domains has been well documented in several longitudinal studies, although most of them included only cancer-free older patients [24-28]. In a prospective cohort study of 294 patients aged 75 and older, Jyrkka and colleagues observed an independent association between polypharmacy and declining functional ability over a 3-year follow-up period [24]. In another 3-year follow-up study of 456 frail, community-dwelling older adults aged 65 and over, participants with severe cognitive decline also showed a substantial functional deterioration over time [26]. In a large longitudinal study of 103 384 older patients, longitudinal regression analyses revealed that functional impairment worsened significantly with the occurrence of depression and cognitive impairment and the number of chronic conditions [27]. The few studies to have evaluated these relationships in older cancer patients had small sample sizes. In a study of 376 older cancer survivors, patients with a higher comorbidity burden had a significantly greater functional impairment after adjustment for age, sex, race, education, marital status, depression, and cognitive status [29]. In another study of 364 older patients receiving first-line chemotherapy for various cancer types, only depression (evaluated on the 15-item GDS) was independently associated with an increased risk of functional decline (defined as a decrease in the ADL score of ≥ 0.5 points) [30], while comorbidities and impaired cognition were not. Conversely, in a study of 196 older cancer outpatients, cognitive impairment, depressive mood, and polypharmacy were independently associated with disability (i.e. impaired ADL or IADL scores) [31]; this finding is in line with our present results.

Secondly, nutritional status was affected by comorbidities, cognitive impairment, and depression and was also strongly correlated with functional impairment and poor social support. These findings are consistent with the literature data indicating that a wide range of factors (including those mentioned above) can affect nutritional status. Indeed, risk factors for malnutrition and weight loss can have different underlying causes, including cognitive decline, social isolation, depression, polypharmacy, dental issues, and functional dependence [32]. A recent systematic review of longitudinal studies found 15 risk factors for malnutrition in older adults; these notably included excessive polypharmacy, functional and cognitive decline, dementia, and loss of interest in life [33]. Older patients with cancer have rarely been studied in this respect. A cross-sectional study of 249 Asian patients aged 70 and older with

various cancer types identified poor performance status, depression, anaemia, and late-stage cancer as independent factors associated with a moderate-to-high nutritional risk [12]. Late-stage cancer was also identified as a risk factor for malnutrition in a study of 8895 hospitalized cancer patients (mean age: 55.3); malnutrition also depended on the cancer site because it was more severe in patients with digestive tract cancers in general and liver and stomach tumours in particular [34]. These data are in line with our study, which found that (i) patients with cancers of the upper digestive tract, liver or pancreas had a worse nutritional status than patients with non-metastatic colorectal cancer, and (ii) the patients with the best nutritional status were those with non-metastatic breast or urinary tract cancers.

As mentioned above, nutritional status was strongly associated with functional impairment. However, the causal direction of this association is subject to debate. Malnutrition is accompanied by loss of body weight, muscle mass, and strength, which can lead to sarcopenia. A loss of physical functioning is accompanied by difficulty cooking and eating, which may then impact the person's nutritional status. Furthermore, older people with functional impairment tend to adapt their diet, which leads to inadequate food consumption [35]. With regard to the association between social support and nutritional status, the findings of a study of 1200 older adults aged 65 and over were in line with our results; it showed that poor social support was an independent factor for malnutrition [36]. The social isolation often associated with older age might decrease the food intake, which in turn would increase the risk of malnutrition. Various researchers have emphasized that social support can increase well-being and thus improve a person's appetite [37, 38].

Third, we found that depression was influenced by comorbidities. Our results are in line with literature data on older patients with cancer [30, 39, 40]. In a longitudinal study of 154 patients with colorectal cancer aged 65 and over, comorbid conditions were significant predictors of depressive symptoms within 12 months of the cancer diagnosis. Patients with two or more co-morbid conditions at baseline showed a consistently greater depressive symptom burden. Restricted physical and social functioning (according to the SF-36 questionnaire) was also linked to a greater depressive symptom burden. In a study of 500 older patients with various types of cancer, a multivariable analysis identified a lack of social support, a greater number of comorbidities, and late-stage cancer as significant independent factors associated with depression [40]. In contrast to our present results, poor social support was not significantly associated with depression in the latter study.

Lastly, our analysis demonstrated that comorbidities and depression affected cognition. Longitudinal studies of older patients have already shown that cognitive impairment can be

associated with comorbidities and depression [24, 41, 42]. Jyrkka and colleagues' findings indicated that excessive polypharmacy (defined as at least 10 regularly taken medications) was strongly associated with a decline in cognitive status in older adults aged 75 and older [24]. In another study of 598 older adults aged 60 and older, the researchers concluded that depression independently increased the risk of cognitive decline [42]. In our study, cognition was negatively associated with social support – perhaps reflecting the lower need for social support by self-sufficient patients without cognitive impairment. Although most of the literature data show that social support has a beneficial effect on cognitive function [43], other cross-sectional studies have observed the same phenomenon as we did here, i.e. patients with a lower degree of cognitive impairment have less social support. Moreover, physical function might be a confounding factor in the association between social support and cognition.

Strengths and weaknesses

Our study's strengths included the use of novel methods to address the research question, the large population size, and the number and variety of explanatory indicators investigated. The study's main limitation is selection bias: the participants had all been referred to a geriatrician for a GA, and so our results should be extrapolated cautiously to the broader population of older patients with cancer. Secondly, we focussed on mortality and not on other relevant outcomes, such as quality of life and unscheduled hospital admissions.

Implications

Our findings confirm that interrelations between geriatric factors influence the latter's effects on patient outcomes (mortality, in the present study). Our work's main clinical implication is that a wide-ranging, multidomain approach to geriatric oncology is needed both for clinical evaluation and patient management. Thus, the correction of one impaired domain (e.g. malnutrition) needs to take into account of possible impairments in other domains (e.g. depression, cognition, and comorbidities) because the latter may also contribute to impairment of the targeted domain. From a research point of view, our present results suggest that it would be useful to study changes over time in geriatric factors; this might facilitate the characterization of (i) changes in distinct health trajectories over time, and (ii) the time sequence of the causal relationships at play (e.g. from comorbidity and neurocognitive deterioration to functional and nutritional impairments).

Conclusion

Our results highlight the complex nature of the relationships between geriatric variables and thus the development of impairments in older patients with cancer. Functional and nutritional status was compromised by comorbidities, depression, and cognitive impairment. Individuals with a higher comorbidity burden had a greater risk of developing symptoms of depression, and individuals with depression or comorbidities had a greater risk of cognitive impairment. Functional and nutritional impairments were the strongest, direct prognostic factors for 6- and 12-month overall survival, independently of oncological factors. In contrast, the effects of comorbidities, depression, and cognitive impairment on survival were mediated by the patient's functional and nutritional status.

Funding: The ELCAPA study was funded by a grant [RINC4] from the French National Cancer Institute (*Institut National du Cancer*, INCa), *Canceropôle Ile-de-France*, and *Gerontopôle Ile-de-France* (Géront'if), neither of which had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

Declarations of interest: None

Author contributions: **Florence Canoui-Poitrine:** Conceptualization, Funding acquisition, Project administration, Methodology, Writing - original draft, Supervision. **Claudia Martinez-Tapia:** Data curation, Formal analysis, Methodology, Writing - original draft. **Elena Paillaud:** Funding acquisition, Resources, Project administration, Writing - review & editing. **Simone Mathoulin-Pelissier:** Interpretation of data, Writing - review & editing. **Frédéric Pamoukdjian:** Interpretation of data, Writing - review & editing. **Matthieu Frasca:** Interpretation of data, Writing - review & editing. **Anna-Maija Tolppanen:** Interpretation of data, Writing - review & editing. **Michael Bringuier:** Investigation, Writing - review & editing. **Etienne Brain:** Investigation, Writing - review & editing. **Amaury Broussier:** Interpretation of data, Writing - review & editing. **Sylvie Bastuji-Garin:** Methodology, Writing - review & editing. **Marie Laurent:** Investigation, Resources, Writing - review & editing. **Etienne Audureau:** Conceptualization, Methodology, Writing - original draft, Supervision. All authors approved the final version of the manuscript to be submitted.

Acknowledgments: The ELCAPA Study Group consists of geriatricians (Amelie Aregui, Michaël Bringuier, Philippe Caillet, Pascale Codis, Tristan Cudennec, Anne Chahwakilian, Amina Djender, Narges Ebadi, Virginie Fossey-Diaz, Mathilde Gisselbrecht, Marie Laurent, Soraya Mebarki, Galdric Orvoen, Frédéric Pamoukdjian, Anne-Laure Scain, Godelieve Rochette de Lempdes , Florence Rollot-Trad, Gwenaëlle Varnier, Helène Vincent, Elena Paillaud), oncologists (Pascaline Boudou-Rouquette, Stéphane Culine, Etienne Brain, Christophe Tournigand), a digestive oncologist (Thomas Aparicio), a gynaecological oncologist (Cyril Touboul), a radiation oncologist (Jean-Léon Lagrange), epidemiologists (Etienne Audureau, Sylvie Bastuji-Garin, Florence Canouï-Poitrine), a medical biologist (Marie-Anne Lorient), a pharmacist (Pierre-André Natella), a biostatistician (Claudia Martinez-Tapia), a clinical research physician (Nicoleta Reinald), a clinical research nurse (Sandrine Rello), a data manager (Mylène Allain, Clélia Chambraud), and clinical research assistants (Aurélie Baudin, Margot Bobin, Salim Chalal, Laure Morisset, Johanna Canovas).

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Table captions

Table 1. The characteristics of the study population.

Figure legends

Figure 1 a Conceptual framework of the hypothetical relationships between the latent constructs, individual clinical characteristics, and mortality. *Ellipses*: latent variables; *boxes*: observed variables. The direction of an arrow indicates the variable affected by the other variable. Gray attenuated arrows indicate the indicators for the corresponding construct. **b** The final structural equation model (N=1434 patients). *Ellipses*: latent variables. The direction of an arrow indicates the variable affected by the other variable. The model was adjusted for age and sex

Figure 2 Flow chart of study patients

Abbreviations: MMSE, Mini Mental Statement Examination; SEM, Structural Equation Modeling