Thesis

Prédiction des issues défavorables des hospitalisations gériatriques

ZEKRY, Dina Selma

Abstract

This research project was undertaken to assess the relative contribution of cognitive, functional and nutritional status, comorbidities and biomarkers predicting adverse outcomes in the hospitalized elderly. In older people, dementia is frequently associated with adverse health outcomes (poor functional and nutritional status; higher rates of institutionalization and of readmission; and lower survival rates). The relative weight of dementia of varying type and severity as predictors of adverse health outcomes after other risk factors taken into account remains unclear. In this context, we performed, since 2004, a prospective clinico-biological study aiming to investigate the relationship among clinical and specific biological markers and adverse health outcomes in a population of very old, acutely ill patients discharged from a geriatric hospital. We assessed the extent to which a clinical or a biological marker was of greater added prognostic value than other markers of risk for the adverse outcomes. The studied adverse outcomes were death in hospital, greater length of stay, institutionalization and increase formal home [...]

Reference

ZEKRY, Dina Selma. *Prédiction des issues défavorables des hospitalisations gériatriques*. Thèse de privat-docent : Univ. Genève, 2012

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG
Hôpitaux Universitaires de Genève

Clinical Medicine Section
Department of Internal Medicine, Rehabilitation and Geriatrics
Service of Geriatrics

" PREDICTING ADVERSE OUTCOMES IN HOSPITALIZED ELDERLY: RELATIVE CONTRIBUTIONS OF COGNITIVE, FUNCTIONAL AND NUTRITIONAL STATUS, COMORBIDITIES AND BIOMARKERS "

Thesis submitted to the Medical School of Medicine of
the University of Geneva

for the degree of Privat-Docent
by

Dina ZEKRY

Genève

2012

Ao meu irmão Beny
Aos meus avós
Chana e Moysés
Dina e Benjamin
A Paulette Lelous

Aos meus pais Paulina e Bernardo

Ao meu irmão Marcelo

Ao meu marido Kalman

Ce travail a été réalisé au sein de l'Hôpital des Trois-Chêne, Département de Réhabilitation et Gériatrie, Hôpitaux Universitaires de Genève, Université de Genève.

Je remercie

Monsieur le Professeur Jean-Pierre MICHEL

de son accueil chaleureux à Genève, de m'avoir transmis son amour de la Gériatrie

de m'avoir accordé sa confiance et son soutien dans l'accomplissement de ce travail.

Qu'il accepte cette thèse en gage de ma gratitude et de mon admiration.

Monsieur le Professeur Gabriel GOLD

de m'avoir transmis son intérêt pour la recherche dans le domaine des démences des personnes âgées,

de sa collaboration et surtout de son encouragement, même dans les moments les plus difficiles.

Qu'il trouve ici l'assurance de ma reconnaissance et de mon amitié.

Monsieur le Professeur Karl-Heinz KRAUSE

d'avoir bien voulu me confier ce travail et de m'avoir guidée tout au long du projet et de la réalisation

de ce travail avec le même enthousiasme et la même disponibilité.

Que cette thèse soit l'expression de ma profonde reconnaissance et de toute mon estime.

Monsieur le Docteur François HERRMANN

pour la rigueur de son travail d'analyse statistique et pour la disponibilité dont il a su faire preuve.

Qu'il trouve ici l'assurance de ma reconnaissance et de mon amitié.

Messieurs les Professeurs René RIZZOLI et Jean-Jacques PERRENOUD

de leur amabilité, leurs encouragements et conseils précieux.

Monsieur le Professeur Ezio GIACOBINI

pour l'intérêt qu'il a manifesté à ce travail et ses nombreux conseils.

Qu'il trouve ici l'expression de mon plus sincère respect et de mon admiration.

Monsieur le Professeur Alain MALAFOSSE

de son amabilité et mise à disposition de son laboratoire.

Madame la Professeure Frauke MUELLER

pour la fructueuse et agréable collaboration et la mise à disposition de la clinique dentaire de Genève.

Monsieur le Docteur Patrick DESCOMBES

pour son expertise, sa collaboration et la mise à disposition du"core facilities Genomic Platform" de Genève.

Mesdames Brigitte FALEUR et Nathalie MANNINO

qui ont apporté les qualités d'ordre à ce travail.

Qu'elles soient assurées de mon amitié et du plaisir partagé au travail.

Mesdames Marie-Pierre MEYNET, Maria de Fatima PINHO, Chantal GENET,

Sylviane BOTTONE, Sabrina CARLIER, Anna-Maria VITALE, Claudia LARDI et Fabienne ESPOSITO

de leur travail très attentionné, rigoureux et énergique.

Que ce mémoire soit le témoin de mon amitié et la récompense de leurs efforts.

Mesdames les Doctoresses Homa ATTAR, Silvia SORCE, Karen BEDARD, Christine DUFFET,

Michela TEMPIA-CALIERA, Mesdames Laura ORTOLAN-TRIGUI, Elena DUVERNAY et Fanny ELSIG

de leur expertise et travail de grande qualité.

Qu'elles trouvent ici l'expression de ma respectueuse gratitude et de mon amitié.

Tous mes collègues du Département de Réhabilitation et Gériatrie

qui m'ont beaucoup aidée pour mener cette thèse à son terme dans une ambiance très agréable.

Monsieur Pierre GATTELET et ses collaborateurs, Madame Michèle COS et ses collaborateurs,

Madame Laure HUMBLOT, Madame Nathalie DALLOUX et ses collaborateurs, Madame Simone BOUZIDI,

l'équipe de la consultation mémoire, l'équipe de la réception de l'Hôpital des Trois Chêne

de leur aide précieuse. Qu'ils soient assurés de ma gratitude.

Tous ceux qui, de façon directe ou indirecte, ont rendu ce travail possible, en particulier

Mesdames les Doctoresses Marie-Claire JACQUES, Véronique TROMBERT, Anne-Françoise ALLAZ,

Sandra GIANNELLI, Sophie PAUTEX, Henriette HILLERET, Claudia SCHMEER, Nathalie SALLES,

Muriel DROZ DIT BOUSSET, Emilia FRANGOS, Karine BECH, Rachel LUCHETTA,

Anne Claude JUILLERAT, Madame Joelle EMMENEGGER;

Messieurs les Docteurs Christophe GRAF, Martin ZARATE, Martin SCHIMMEL, Patrick AMMANN,

Philippe HUBER, Gorki CARMONA, Gaëton GAVAZZI et Raphael GRANDJEAN.

Qu'ils acceptent cette thèse en gage de ma reconnaissance et de mon amitié.

Muito obrigada

TABLE OF CONTENTS

SUMMARY 1

INTRODUCTION 5

PAPERS 14

PAPER 1: Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status 15

PAPER 2: Geriatrics index of comorbidity was the most accurate predictor of death in geriatric hospital among six comorbidity scores 20

PAPER 3: Prospective comparison of 6 comorbidity indices as predictors of 1-year post-hospital discharge institutionalization, readmission, and mortality in elderly individuals 26

PAPER 4: Prospective comparison of six comorbidity indices as predictors of 5 years post hospital discharge survival in the elderly 31

PAPER 5: Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients 36

PAPER 6: Mild cognitive impairment, degenerative and vascular dementia as predictors of intra-hospital, short- and long-term mortality in the oldest old 42

PAPER 7: High levels of comorbidity and disability cancel out the dementia effect in predictions of long-term mortality after discharge in the very old 47

PAPER 8: Telomere length, comorbidity, functional, nutritional and cognitive status as predictors of 5 years post hospital discharge survival in the oldest old 52

PAPER 9: Telomere length is not predictive of dementia or MCI conversion in the oldest old 56

PAPER 10: Telomere length and ApoE polymorphism in mild cognitive impairment, degenerative and vascular dementia 66

DISCUSSION AND CONCLUSIONS 69

REFERENCES 77

ABBREVIATIONS

AD	Alzheimer's disease
ApoE	apolipoprotein E
CDS	chronic disease score
CCI	Comorbid Charlson index
CIRS	cumulative illness rating scale
GIC	geriatrics index of comorbidity
ICED	index of coexistent diseases
Kaplan	Kaplan scale
MCI	mild cognitive impairment
MD	mixed dementia
MMSE	mini mental status examination
VaD	vascular dementia

SUMMARY

This research project was undertaken to assess the relative contribution of cognitive, functional and nutritional status, comorbidities and biomarkers predicting adverse outcomes in the hospitalized elderly. In older people, dementia is frequently associated with adverse health outcomes (poor functional and nutritional status; higher rates of institutionalization and of readmission; and lower survival rates). The relative weight of dementia of varying type and severity as predictors of adverse health outcomes after other risk factors taken into account remains unclear. In this context, we performed, since 2004, a prospective clinico-biological study aiming to investigate the relationship among clinical and specific biological markers and adverse health outcomes in a population of very old, acutely ill patients discharged from a geriatric hospital. We assessed the extent to which a clinical or a biological marker was of greater added prognostic value than other markers of risk for the adverse outcomes. The studied adverse outcomes were death in hospital, greater length of stay, institutionalization and increase formal home care need after discharge; 1-year risk of rehospitalization, institutionalization and death; and long-term mortality after 5-years of follow-up. The studied clinical markers were cognitive diagnosis (various etiologies and severity of dementia), functional and nutritional status, comorbidities and the studied biomarker was leukocytes telomere length. As few comorbidity indices are valid and reliable in the elderly and were rarely compared, first we compared the performance, relevance and ability of six widely used comorbidity indices (comorbid Charlson index, cumulative illness rating scale (CIRS), index of coexistent diseases (ICED), Kaplan scale, geriatrics index of comorbidity (GIC) and chronic disease score (CDS) to predict the adverse outcomes. As there is evidence of association between telomere length and aging but data investigating the association between telomere length and dementia remained scarce; first, we determined whether telomere length may contribute to the diagnosis of AD and whether they allow to discriminate AD from other dementias; secondly, we assessed whether telomere length alone is associated to the studied adverse outcomes or when combined to the clinical markers provided an additional predictive value.

In our cohort of 449 very old inpatients (mean age = 85yrs), we were able to demonstrate, that:

- Demented patients, non-demented patients and patients with mild cognitive impairment (MCI) had similar levels of comorbidity, but demented patients had a poorer functional and nutritional status. Till now, demented patients have been reported to be healthier than other old people and these findings could be a consequence of inaccurate symptoms reporting, delaying diagnosis; or may reflect a failure on the part of screening strategies to investigate thoroughly and to diagnose disease in these patients.

- Comorbidity scores performed differently predicting the studied adverse outcomes and, according to our results, the CIRS and the GIC are those that we recommend to use in the elderly for clinical and research purposes. The GIC was the most accurate predictor of death during hospitalization, the risk of death being 30 times higher; followed by the CIRS. The CIRS was the strongest predictor of a prolonged hospital stay and institutionalization. Concerning 1-year risk, the GIC and the CIRS were the best predictors for mortality and for readmission. The GIC was the only significant predictor of institutionalization. The CIRS was the strongest risk predictor of 5 years survival after hospital discharge, followed by the GIC.

- Dementia predicted only institutionalisation immediately after discharge; whereas higher comorbidity score predicted death in hospital or longer hospital stay, regardless of cognitive status. Functional status was the best predictor of greater home care needs. Regarding the 5-year risk of mortality, the univariate model showed that being older, male and having vascular and severe dementia, higher comorbidity and functional disability were predictive of shorter survival. However, in the full multivariate model adjusted for age and sex, the effect of dementia type or severity completely disappeared when all the variables were added. In multivariate analysis, the best predictor of long-term mortality was higher comorbidity score, followed by functional status.

- Telomere length could not be used to distinguish between demented and non demented patients, regardless of the type of dementia, or to predict dementia or MCI conversion. No significant difference in telomere length was observed between cognitively normal patients, demented patients and patients with MCI. Similarly, no significant differences in telomere length were found between patients with different etiologies or severities of dementia. In addition, the combination of telomere length and ApoE polymorphism did not confer a significantly higher dementia risk than ApoEε4 alone. Telomere length and change in cognitive status (from normal to MCI or dementia, or from MCI to dementia) were not associated after two years of follow-up.

- Telomere length is not associated with 5-year survival beyond the impact of other risk factors of mortality like comorbidity, functional, nutritional and cognitive status.

INTRODUCTION

Elderly patients often suffer from multiple chronic conditions that individually and jointly affect their quality of life, use of health services, morbidity and mortality [Gijsen et al, 2001].

Dementia is a serious health problem with a significant economic impact and may probably play a role as a risk factor for some adverse outcomes like mortality [Herrmann et al, 1999].

Previous studies have reported that survival is reduced among patients with dementia, particularly in a setting of cerebrovascular disease [Barclay et al, 1985; Nielsen et al, 1991; McGonigal et al, 1992; Katzman et al, 1994; Tatemichi et al, 1994].

Studies of the population-based cohort type, have evaluated survival in relation to dementia, with most reporting that the risk of death is higher in the presence of dementia than in its absence [Aevarsson et al, 1998; Bonsignore et al, 2003; Larson et al, 2004; Tschanz et al, 2004; Ganguli et al, 2005; Rait et al, 2010]. A recent Danish population-based cohort study (14 years of follow-up) involving 3,065 non-demented (73.7 ± 6.8 years) and 234 demented (83.3 ± 7.0 years) subjects at baseline showed that the hazard ratio (HR) of death increased from 1.82 for the very mildly demented to 9.52 for severely demented subjects [Andersen et al, 2010].

In older people living at home, cognitive impairment is frequently associated with other adverse health outcomes like poor functional and nutritional status, and higher rates of institutionalization [Aguero-Torres et al, 1998; Aguero-Torres et al, 1998; Mehta et al, 2002; Ramos et al, 2001; Soto et al, 2006; Stump et al, 2001].

In addition, cognitive impairment is also often used as a predictor of poorer hospitalization outcomes but in the majority of these studies, comorbid medical conditions, functional and nutritional status are not taking into account [Bertozzi et al, 1996; Di Iorio et al, 1999; Fogel et al, 2000; Inouye et al, 1998; Lang et al, 2006; Marengoni et al, 2004]. The

relative contributions of a full, accurate dementia diagnosis and of other risk factors to the prediction of adverse hospitalization outcomes remain unclear.

Recently, a retrospective study based on hospital discharge database records dated 1998-2003 from public hospitals in Andalusia, Spain, identified 40,482 cases of dementia and reported that the intra-hospital mortality rate was greater (19.3% vs. 8.7%) for patients with dementia compared to those without dementia. Dementia was an independent predictor of mortality (OR 1.77; 95% CI 1.72-1.82) [Guijarro et al, 2010]. This study was conducted in general hospitals, all ages confounded.

In most of these previous studies, "cognitive impairment" was defined based on MMSE score alone, with no accurate diagnosis of dementia, its aetiology and severity [Folstein et al, 1975]. In addition, most studies have analyzed mortality in patients with cognitive impairment as a global diagnosis [Andersen et al, 2010] or only in patients with Alzheimer's disease (AD) [Larson et al, 2004; Ganguli et al, 2005].

Only a few rare studies have considered mortality for other types of dementia, such as mixed dementia (AD plus vascular), which is highly prevalent in the very old [Zekry et al, 2002a; Zekry et al, 2002b; Zekry et al, 2002c; Zekry et al, 2005], or in mild cognitive impairment (MCI) [Koedam et al, 2008; Guehne et al, 2006]. Furthermore, the non-demented subjects in these studies are often significantly younger [Bonsignore et al, 2003; Larson et al, 2004] and have significantly fewer comorbid conditions than the group of demented patients. In addition few studies have examined short and long-term mortality in acutely ill very old patients after hospitalization discharge and information on the same population remains scarce.

Thus, the relative contributions of a full, accurate dementia diagnosis etiology taking into account other risk factors like comorbidity, functional and nutritional status to the prediction

of adverse intra-hospital, short and long-term post-discharge outcomes, in the very old, remain unclear.

In addition, older patients often suffer from multiple comorbid conditions. Few comorbidity indices are valid and reliable in elderly patients and were rarely compared. Comparison between the most widely known comorbidity indices predicting adverse hospitalization outcomes inthe elderly is urgently needed.

The most widely studied comorbidity indices are:

- **Charlson Comorbidity Index** (CCI) [Charlson et al, 1987]

  The CCI is a list of 19 conditions; each is assigned a weighting (1 to 6). Weightings reflect the ability of each condition to predict one-year mortality, as originally reported for cancer patients. They are fixed for each diagnosis and range from 1 (for conditions, such as myocardial infarction or mild liver disease, with a relative risk ≥1.2 and <1.5) to 6 (assigned to metastatic cancer, with a relative risk ≥6). The CCI is the sum of the weightings for all conditions observed in a patient - higher scores indicated greater comorbidity.

- **Cumulative illness rating scale** (CIRS) [Parmelee et al, 1995]

  The CIRS identifies 14 items, corresponding to different systems. Each system is scored as follows: 1 (none), no impairment to that organ/system; 2 (mild), impairment does not interfere with normal activity; treatment may or may not be required; prognosis is excellent; 3 (moderate), impairment interferes with normal activity, treatment is needed, prognosis is good; 4 (severe), impairment is disabling, treatment is urgently needed, prognosis is guarded; 5 (extremely severe), impairment is life-threatening, treatment is urgent or of no avail; poor prognosis. The Illness Severity Index (summary score based on the average of all CIRS items, excluding psychiatric/behavioral factors) and the comorbidity index (summary score based on a count of organ system with moderate or

greater impairment, excluding psychiatric/behavioral) can then be calculated using these scores.

- **Index of coexistent diseases** (ICED) [Greenfield et al, 1995]

  The ICED is based on the presence and severity of 19 medical conditions and 11 physical impairments, using two scales: the Index of Disease Severity (IDS) and the Index of Physical Impairment (IPI). The final ICED score is determined by an algorithm combining the peak scores for the IDS and IPI. The ICED score ranges from 0 to 3 (four classes), reflecting increasing severity.

- **Kaplan scale** [Kaplan and Feinstein, 1974]

  This index uses two forms of classification, focusing on the type of comorbidity and the pathophysiologic severity of the comorbid conditions present, respectively. The type of comorbidity can be classified as vascular (hypertension, cardiac disorders, peripheral vascular disease, retinopathy, and cerebrovascular disease) or nonvascular (lung, liver, bone, and no diabetic renal diseases). Pathophysiologic severity is rated on a four-point scale, ranging from 0 (comorbidity is absent or easy to control) to 3 (recent full decompensation of comorbid disease). The rating of the most severe condition determines the overall comorbidity score. Scores for vascular and nonvascular comorbidity can be calculated, based on the most severe condition in each subscale.

- **Geriatric index of comorbidity** (GIC) [Rozzini et al, 2002]

  In computing the GIC, each of the 15 more prevalent clinical conditions (ischemic or organic heart diseases, primary arrhythmias, heart diseases with a non-ischemic or – organic origin, hypertension, stroke, peripheral vascular diseases, diabetes mellitus, anemia, GI diseases, hepatobiliary diseases, renal diseases, respiratory diseases, parkinsonism and nonvascular neurologic diseases, musculoskeletal disorders, malignancies) is graded on a 0 to 4 disease severity scale on the basis of the following

general framework: 0 = absence of disease, 1 = asymptomatic disease, 2 = symptomatic disease requiring medication but under satisfactory control, 3 = symptomatic disease uncontrolled by therapy, and 4 = life-threatening or the most severe form of the disease. The GIC classifies patients into four classes of increasing somatic comorbidity. Class 1 includes patients who have one or more conditions with a disease severity grade equal to or lower than 1. Class 2 includes patients who have one or more conditions with a disease severity grade of 2. Class 3 includes patients who have one condition with a disease severity of 3, other conditions having a disease severity equal to or lower than 2. Class 4 includes patients who have two or more conditions with a disease severity of 3 or one or more conditions with disease severity of 4.

- **Chronic disease score** (CDS) [von Korff et al, 1992]

  This is a measure of comorbidity obtained from a weighted sum of scores based on the use of 30 different classes of medication. An integer weight between 1 and 5 is given to each of the selected classes of medication; the overall score is then the sum of the weightings.

In the same way there is no study assessing whether a biological marker, either alone or combined to the clinical markers described before, represents a predictor of adverse outcomes in the elderly. The open question is whether a specific biological marker provides incremental prognostic value beyond existing other markers of risk.

In this context leucocyte telomere length represents a potential candidate to be studied. Telomere length has been considered in many cross-sectional studies as a biomarker of aging. However the association between shorter telomeres with lower survival at advanced ages remains a controversial issue. Most [Njajou et al, 2007; Cawthon et al, 2003; Bischoff et al, 2005] but not all studies [Bischoff et al, 2006; Martin-Ruiz et al, 2005] have shown a positive association between telomere length and overall survival in humans. Evidence accumulates

that telomere shortening reflects lifestyle and predicts remaining lifespan by a direct biological effect. More recent findings suggest that telomere length may not be a strong biomarker of survival in older individuals, but may be an informative biomarker of healthy aging [Njajou et al, 2009]. This association could reflect the impact of other health conditions than a direct biological effect. There is no longitudinal data examining the prognostic value of leukocyte telomere length in the context of other health variables such as comorbidity, functional, nutritional and cognitive status. This approach is original.

Telomeres are essential elements at the ends of chromosomes, made of non-coding repetitive DNA sequences (GGGTAA) and telomere binding proteins. This telomere structure protects against erosion of coding sequences and prevents illegal fusion with other chromosome ends. Due to the inherent mechanism of DNA replication, the ends of chromosomes remain single stranded and telomeres shorten gradually with each round of cell division by about 200 pairs of bases (bp). It is well established that *in vitro* cells undergo a limited number of cell divisions dictated by the length of telomeres. Critical shortening of telomeres leads to cell cycle arrest and cellular senescence, a phenomenon termed replicative senescence. Based on the theory of limited proliferative potential, the length of telomeres could be used as a marker for biological age of a specific tissue [Harley et al, 1990; Harley et al. 1992; DePinho, 2000; Gasser, 2000; von Zglinicki et al, 2000; Blackburn, 2001; Campisi et al, 2001; Chan and Blackburn, 2003].

A causal relationship between the reduction of replicative potential and the induction of cellular senescence with the shortening of telomeres has been established in vitro, and the diminishing of telomere length during aging has been demonstrated in vivo. Telomere shortening and loss has been associated with DNA damage. Oxidative stress generated throughout the lifetime of a cell can lead to DNA damage. Oxidative stress therefore is another major cause of telomere shortening [von Zglinicki et al, 2000]. Therefore the measurement of telomere length should not only reflect biological age but also the capacity of

stress management. The goal is to determine whether increased stress provokes an acceleration of telomere shortening and accelerated aging.

The telomere hypothesis of aging is based on the notion that telomeres shorten with each cell division and therefore with age. Consequently, short telomeres cause cell senescence, and senescent cells may contribute to aging. Thus, telomere shortening is currently thought to play an important role in cellular senescence in vivo and telomere length is therefore seen as a potential biomarker of aging. This leads us to the hypothesis of whether telomere shortening contributes also to the genesis of certain age-related diseases, such as dementia.

In addition, distinguishing accurately between different types of dementia, especially from degenerative and vascular origin is not always possible on purely clinical bases. The identification of biological markers would complement clinical approaches facilitating risk prediction, early and accurate diagnosis, and monitoring newly developed treatments [Papassotiropoulos and Hock, 2002].

Telomere length is also emerging as an important mechanism in vascular aging and, consequently, in the pathogenesis of hypertension, atherosclerosis, and heart failure [Allsopp et al, 1992; Vaziri et al, 1996; Aviv and Aviv 1997; Oexle et al, 1997; Davis and Kipling 2005; Jeanclos et al, 1998; Lindsey et al, 1991] and represents a potential biomarker to accurately separate cognitive impairment of vascular from degenerative origin. Another study suggests that telomere length may be an independent predictor of the risk of VaD [von Zglinicki et al, 2000].

No prospective studies investigating the relationship between telomere length as an independent predictor of the risk of dementia, AD or VaD, and/or the risk of conversion of MCI to dementia have been performed so far.

In this prospective study, clinical and biological complementary axes were conducted in the same population, and aimed to:

- Evaluate the relative contributions of accurate diagnosis of dementia, its aetiology and severity, in a population of very old, acutely ill patients discharged from a geriatric hospital, when taking into account comorbidity, functional, nutritional status and even a biomarker of aging like telomere length, to predict:

  - ✓ Adverse hospitalization outcomes: death in hospital, longer length of stay, higher rates of institutionalization and increase formal home care needs.

  - ✓ Adverse outcomes after discharge: 1-year risk of rehospitalization, institutionalization and death and long-term mortality after 5-years of follow-up

- Compare the performance, relevance and ability of six widely used comorbidity indices (comorbid Charlson index, cumulative illness rating scale (CIRS), index of coexistent diseases, Kaplan scale, geriatrics index of comorbidity (GIC) and chronic disease score (CDS) to predict the same adverse outcomes;

- Determine whether the proposed specific biological marker is important diagnostic marker of AD and to test it ability to discriminate AD from other dementias;

- Assess the risk of developing AD, the risk of MCI conversion and dementia progression based in leukocyte telomere threshold length and it predictor value;

- Investigate whether leukocyte telomere length, might be a co-risk factor associated with another previously known risk factor such as the ApoE polymorphism which is, actually, the best studied polymorphism associated with the risk of developing AD.

- Evaluate whether leukocyte telomere length is associated with 5-year survival beyond the impact of other risk factors of mortality like comorbidity, functional, nutritional and cognitive status.

PAPERS

PAPER 1

Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status

Dina Zekry, François R. Herrmann, Raphael Grandjean, Marie-Pierre Meynet, Jean-Pierre Michel, Gabriel Gold, Karl-Heinz Krause

Age and Ageing 2008;37:83-89

Previous studies reported that demented patients are healthier than other old people of the same age. Comparisons of the various subtypes have shown that patients with AD are the healthiest. However, these findings could be a consequence of inaccurate symptom reporting, delaying diagnosis, or may reflect a failure on the part of screening strategies to investigate thoroughly and to diagnose disease in these patients. This would suggest that demented patients may present more medical illnesses than generally thought, but that these diseases remain undetected. The studies investigating these issues were carried out retrospectively; cognitive assessment was based only on the MMSE and/or populations of community-dwelling subjects at least 10 years younger than patients from geriatric wards.

In this first study, we hypothesized and confirmed that elderly people with dementia may have more unrecognized illnesses than non-demented elderly people. In this prospective cohort of very old inpatients; including a systematic assessment of cognitive impairment; demented patients, non-demented patients and patients with MCI have similar levels of comorbidity. However, functional and nutritional status was poorer in the demented patients. Patients with vascular dementia had poorer health than other demented patients, with a higher average comorbidity score, more frequent hypertension, stroke and hyperlipidaemia. Comorbidity did not increase with dementia severity.

Age and Ageing 2008; **37:** 83–89
doi:10.1093/ageing/afm132
Published electronically 30 October 2007

Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status

Dina Zekry[1], François R. Herrmann[2], Raphael Grandjean[1], Marie-Pierre Meynet[1], Jean-Pierre Michel[1], Gabriel Gold[1], Karl-Heinz Krause[2]

[1]Geneva University, Rehabilitation and Geriatrics Department, 3, chemin du Pont-Bochet, CH-1226 Thônex, Switzerland
[2]Geneva University, Department of Pathology and Immunology, 1, rue Michel-Servet, CH-1211 Geneva 4, Switzerland

Address correspondence to: D. Zekry. Tel: (+41)223056355 Fax: (+41)2230561l5. Email: dina.zekry@hcuge.ch

Abstract

Background demented patients have been reported to be healthier than other old people of the same age.
Objectives to assess comorbid conditions, functional and nutritional status in medically ill hospitalised patients with normal cognition or affected by dementia of various causes and severities, or mild cognitive impairment (MCI).
Design and Setting a prospective study was carried out, between January and December 2004, in the Rehabilitation and Geriatric Hospital (HOGER).
Methods activities of daily living (ADL), instrumental activities of daily living (IADL) and mini nutritional assessment (MNA) scores were assessed as a function of the status of the patient two weeks before admission to hospital. On admission, cognitive status was assessed by a systematic battery of neuropsychological tests, comorbid conditions were assessed with the Charlson comorbidity index (CCI), and body mass index (BMI) and functional independence measure (FIM) were determined. BMI and FIM were also determined on discharge.
Results we studied 349 patients (mean age 85.2 ± 6.7; 76% women): 161 (46.1%) cognitively normal, 37 (10.6%) with MCI and 151 (43.3%) demented (61 Alzheimer's disease (AD), 62 mixed dementia (MD) and 17 vascular dementia (VaD)). ADL, IADL, FIM and MNA scores on admission decreased with cognitive status, regardless of the type of dementia. Functionality at discharge remained significantly lower in demented patients than in other patients. CCI was high and similar in all three groups (mean 4.6 ± 2.7). Patients with VaD had poorer health than other demented patients, with a higher average comorbidity score, more frequent hypertension, stroke and hyperlipidaemia. Comorbidity did not increase with severity levels of dementia.
Conclusions in this cohort of very old inpatients, demented patients, non-demented patients and patients with MCI had similar levels of comorbidity, but demented patients had a poorer functional and nutritional status.

Keywords: *comorbidity, dementia, Alzheimer's disease, aged, elderly*

Introduction

Demented patients have been reported to be healthier than other old people [1–5]. Comparisons of the various subtypes of dementia have shown that patients with Alzheimer's disease (AD) are the healthiest [2, 4, 6]. However, these findings could be a consequence of inaccurate symptom reporting, delaying diagnosis, or may reflect a failure on the part of screening strategies to investigate thoroughly and to diagnose disease in these patients [1, 7]. This would suggest that demented patients may present more medical illnesses than generally thought, but that these diseases remain undetected [5, 8]. A few series of autopsies have confirmed this hypothesis, showing that demented patients often have a number of comorbid conditions that are frequently underestimated by clinicians [9, 10]. The studies investigating these issues were carried out retrospectively [1–3, 5, 6, 11]; cognitive assessment was based only on the Mini Mental State Examination (MMSE) [1, 2, 8, 12] and/or populations of community-dwelling subjects at least 10 years younger than patients from geriatric wards [7, 8, 11]. We carried out a prospective study in the Geriatric Hospital (HOGER), including the systematic assessment of comorbid conditions and cognitive, functional and nutritional status. We compared these correlates in cognitively normal and demented patients.

Methods

Study population

A prospective study was carried out in the Geriatric Hospital (HOGER) of the Geneva University. Patients were recruited by clinically trained staff. The sampling frame consisted of consecutive admissions of patients over 75 years of age, on selected days during 2004. A random sample of patients was selected each day, using a computer-generated randomisation table. The exclusion criteria were disorders interfering with psychometric assessment, terminal illness and residence outside the canton of Geneva. The local ethics committees approved the study protocol, and signed written informed consent was obtained from all patients or their families or legal representatives. We checked that the study sample was representative of the hospital population as a whole, by comparing demographic data for the included sample with data for all admitted patients, and for those who refused to participate. We checked for selection bias based on cognitive screening for patients who refused to participate.

The study protocol included a planned 4-year follow-up period, with an annual visit carried out by the same geriatrician and nurse team.

Measures

Socio-demographic data and pre-morbid functional status.

The data recorded included age, sex, native language, education level, marital status, living conditions, alcohol and nicotine consumption. Basic and instrumental activities of daily living (IADL/ADL) [13, 14] were determined by the same nursing team on the admission day of the patient (please see Appendix 1 in the supplementary data on the journal website (http://www.ageing.oupjournals.org/)). The information regarding the previous 2 weeks was supplied by the patient when he was capable of answering and by an informal and/or formal caregiver.

Cognitive assessment

The same neuropsychologist assessed all subjects at least one week after patient inclusion. The following neuropsychological battery was applied: the MMSE [12] and the short cognitive evaluation [15, 16] (Appendix 2). The short version of the geriatric scale was used to screen for depression [17]. Based on this screening, a comprehensive standardised neuropsychological battery used in our routine clinical practice was carried out by the same neuropsychologist, with formal clinical criteria used to determine the aetiology and severity of clinical dementia (Appendix 3). Cerebral imaging was also carried out. Thereafter, patients were assigned to three groups: (i) cognitively normal, (ii) patients with mild cognitive impairment (MCI) [18] and (iii) patients with various types of dementia.

Comorbidity

The Charlson Comorbidity Index (CCI) was determined by extensive review of the patient's medical records for diagnoses established at/or before enrolment in this study [19], higher scores indicating greater comorbidity. The various classes of medication taken before admission were also listed.

Functionality

The functional independence measure (FIM) scores range from 18 (completely dependent) to 126 (completely independent) (Appendix 4) [20]. The FIM was determined in the first three days after admission and at discharge.

Nutritional assessment

Body mass index (BMI) was estimated (kg/m^2) on admission and at discharge. The short version of the mini nutritional assessment (MNA) (MNA-15, score ranging from 0 to 14, $\geq 12 =$ normal) was evaluated on admission of the patient [21]. The reference period for the MNA was 2 weeks before admission.

Statistical methods

We checked the normality of the data distribution with skewness and kurtosis tests, and carried out standard transformations to normalise non-Gaussian variables. Data for continuous variables are presented as means ± 1 standard deviation (SD).

Mann–Whitney U tests were used to compare data between groups: the studied sample versus all hospitalised patients, or the studied sample versus patients who refused to participate.

Analysis of variance (ANOVA) or Kruskal–Wallis tests were performed to compare data between the following groups: (i) the studied sample, patients refusing to participate and patients excluded from the study; (ii) cognitively normal patients, patients with MCI and demented patients; (iii) patients affected with dementia of various aetiologies. Statistical analyses were performed with Stata version 9.2.1 [22].

Results

Of the 459 patients randomised, 49 were not eligible (10.7%): 20 had major behavioural problems (psychotic, suicidal), nine were unable to communicate, eight were terminally ill, seven lived outside the canton of Geneva, and no family or legal representative could be contacted for five patients. Of the 410 patients who met the eligibility criteria, 61 (14.9%) refused to participate (the patient in 58 cases and the family in 3 cases). Our analysis was therefore based on a cohort of 349 patients.

No differences in demographic characteristics were found between the study sample and the entire population of patients admitted to the HOGER during 2004, or between the study sample and excluded patients or patients who

refused to participate (Table 1). Functionality scores were similar in the study cohort and in the patients who refused to participate. The functionality scores of both these groups were slightly higher than those for the entire population of patients admitted to the hospital, but were significantly lower for the excluded group.

In total, 151 of the 349 patients (43.3%) were diagnosed as demented and 37 (10.6%) were found to have MCI. Table 2 summarises the demographic and pre-admission characteristics of the patients, and assessment data on admission and discharge as a function of cognitive status. The groups compared were similar in age, sex, education level, smoking habits and alcohol intake. However, they differed in terms of living conditions, with non-demented patients more likely to live alone, and demented patients more likely to live in a nursing home ($P = 0.005$). Pre-morbid ADL and IADL scores, and FIM and MNA scores on admission decreased with cognitive status. At discharge, functionality scores remained lower for demented patients than for the other two groups. A similar trend was observed for BMI, which was lower at admission in demented patients, although this trend was not statistically significant at discharge. Patients with MCI had better scores than demented patients but worse scores than non-demented patients, except for FIM at discharge, which was highest for the MCI group. The number of different classes of medication taken was significantly higher in demented patients than in the other two groups, with non-demented and MCI patients taking similar numbers of drugs. CCI was similar in all three groups, with demented patients having levels of comorbidity similar to those for the non-demented and MCI groups. The CCI assesses several different diseases. For these diseases, demented patients were found to be significantly more likely than the patients in the other two groups to suffer from cerebrovascular disease and stroke. For diseases not assessed in the CCI, hypertension was found to be more prevalent in non-demented than in demented patients.

We determined the type of dementia for the 151 patients diagnosed as demented: 61 were classified as having AD, 17 as having vascular dementia (VaD), 62 as having mixed dementia (MD), and 11 as having other types of dementia (3 cases of dementia with Lewy bodies, two of Parkinson's disease with dementia, one case of Creutzfeld–Jacob disease, one case of cortico-basal dementia, one of fronto-temporal dementia, one of hydrocephaly with normal pressure, one case of glioblastoma and one case of cerebral metastasis). The 'other types of dementia' group was excluded from the analysis due to its heterogeneity and small size.

For most of the factors considered, no significant differences were found between patients with the various types of dementia (Table 3). Patients in the VaD group tended to be younger and to be taking larger numbers of different classes of medication. They were more likely to be male ($P = 0.002$) and had the highest average Charlson comorbidity score ($P = <0.0001$). The prevalence of hypertension, peripheral vascular disease, stroke, cerebrovascular disease and hyperlipidaemia ($P = 0.033$; 0.043; <0.0001; <0.0001; <0.0001, respectively) were higher in this group of patients, in which BMI was also higher on admission ($P = 0.026$). The prevalence of comorbid medical conditions did not differ significantly ($P = 0.173$) between patients with mild (mean 4.37 ± 2.4), moderate (mean 5.3 ± 3.0) and severe (mean 4.55 ± 2.1) dementia.

Discussion

This series of elderly inpatients (mean age of 85 years) was found to be representative of the overall population hospitalised in a geriatric ward. The prevalence of dementia (44%) was very high. The reported prevalence of dementia in elderly inpatients (geriatric acute wards) varies between 20 and 30%. A previous study in the same hospital 6 years ago reported a prevalence of 30%. This difference is statistically significant ($P = 0.000$) [24]. These findings probably reflect the systematic and complete assessment of cognitive impairment in the random sample used to determine dementia prevalence. The rate of refusal to participate in this study was very low (15%). The homogeneity

Table 1. Demographic data and clinical features of the patients included in this study, excluded patients and patients who refused to participate in the study. Demographic data and functionality scores for the included patients and for all patients admitted to the HOGER during 2004

	Study cohort	Excluded	Refused	All patients admitted	*P*-value[c]	*P*-value[b]
Number of patients	349	49	61	1,473		
Age[a]						
Total	85.2 ± 6.7	84.0 ± 8.7	85.5 ± 7.2	84.5 ± 7.1	0.075	0.413
Female	85.6 ± 6.4	85.6 ± 8.1	86.6 ± 5.7	85.0 ± 7.1	0.206	0.648
Male	84.1 ± 7.6	80.4 ± 5.1	82.5 ± 6.6	83.2 ± 7.1	0.265	0.276
Female[b]	265 (76)	34 (69)	44 (72)	1,071 (72)	0.221	0.542
Length of stay [days][a]	48.8(31) ± 53.1(38)	65.6 (41) ±74.4 (62)	40.1 (27) ±38.5 (39)	40.6 ± 39.4	0.482	0.152
FIM[a]	86.0(88) ± 26.1(41)	65.7 (64) ±26.3 (37)	86.1 (91) ±27.1 (42)	82.2 ± 27.6	0.006	0.000

[a] Data are expressed as means ± SD (median–IQR), [b] number of cases (%).

[b] *P*-value for Mann–Whitney U test comparing two groups (study cohort versus all patients admitted).

[c] *P*-value for Kruskal–Wallis test comparing three groups (study cohort versus excluded and refused patients).

FIM, Functional independence measure at admission.

Table 2. Socio-demographic data, clinical features, hospitalisation correlates and outcomes as a function of cognitive impairment diagnosis

Characteristics	Demented $n = 151$		MCI $n = 37$		Non-demented $n = 161$		p-value[c]
Demographics and pre-admission characteristics							
Age[a]	85.60	6.47	85.90	6.42	84.80	7.03	0.498
Female[b]	111	73.5%	33	89.2%	121	75.2%	0.129
Education (years)[b]							
Level 1	86	57.0%	24	66.7%	101	63.1%	0.568
Level 2	51	33.8%	8	22.2%	48	30.0%	
Level 3	14	9.3%	4	11.1%	11	6.9%	
Living conditions[b]							
Alone	74	49.7%	19	52.8%	104	65.0%	0.005
With family	12	8.1%	4	11.1%	10	6.3%	
With spouse	39	26.2%	7	19.4%	35	21.9%	
Nursing home	16	10.7%	1	2.8%	2	1.3%	
In protected housing	8	5.4%	5	13.9%	9	5.6%	
Cigarette smoking[b]	43	28.5%	15	40.5%	52	32.3%	0.352
Cigarette smoking[a] [packs/year]	18.37	21.97	16.65	25.69	18.97	25.35	0.977
Alcohol intake[b]	64	42.4%	12	32.4%	77	47.8%	0.210
Alcohol intake[a] [glasses/day]	1.23	1.12	1.38	1.54	1.78	2.75	0.950
Functional status[a]							
Pre-morbid ADL	4.43	1.34	5.06	1.12	5.23	0.90	<0.0001
Pre-morbid IADL	3.27	2.23	4.83	1.90	5.30	2.00	<0.0001
Number of different classes of medication[a]	2.58	1.30	2.19	1.02	2.20	1.15	0.009
Comorbid conditions							
CCI[a]	4.87	2.56	3.97	2.70	4.50	2.79	0.154
Diseases assessed in the CCI							
Ischaemic cardiopathy[b]	41	27.2%	13	35.1%	50	31.1%	0.568
Heart failure[b]	80	53.0%	24	64.9%	86	53.4%	0.403
Peripheral vascular disease[b]	53	35.1%	9	24.3%	67	41.6%	0.119
Cerebrovascular disease[b]	73	48.3%	7	18.9%	39	24.2%	0.000
Chronic pulmonary disease[b]	25	16.6%	8	21.6%	36	22.4%	0.418
Connective tissue disease[b]	15	9.9%	4	10.8%	21	13.0%	0.684
Ulcer disease[b]	23	15.2%	9	24.3%	35	21.7%	0.243
Diabetes mellitus[b]	29	19.2%	6	16.2%	35	21.7%	0.707
Chronic renal failure[b]	48	31.8%	10	27.0%	59	36.7%	0.447
Diabetes (end organ damage)[b]	6	4.0%	3	8.1%	10	6.2%	0.515
Any tumour[b]	44	29.1%	13	35.1%	53	32.9%	0.682
Cirrhosis[b]	5	3.3%	1	2.7%	6	3.7%	0.947
Other diseases not assessed in the CCI							
Hypertension[b]	101	66.9%	19	51.4%	117	72.7%	0.041
Atrial fibrillation[b]	40	26.5%	10	27.0%	37	23.0%	0.737
Stroke	33	21.9%	4	10.8%	20	12.4%	0.050
Hypercholesterolaemia[b]	24	15.9%	6	16.2%	26	16.2%	0.998
Assessment at admission							
FIM[a]	77.32	25.89	86.69	24.72	93.48	24.98	0.000
BMI[a]	23.30	4.81	24.12	5.07	24.76	5.10	0.026
MNA[a]	8.51	2.85	8.89	3.09	9.70	2.86	0.001
Assessment at discharge							
FIM[a]	84.87	27.88	107.40	16.62	99.56	28.81	<0.0001
BMI[a]	22.83	5.04	24.13	4.91	24.06	5.38	0.069

[a] Data are expressed as means ± SD.

[b] Number of cases (%).

[c] P-value of Kruskal–Wallis test or ANOVA comparing three groups.

Education level: (level 1 = ≤ 11; level 2 = 12–14; level 3 ≥15 years of schooling). ADL = Activities of Daily Living [14], IADL, Lawton's Instrumental Activities of Daily Living [15]; CCI, The Charlson Comorbidity Index [19]; FIM, Functional independence measure [20]; BMI, body mass index; MNA, Mini Nutritional Assessment [21].

Table 3. Socio-demographic data, clinical features, hospitalisation correlates and outcomes as a function of dementia aetiology (11 cases with other types of dementia are not shown)

Characteristics	Alzheimer's disease $n = 61$		Mixed dementia $n = 62$		Vascular dementia $n = 17$		P-value[c]
Demographics and pre-admission characteristics							
Age[a]	86.1	6.0	86.4	5.4	84.3	7.5	0.452
Female[b]	51	83.6%	45	72.6%	7	41.2%	0.002
Education (years)[b]							
Level 1	39	63.9%	32	51.6%	10	58.8%	0.435
Level 2	15	24.6%	25	40.3%	6	35.3%	
Level 3	7	11.5%	5	8.1%	1	5.9%	
Living conditions[b]							
Alone	33	54.1%	32	52.5%	6	37.5%	0.888
With family	3	4.9%	6	9.8%	1	6.3%	
With spouse	15	24.6%	14	23.0%	6	37.5%	
Nursing home	6	9.8%	7	11.5%	2	12.5%	
In protected housing	4	6.6%	2	3.3%	1	6.3%	
Cigarette smoking[b]	17	27.9%	19	30.7%	7	41.2%	0.575
Cigarette smoking[a] [packs/year]	17.77	21.27	20.09	24.36	23.36	18.96	0.554
Alcohol intake[b]	27	44.3%	30	48.4%	4	23.5%	0.185
Alcohol intake[a] [glasses/day]	1.16	1.03	1.53	1.25	1.00	1.00	0.337
Functional status[a]							
Pre-morbid ADL	4.70	1.26	4.47	1.20	4.00	1.62	0.218
Pre-morbid IADL	3.66	2.30	3.29	2.17	2.53	2.27	0.195
MMSE[a]	16.3	4.7	15.6	4.9	17.5	6.7	0.3656
CDR 0.5[b]	1	1.6%	1	1.6%	1	5.9%	0.612
CDR 1[b]	27	44.3%	25	40.3%	9	52.9%	
CDR 2[b]	26	42.6%	28	45.2%	4	23.5%	
CDR 3[b]	7	11.5%	8	12.9%	3	17.7%	
Number of different classes of medication[a]	2.28	1.27	2.73	1.24	3.00	1.17	0.067
Comorbid conditions							
CCI[a]	4.18	2.49	5.11	2.33	6.35	2.55	<0.0001
Diseases assessed in the CCI							
Ischaemic cardiopathy[b]	14	23.0%	20	32.3%	7	41.2%	0.272
Heart failure[b]	28	45.9%	37	59.7%	12	70.6%	0.119
Peripheral vascular disease[b]	20	32.8%	21	33.9%	11	64.7%	0.043
Cerebrovascular disease[b]	14	23.0%	36	58.1%	16	94.1%	<0.0001
Chronic pulmonary disease[b]	10	16.4%	9	14.5%	5	29.4%	0.345
Connective tissue disease[b]	10	16.4%	5	8.1%	0	0.0%	0.103
Ulcer disease[b]	10	16.4%	12	19.4%	1	5.9%	0.414
Diabetes mellitus[b]	8	13.1%	13	21.0%	4	23.5%	0.424
Chronic renal failure[b]	8	13.1%	13	21.0%	4	23.5%	0.424
Diabetes (end organ damage)[b]	3	4.9%	1	1.6%	1	5.9%	0.529
Any tumour[b]	16	26.2%	21	33.9%	3	17.8%	0.366
Cirrhosis[b]	2	3.3%	2	3.2%	0	0.0%	0.752
Other diseases not assessed in the CCI							
Hypertension[b]	37	60.7%	41	66.1%	16	94.1%	0.033
Atrial fibrillation[b]	12	19.7%	21	33.9%	4	23.5%	0.195
Stroke[b]	4	6.6%	16	25.8%	11	64.7%	<0.0001
Hypercholesterolaemia[b]	5	8.2%	8	12.9%	9	52.9%	<0.0001
Assessment at admission							
FIM[a]	78.83	25.51	76.24	26.20	78.13	27.11	0.887
BMI[a]	23.24	4.40	22.50	4.62	26.05	6.15	0.026
MNA[a]	8.64	2.42	8.29	3.14	9.06	3.43	0.521
Assessment at discharge							
FIM[a]	89.56	24.19	80.34	31.02	88.60	22.66	0.498
BMI[a]	22.17	5.30	22.66	4.46	25.81	6.05	0.081

[a]Data are expressed as means ± SD.
[b]Number of cases (%).
[c]P-value for Kruskal–Wallis test, or ANOVA, comparing three groups.
ADL, Activities of Daily Living [14], IADL, Lawton's Instrumental Activities of Daily Living [15],
MMSE, The Mini Mental State Examination (scores 0–30) [12]; CDR, The Clinical Dementia Rating Scale [23]
(score 0.5 for MCI, score 1 for mild, score 2 for moderate and score 3 for severe dementia); CCI, The Charlson Comorbidity Index [19];
FIM, Functional independence measure [20]; BMI, body mass index; MNA, Mini Nutritional Assessment [21].

of the group of patients studied and the group consisting of all the patients admitted to the HOGER in the same year shows that our sample was representative of the total population of patients admitted and highlights the quality of randomisation in this study. The principal strength of this study is its clinically rich prospective data collection from a large group of very ill hospitalised elderly patients. The comorbidity index was much higher (mean 4.6 ± 2.7) than reported in other studies [7, 11]. The second major strength of this study is that the same neuropsychologist carried out a systematic, complete neuropsychological assessment of all the included patients, increasing the accuracy of cognitive diagnosis. This is the first study of its type to consider a group of patients with MCI in addition to demented and non-demented patients.

In line with increasing numbers of reports, the functional and nutritional status of demented patients was significantly worse than that of the other patients at both admission and discharge, regardless of the type of dementia. In a cohort of 830 Italian patients aged 65 years or older consecutively admitted to an acute care geriatric ward, and in a cohort of 1,358 Japanese subjects aged 61 years or older living in the community, poor cognitive status was independently associated with functional disability at all ages [25, 26].

In our series, the prevalence of comorbid medical conditions was similar in demented patients, patients with MCI and patients of the same age with no cognitive impairment, but demented patients took larger amounts of medication. Some studies have reported the occurrence of larger numbers of comorbid medical conditions in cognitively normal old subjects [1–5]. One study of elderly subjects living in their own homes showed that patients with AD had fewer medical diagnoses—three in this cohort—than subjects without cognitive impairment [1]. Similar results were obtained in a French geriatric hospital that also showed, in contrast to our results, that patients with dementia took fewer drugs than non-demented subjects, and that they took different kinds of drugs, with more psychotropes and fewer cardiovascular drugs than non-demented patients [2]. Most of these studies were retrospective [1, 2, 4]. More recent population-based prospective studies have shown, as in this study, that missed diagnoses are more common in patients with dementia and that these patients complain almost exclusively of cognitive impairment. One such study showed that 66% of the 112 demented patients included had at least one undiagnosed disease, versus only 48% of the non-demented patients [8]. The demented patients were more likely than the controls to have undiagnosed hyperlipidaemia or hypothyroidism. In another study of patients in the early stages of AD, identical CCI values were obtained for demented and non-demented subjects but, over the two years of follow-up, patients with dementia complained almost exclusively of cognitive impairment whereas the controls also complained of joint pains, gastrointestinal problems and vision loss [7]. A large retrospective study of 3,934 patients with dementia and 19,300 control subjects matched for sex and age enrolled in a large Medicare-managed care organisation showed that demented patients had significantly larger numbers of comorbid conditions (mean CCI = 1.9) than patients without dementia (mean CCI = 1.0). For congestive heart failure and cerebrovascular disease, major differences have been reported [11]. This cohort was younger (mean age = 78 years) and the percentage of women (60%) was much closer to that of men.

According to the most recent studies, the number of comorbid conditions seems to be similar in demented and non-demented subjects, but some studies have shown differences in the prevalence of particular diseases. For example, cancer has been reported to be more prevalent in non-demented subjects than in demented subjects in clinical and autopsy series [1, 2, 27, 28].

There may also be differences in the prevalence of co-existing medical conditions between the various types of dementia and between different levels of severity of dementia. We found that health was poorest in the VaD group: highest average comorbidity score, higher frequency of hypertension, peripheral vascular disease, stroke, cerebrovascular disease, hyperlipidaemia and a higher BMI on admission, probably associated with these patients being overweight. These findings are consistent with previous studies [2, 6, 29]. In contrast, Doraiswamy *et al.* showed in a cross-sectional study including 679 AD patients from the community and nursing homes that medical comorbidity increased with severity of dementia [30]. However, most of the patients with mild dementia were living at home, whereas those with severe dementia were up to 10 years older and lived in nursing homes.

Our results show that hospitalised demented patients have a poorer functional and nutritional status than cognitively normal patients of the same age. They also seem to have more other illnesses than generally thought, but these illnesses are more likely to remain undiagnosed and thus untreated. Special efforts should be made to investigate existing comorbidities and to detect unreported problems in demented patients, with the development of screening strategies for detecting comorbid conditions in demented patients. Improving the detection and treatment of comorbid diseases represents a challenge for health professionals caring for patients with dementia. Greater attention to these complex issues on the part of families, carers and clinicians should improve outcomes for these patients.

Key points

- In this prospective cohort of very old inpatients, demented patients, non-demented patients and patients with MCI had similar levels of comorbidity. However, demented patients had poorer functional and nutritional status. Health was poorest in patients with VaD.

- Special efforts should be made to deal with existing comorbidities and to detect unreported problems in demented patients. Improvements in the detection and treatment of comorbid diseases should improve outcomes for these patients.

Acknowledgements

There are no conflicts of interest.

We would like to thank Mrs. O. Baumer, L Humblot and M Cos and their teams for technical assistance. This work was supported by grant 3200B0-102069 from the Swiss National Foundation.

Supplementary data

Supplementary data for this article is available online at http://ageing.oxfordjournals.org.

References

1. Wolf-Klein GP, Siverstone FA, Brod MS *et al*. Are Alzheimer patients healthier? J Am Geriatr Soc 1988; 36: 219–24.
2. Holstein J, Chatellier G, Piette F *et al*. Prevalence of associated diseases in different types of dementia among elderly institutionalized patients: analysis of 3447 records. J Am Geriatr Soc 1994; 42: 972–7.
3. Landi F, Onder G, Cattel C *et al*.. Functional status and clinical correlates in cognitively impaired community-living older people. J Geriatr Psychiatry Neurol 2001; 14: 21–7.
4. Sanderson M, Wang J, Davis DR *et al*.. Co-morbidity associated with dementia. Am J Alzheimers Dis Other Demen 2002; 17: 73–8.
5. Landi F, Gambassi G, Lapane KL *et al*. Comorbidity and drug use in cognitively impaired elderly living in long-term care. Dement Geriatr Cogn Disord 1998; 9: 347–56.
6. Landi F, Gambassi G, Lapane KL *et al*. Impact of the type and severity of dementia on hospitalization and survival of the elderly. The SAGE Study Group. Dement Geriatr Cogn Disord 1999; 10: 121–9.
7. McCormick WC, Kukull WA, van Belle G *et al*. Symptom patterns and comorbidity in the early stages of Alzheimer's disease. J Am Geriatr Soc 1994; 42: 517–21.
8. Lopponen MK, Isoaho RE, Raiha IJ *et al*. Undiagnosed diseases in patients with dementia-a potential target group for intervention. Dement Geriatr Cogn Disord 2004; 18: 321–9.
9. Kammoun S, Gold G, Bouras C *et al*. Immediate causes of death of demented and non-demented elderly. Acta Neurol Scand 2000; 176: 96–9.
10. Fu C, Chute DJ, Farag ES *et al*. Comorbidity in dementia an autopsy study. Arch Pathol Lab Med 2004; 128: 32–8.
11. Hill JW, Futterman R, Duttagupta S *et al*. Alzheimer's disease and related dementias increase costs of comorbidities in managed Medicare. Neurology 2002; 58: 62–70.
12. Folstein MF, Folstein SE, MacHugh PR. Mini Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.
13. Katz S, Ford AB, Moskowitz RW *et al*. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. JAMA 1963; 185: 914–9.
14. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9: 179–86.
15. Salomon PR, Hirschoff A, Kelly B *et al*. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998; 55: 349–55.
16. Robert PH, Schuck S, Dubois B *et al*. Screening for Alzheimer's Disease with the short cognitive evaluation battery. Dement Geriatr Cogn Disord 2003; 15: 92–8.
17. van Marwijk HW, Wallace P, de Bock GH *et al*. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. Br J Gen Pract 1995; 45: 195–9.
18. Petersen RC, Smith GE, Waring SC *et al*. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56: 303–8.
19. Charlson ME, Pompei P, Ales KL *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–83.
20. Keith RA, Granger CV, Hamilton BB *et al*. The functional independence measure: a new tool for rehabilitation. Adv Clin Rehabil 1987; 1: 6–18.
21. Rubenstein LZ, Harker JO, Salva A *et al*. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001; 56: 366–72.
22. Stata Statistical Software version 9.2 [program]. College Station, Texas: Stata Corporation 2005.
23. Morris JC. The clinical dementia rating Current version and scoring rules. Neurology 1993; 43: 2412–4.
24. Herrmann F, Mermod J-J, Henderson S, Michel J. Epidemiology of dementia in Geneva. In: Michel J-P, Hof PR, eds. Management of Aging, The University of Geneva Experience. Basel: Karger, 1999; 94–100.
25. Marengoni A, Aguero-Torres H, Cossi S *et al*. Poor mental and physical health differentially contributes to disability in hospitalized geriatric patients of different ages. Int J Geriatr Psychiatry 2004; 19: 27–34.
26. Sauvaget C, Yamada M, Fujiwara S *et al*. Dementia as a predictor of functional disability: a four-year follow-up study. Gerontology 2002; 48: 226–33.
27. Tirumalasetti F, Han L, Birkett DP. The relationship between cancer and Alzheimer's disease. J Am Geriatr Soc 1991; 39: 840.
28. Desouky LA. The relationship between cancer and Alzheimer's disease. J Am Geriatr Soc 1992; 40: 1075.
29. Eaker ED, Mickel SF, Chyou PH *et al*. Alzheimer's disease or other dementia and medical care utilization. Ann Epidemiol 2002; 12: 39–45.
30. Doraiswamy PM, Leon J, Cummings JL *et al*. Prevalence and impact of medical comorbidity in Alzheimer's disease. J Gerontol A Biol Sci Med Sci 2002; 57: M173–7.

Received 19 September 2006; accepted in revised form 26 July 2007

PAPER 2

Geriatrics index of comorbidity was the most accurate predictor of death in geriatric hospital among six comorbidity scores

Dina Zekry, Bernardo Hermont Loures Valle, Claudia Lardi, Christophe Graf, Jean-Pierre Michel, Gabriel Gold, Karl-Heinz Krause, François R. Herrmann

Journal of Clinical Epidemiology 2010;63:1036-1044

Our main research question of this prospective clinical study was: “How cognitive, functional and nutritional status, and comorbidities; in a population of very old patients hospitalized in acute care, influence the adverse outcomes after discharge?" However, first of all, in this second article, we asked the question: “Which comorbidity score to use?”

Older patients often suffer from multiple comorbid conditions. However, few comorbidity indices are valid and reliable in the elderly and were rarely compared. In addition, previous studies have used only one comorbidity score and have mostly been retrospective. For these reasons, in a first step, we compared the performance, relevance and ability of six widely used comorbidity indices (comorbid Charlson index, cumulative illness rating scale (CIRS), index of coexistent diseases (ICED), Kaplan scale, geriatrics index of comorbidity (GIC) and chronic disease score (CDS) to predict the studied adverse outcomes. As a result, based in our own data it was possible to make the choice of the best comorbidity index as a clinical marker of adverse outcomes risk.

Firstly, we studied short-term hospitalization adverse outcomes: death in hospital, longer length of stay; and higher rates of institutionalization and increase formal home care needs after discharge. In univariate analyses, GIC was the best predictor for all outcomes. The risk of death was 30 times higher; the risk of prolonged hospitalization and being institutionalized was eight to nine times higher in patients with scores of class 3 or 4. In adjusted logistic regression models, GIC remained the best predictor of death during hospitalization; however, the CIRS performed better than the other indices in predicting a prolonged hospital stay and institutionalization.

ELSEVIER

Journal of Clinical Epidemiology 63 (2010) 1036−1044

Journal of Clinical Epidemiology

Geriatrics index of comorbidity was the most accurate predictor of death in geriatric hospital among six comorbidity scores

Dina Zekry[a,*], Bernardo Hermont Loures Valle[b], Claudia Lardi[a], Christoph Graf[a], Jean-Pierre Michel[a], Gabriel Gold[a], Karl-Heinz Krause[c], François R. Herrmann[a]

[a]*Rehabilitation and Geriatrics Department, Geneva University, 3, chemin du Pont-Bochet, 1226, Thônex, Switzerland*
[b]*Clementino Fraga Filho Hospital, Rio de Janeiro Federal University, Rio de Janeiro, Brazil*
[c]*Pathology and Immunology Department, Geneva University, Geneva, Switzerland*

Accepted 18 November 2009

Abstract

Objectives: To compare the abilities of six validated comorbidity indices (Charlson index, cumulative illness rating scale [CIRS], index of coexistent diseases, Kaplan scale, geriatrics index of comorbidity [GIC], and chronic disease score) to predict adverse hospitalization outcomes (death during hospitalization, length of stay, and institutionalization).

Study Design and Setting: Prospective cohort of 444 elderly inpatients (mean age 85.3) was randomly selected from Geneva geriatric hospital.

Results: In univariate analyses, GIC was the best predictor for all outcomes. The risk of death was 30 times higher and the risk of prolonged hospitalization and being institutionalized was eight to nine times higher in patients with scores of class 3 or 4. In adjusted logistic regression models, GIC remained the best predictor of death during hospitalization. Higher GIC scores accounted for 25% of the variance of this outcome, with mortality rates differing by a factor of four between the highest and the lowest scores. CIRS was a strong predictor of a prolonged hospital stay and institutionalization, accounting for 10% of the variance of these outcomes.

Conclusion: GIC was the most accurate predictor of death during hospitalization. CIRS could be used to select elderly patients at admission as an indicator of improvement at discharge.

Keywords: Comorbidity scores; Aged; Elderly; Death; Length of stay; Institutionalization

1. Introduction

Elderly patients often suffer from multiple chronic conditions that individually and jointly affect their quality of life, use of health services, morbidity, and mortality [1]. Several indices have been proposed to quantify comorbidity in adults. However, only some of them are valid and reliable for use as a measure of comorbidity in applied clinical research [2] or in elderly patients [3,4]: (1) The Charlson comorbidity index (CCI) is the most extensively studied comorbidity index (CI) for predicting mortality. It is a weighted index that takes into account the number and severity of comorbid conditions [5]. This index was created to enhance the prediction of 1-year mortality in a cohort of medical young patients, but it has been used to predict other health outcomes, such as functional status. It gives a highest weight for conditions that are not frequent (i.e., AIDS) in the elderly; and for other conditions, so frequent in elderly patients (i.e., dementia) the weight is lower, (2) the cumulative illness rating scale (CIRS) addresses all relevant physiological systems rather than being based on specific diagnoses and consists of two parts: the CI and the severity index [6]. The advantage of this scale built for geriatrics patients is that it assesses the severity of diseases according to their impact of disability, (3) The index of coexisting disease (ICED) was developed to predict in-hospital postoperative complications and 1-year health-related quality of life of patients who underwent total hip replacement surgery. This index has a 2-dimensional structure, measuring disease severity and disability, which can be useful when considering mortality and disability as the outcomes of interest [7]. A major limitation of the ICED is that it requires medical records and highly trained reviewers who must follow complex decision rules in creating the index, (4) The Kaplan index was developed specifically for use in diabetes research [8], (5) the geriatrics index of comorbidity (GIC) takes into account the number and severity of diseases,

No author received any consultancy fees or has any company holdings or patents. There are no conflicts of interest.

* Corresponding author. Tel.: +41-22-3056355; fax: +41-22-3056115.
E-mail address: dina.zekry@hcuge.ch (D. Zekry).

0895-4356/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi: 10.1016/j.jclinepi.2009.11.013

but although it was built for geriatric patients, it has the peculiarity of not including disability [9], and (6) the chronic disease score (CDS) is an alternative CI based on the drugs taken by the patient rather than clinical diagnoses [10].

These tools were initially validated in institutionalized elderly patients in a retrospective manner. A previous study examined the prognostic value of the CCI in predicting a 3-year mortality and functional decline in patients receiving long-term care from 88 residential care facilities in Quebec, Canada (291 dependent elderly adults with a mean age of 83.3 years). The CCI performed well in predicting both outcomes [11]. The CIRS is significantly associated with mortality, acute hospitalization, medication usage, laboratory test results, and functional disability among frail elderly institutionalized patients [6]. Recently, Di Bari et al. [12] showed that these measures of comorbidity (CCI, ICED, GIC, and CDS) predicted death and disability in basic activities of daily life in 688 Italian community dwellers with a mean age of 74 years. However, the value, relevance, and pertinence of these CIs as predictors of hospitalization adverse outcomes in the very elderly remain unknown.

In this prospective study, we compared the performance of these six validated and widely used CIs in predicting adverse hospitalization outcomes in the elderly, including death during the hospitalization period, a prolonged hospital stay, and institutionalization. The study population was derived from a study cohort of very elderly, acutely ill geriatric inpatients.

2. Methods

2.1. Patients and data collection

We carried out a prospective study in a 300-bed geriatric hospital (HOGER) of the University Hospitals of Geneva, Switzerland, for acute illness. Patients and data collection have been described elsewhere [13]. Briefly, patients were recruited by clinically trained staff. All patients older than 75 years and consecutively admitted on selected days between January 2004 and December 2005 were included. We selected a random sample of patients for each day, using a computer-generated randomization table. The local ethics committee approved the protocol, and the patients or their families or legal representatives gave signed written informed consent. Demographic data for the patients studied did not significantly differ from data for all patients admitted to the HOGER during 2004−2005. Our sample was therefore representative of all patients admitted to this hospital, demonstrating the reliability of the randomization procedure used in this study.

Medical history was recorded on a standardized form and the same geriatrician carried out physical examinations on all patients. Annual follow-up over a 4-year period, with the same assessment carried out each year, was planned in the study protocol.

2.2. Sociodemographic data

The data recorded included age, sex, native language, marital status, living arrangement, and educational level.

2.3. Cognitive diagnosis

The same neuropsychologist assessed all subjects for clinical dementia, at least 1 week after admission, to avoid the effects of concomitant delirium. The mini-mental state examination scores (0−30) [14] and the short cognitive evaluation battery [15,16] were used. Based on screening results, the same neuropsychologist then carried out a comprehensive standardized neuropsychological assessment to determine the etiology and severity of clinical dementia, as previously described [13].

2.4. Assessment of comorbidity

The same geriatrician calculated all six scores for each patient by extensive review of the patient's medical records and administrative data for diagnoses established at or before enrollment in this study.

1. Charlson comorbidity index [5]

   The CCI is a list of 19 conditions; each is assigned a weighting (1−6). Weightings reflect the ability of each condition to predict 1-year mortality, as originally reported for cancer patients. They are fixed for each diagnosis and range from 1 (for conditions, such as myocardial infarction or mild liver disease, with a relative risk $\geq$1.2 and $<$1.5) to 6 (assigned to metastatic cancer, with a relative risk $\geq$6). The CCI is the sum of the weightings for all conditions observed in a patient—higher scores indicated greater comorbidity.

2. Cumulative illness rating scale [6]

   The CIRS identifies 14 items, corresponding to different systems. Each system is scored as follows: 1 (none)—no impairment to that organ or system; 2 (mild)—impairment does not interfere with normal activity, treatment may or may not be required, prognosis is excellent; 3 (moderate)—impairment interferes with normal activity, treatment is needed, prognosis is good; 4 (severe)—impairment is disabling, treatment is urgently needed, prognosis is guarded; 5 (extremely severe)—impairment is life threatening, treatment is urgent or of no avail, poor prognosis. The illness severity index (summary score based on the average of all CIRS items, excluding psychiatric or behavioral factors) and the CI (summary score based on a count of organ system with moderate or greater impairment, excluding psychiatric or behavioral factors) can then be calculated using these scores.

3. Index of coexistent diseases [7]

   The ICED is based on the presence and severity of 19 medical conditions and 11 physical impairments, using two scales: the index of disease severity (IDS) and the index of physical impairment (IPI). The final ICED score is determined by an algorithm combining the peak scores for the IDS and IPI. The ICED score ranges from zero to three (four classes), reflecting increasing severity.

4. Kaplan scale [8]

   This index uses two forms of classification: focusing on the type of comorbidity and the pathophysiologic severity of the comorbid conditions present, respectively. The type of comorbidity can be classified as vascular (hypertension, cardiac disorders, peripheral vascular disease, retinopathy, and cerebrovascular disease) or nonvascular (lung, liver, bone, and nondiabetic renal diseases). Pathophysiologic severity is rated on a 4-point scale, ranging from zero (comorbidity is absent or easy to control) to three (recent full decompensation of comorbid disease). The rating of the most severe condition determines the overall comorbidity score. Scores for vascular and nonvascular comorbidity can be calculated, based on the most severe condition in each subscale.

5. Geriatric index of comorbidity [9]

   In computing the GIC, each of the 15 more prevalent clinical conditions (ischemic or organic heart diseases, primary arrhythmias, heart diseases with a nonischemic or nonorganic origin, hypertension, stroke, peripheral vascular diseases, diabetes mellitus, anemia, gastrointestinal diseases, hepatobiliary diseases, renal diseases, respiratory diseases, parkinsonism and nonvascular neurologic diseases, musculoskeletal disorders, and malignancies) is graded on a 0–4 disease severity scale on the basis of the following general framework: 0 = absence of disease, 1 = asymptomatic disease, 2 = symptomatic disease requiring medication but under satisfactory control, 3 = symptomatic disease uncontrolled by therapy, and 4 = life-threatening or the most severe form of the disease. The GIC classifies patients into four classes of increasing somatic comorbidity. Class 1 includes patients who have one or more conditions with a disease severity grade equal to or lower than 1. Class 2 includes patients who have one or more conditions with a disease severity grade of 2. Class 3 includes patients who have one condition with a disease severity of 3, other conditions having a disease severity equal to or lower than 2. Class 4 includes patients who have two or more conditions with a disease severity of 3 or one or more conditions with disease severity of 4.

6. Chronic disease score [10]

   This is a measure of comorbidity obtained from a weighted sum of scores based on the use of 30 different classes of medication. An integer weight between one and five is given to each of the selected classes of medication; the overall score is then the sum of the weightings.

2.5. Adverse outcomes of hospitalization

The adverse outcomes considered include hospital stays greater than the median value, death during the hospitalization period, and changes in living arrangements at discharge (institutionalization).

2.6. Statistical methods

We checked for the normal distribution of data for continuous scores (CCI, CIRS, Kaplan scale, and CDS) using skewness and kurtosis tests and carried out standard transformations to normalize non-Gaussian variables. As it was not possible to normalize these scores, they were categorized into quartiles to facilitate comparison with the four classes of the other two indices, ICED and GIC. Colinearity among the six indices was checked using Spearman rank correlation coefficient. Multiple logistic regression analysis was then carried out using age, sex, and the six comorbidity scores as independent variables and each outcome as dependent variable to identify the best predicting score for each outcome, whereas adjusting for all the others. Outcomes were considered as dichotomous data (death during hospitalization, a prolonged hospital stay [longer than the median duration], admission to long-term care). Odds ratios and 95% confidence intervals were calculated. Statistical analyses were performed with Stata software version 10.1 (StataCorp LP, College Station, TX, USA).

3. Results

We included 444 patients in this study (mean age 85.3 ± 6.7, 74% women). Table 1 summarizes frequency distribution of patients according to each comorbidity score.

As there were no patients in the ICED classes 1 and 2, we considered only classes 3 and 4, providing binary data for the analyses. Likewise, only 2% of the patients were classified as class 1 by the GIC, allowing us to combine classes 1 and 2 for the analysis.

For the other four indices, the distribution was almost equal among the four quartile ranges, with approximately 25% of the patients per range.

Table 2 shows the patient's destination after hospitalization, comparing living arrangement before and after.

3.1. Univariate and multiple logistic regression analysis

Spearman rho values among the six indices ranged between 0.038 and 0.548, which does not meet the criteria for

Table 1
Quartile range and frequency of six comorbidity scores

	CCI		CIRS		ICED[a]	Kaplan		GIC[a]	CDS	
Level/classes[a]	Quartile range score	*N* (%)	Quartile range score	*N* (%)	*N* (%)	Quartile range score	*N* (%)	*N* (%)	Quartile range score	*N* (%)
1	0−3	165 (37)	0−11	121 (27)	0	0−2	128 (29)	9 (2)	0−3	122 (28)
2	4	91 (20)	12−14	107 (24)	0	3−4	156 (35)	34 (8)	4−6	117 (26)
3	5−6	91 (20)	15−18	119 (27)	93 (21)	5	55 (12)	310 (70)	7−8	109 (24)
4	7−14	97 (23)	19−30	97 (22)	351 (79)	6−16	105 (24)	91 (20)	9−15	96 (22)

Data are expressed as number of cases (%).

Abbreviations: CCI, Charlson comorbid index; CIRS, cumulative illness rating scale; ICED, index of coexistent diseases; Kaplan, Kaplan scale; GIC, geriatrics index of comorbidity; CDS, chronic disease score.

[a] Quartile ranges do not apply to ICED and GIC, because continuous scores were not calculated using these tools and patients were assigned directly to four classes.

colinearity usually set at >0.900. We carried out univariate logistic regression analyses including age, sex, and the six CIs tested predicting the three adverse hospitalization outcomes (Table 3). We then tested full multiple logistic regression models containing all the variables. No new differences were observed; thus, results are presented only with variables that were positive in the univariate models.

3.1.1. Length of stay (median = 32 days)

In univariate analysis, age, quartiles or class 3 or 4 scores were found to be independent predictors of prolonged hospitalization. GIC class 4 scores were the strongest predictors of a prolonged stay in hospital, with a difference of a factor of nine in adverse outcome rate between patients with the highest and lowest scores.

This association was not observed when all variables were introduced into the analysis, with only the third and fourth quartiles of CIRS scores remaining statistically significant and accounting for 10% of the variability of this outcome. Higher classes of the ICED also remained weakly significant, with $P = 0.045$.

3.1.2. Death during hospitalization

Of the 444 patients, 27 died during the hospitalization period (6%). In univariate analysis, mortality was significantly associated with age (not with sex) and with the highest score of the CCI, CIRS, ICED, Kaplan scale, and GIC but not with the CDS. GIC class 4 scores were the strongest predictors of death during hospitalization, with a difference of a factor of 37 in adverse outcome rates between patients with the highest and lowest scores.

When all variables were included in the model, only the GIC classes 3 and 4 remained statistically significant. Higher GIC comorbidity scores accounted for 24% of the variance of this outcome. Higher classes of the ICED score also remained weakly significant, with $P = 0.045$.

3.1.3. Institutionalization

Table 2 summarizes the destinations of patients after hospitalization. Sixty-one (14.3%) patients were institutionalized and 10% of the initial cohort was transferred to another hospital (surgery, intensive care).

Univariate analysis revealed that institutionalization was significantly associated with the highest score of the CIRS, ICED, Kaplan scale, and the GIC but not with the CCI or CDS. GIC class 4 and CIRS fourth quartile scores were the strongest predictors of this outcome, with the rate of institutionalization differing by factors of nine and five, respectively, between patients with the highest and lowest scores.

When all variables were included in the model, only the CIRS classes 3 and 4 remained statistically significant. Higher CIRS comorbidity scores accounted for 10% of the variance of this outcome.

3.1.4. Summary of results

Of the six indices, the GIC explained the largest percentage of variation in the frequency of these three outcomes in

Table 2
Destination after hospitalization ($n = 444$)

Living arrangements		After hospitalization						
Before hospitalization	Total *N* (%)	Alone	Partner	Family	Protected residence	Nursing home	Died in hospital	Transfer
Alone	258 (58)	179	0	0	0	36	16	27
Partner	105 (27)	0	70	0	0	15	7	13
Family	36 (8)	0	0	27	0	3	1	5
Protected residence	27 (6)	0	0	0	16	7	3	1
Nursing home	18 (4)	0	0	0	0	17	0	1
Total *N* (%)		179 (40)	70 (16)	27 (6)	16 (4)	78 (18)	27 (6)	47 (10)

Data are expressed as number of cases (%).

Table 3
Univariate and multivariate logistic regression including all variables for predictors of the three adverse hospitalization outcomes (length of stay greater than the median, death during hospitalization, institutionalization) ($n = 444$)

		Univariate logistic regression		Multiple logistic regression	
Outcomes	Independent variables	Crude OR	95% CI	Adjusted OR	95% CI
Length of stay					
	Age	1.03	1.00−1.06*	1.02	0.99−1.05
	Male vs. female	0.91	0.60−1.39		
	CCI				
	Quartile				
	1	1.00	—		
	2	1.27	0.76−2.12		
	3	1.77	1.07−2.94*	1.24	0.66−2.32
	4	1.89	1.12−3.17*	1.45	0.79−2.65
	CIRS				
	Quartile				
	1	1.00	—		
	2	1.82	1.07−3.09*	1.36	0.72−2.54
	3	3.51	2.03−6.07***	3.00	1.64−5.46***
	4	5.07	2.84−9.04***	4.08	1.91−8.7***
	ICED				
	Class				
	1 + 2 + 3	1.00	—		
	4	2.00	1.24−3.2*	1.73	1.01−2.96*
	Kaplan				
	Quartile				
	1	1.00	—		
	2	1.38	0.73−2.6	0.59	0.27−1.30
	3	2.10	1.30−3.39**	1.10	0.53−2.27
	4	2.40	1.42−4.08***	1.32	0.75−2.29
	GIC				
	Class				
	1 + 2	1.00	—		
	3	8.22	3.46−19.5***	0.88	0.33−2.33
	4	9.03	4.08−20.0***	1.56	0.69−3.52
	CDS				
	Quartile				
	1	1.00	—		
	2	1.88	1.11−3.17*	1.18	0.65−2.14
	3	2.03	1.18−3.50**	1.57	0.83−2.94
	4	2.06	1.23−3.46**	1.61	0.92−2.85
Death in hospital					
	Age	1.07	1.00−1.15*	1.06	0.98−1.15
	Male vs. female	0.99	0.38−2.6		
	CCI				
	Quartile				
	1	1.00	—		
	2	1.68	0.88−3.20		
	3	1.74	0.92−3.27		
	4	2.49	1.34−4.60**	1.15	0.96−1.37
	CIRS				
	Quartile				
	1	1.00	—		
	2	1.72	1.07−3.09		
	3	4.29	2.03−6.07		
	4	6.84	2.84−9.04*	1.21	0.20−7.14
	ICED				
	Class				
	1 + 2 + 3	1.00	—		
	4	[a]	*	1.36	1.01−1.83*

(*Continued*)

Table 3
Continued

Outcomes	Independent variables	Univariate logistic regression		Multiple logistic regression	
		Crude OR	95% CI	Adjusted OR	95% CI
	Kaplan				
	Quartile				
	1	1.00	—		
	2	1.23	0.20−7.50		
	3	4.94	0.88−27.82		
	4	9.70	2.14−43.69**	1.71	0.28−10.50
	GIC				
	Class				
	1 + 2	1.00	—		
	3	34.30	13.75−87.82***	3.68	3.01−6.26***
	4	37.14	14.75−93.53***	4.34	3.92−9.52***
	CDS				
	Quartile				
	1	1.00	—		
	2	0.62	0.14−2.64		
	3	1.60	0.49−5.21		
	4	2.13	0.67−6.70		
Institutionalization					
	Age	1.05	1.00−1.10*	1.03	0.98−1.08
	Male vs. female	0.95	0.50−1.80		
	CCI				
	Quartile				
	1	1.00	—		
	2	1.42	0.66−3.07		
	3	1.50	0.70−3.20		
	4	1.69	0.80−3.57		
	CIRS				
	Quartile				
	1	1.00	—		
	2	1.98	0.77−5.09		
	3	2.98	1.23−7.21*	2.73	1.10−6.77*
	4	5.53	2.31−13.21***	5.56	2.18−14.22***
	ICED				
	Class				
	1 + 2 + 3	1.00	—	—	—
	4	2.31	1.05−5.08*	1.75	0.75−4.03
	Kaplan				
	Quartile				
	1	1.00	—		
	2	1.65	0.69−3.89		
	3	2.22	0.88−5.55		
	4	2.27	1.09−4.72*	1.65	0.91−3.00
	GIC				
	Class				
	1 + 2	1.00	—		
	3	3.25	1.24−11.20***	1.50	0.39−5.79
	4	4.62	3.46−13.20***	1.53	0.32−7.25
	CDS				
	Quartile				
	1	1.00	—		
	2	0.57	0.24−1.43		
	3	0.94	0.44−2.04		
	4	1.40	0.70−2.844		

Abbreviations: OR, odds ratio; CI, confidence interval; CCI, Charlson comorbid index; CIRS, cumulative illness rating scale; ICED, index of coexistent diseases; Kaplan, Kaplan scale; GIC, geriatrics index of comorbidity; CDS, chronic disease score.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

[a] ICED class 4 strongly predicts the outcome.

univariate analyses. When all scores were compared in a logistic regression after controlling for age and sex, the GIC remained a strong predictor for death during hospitalization.

However, the CIRS performed better than the other indices in predicting a prolonged hospital stay and institutionalization. The CDS performed the most poorly for predicting death during hospitalization and institutionalization. The risk of being hospitalized for longer than the median ranged from 1.88 for the lower scores to 2.06 for the higher scores, showing poor discrimination between these groups of patients. CCI scores were not predictive of institutionalization at all and were less predictive of prolonged hospitalization or death during hospitalization than the ICED or Kaplan scale.

4. Discussion

One of the main strengths of this study was the comprehensive and detailed assessment of the presence and extent of comorbidities: the same medical doctor scored the six CIs for all patients to ensure a high accuracy of scoring. The prospective collection of comorbidity data allowed better control over the quality of the data needed to quantify comorbidity. We carried out, for the first time, a prospective study comparing the use of six CIs—the most widely used and validated in elderly subjects—for the prediction of three adverse outcomes of hospitalization in elderly patients with acute disease. Previous studies, as described earlier, have used only one comorbidity score and have mostly been retrospective.

In our prospective study, introducing all parameters into the model, having checked for the absence of colinearity and adjusting for age and sex, the GIC provided a better measure of comorbidity than the other indices tested, when death during hospitalization was the outcome of interest. The CIRS could be used as a method for selecting elderly patients at admission and as a prognostic predictor for improvement at discharge. The results obtained for the CIRS were similar to previous findings in a retrospective analysis of patients aged 90−99 years, admitted over a 6-month period to a district hospital in Australia. One hundred three patients were included in the study with an average age of 92 years and a male-to-female ratio of 1:3. Fifty-five percent of hospitalized patients came from nursing care facilities. Characteristics of patients from nursing homes were compared with those of patients from the community. The physical burden of illness was measured by the CIRS. There was a significant ($P < 0.05$) correlation between high CIRS scores and duration of the hospital stay. The death rate for this group of patients was higher (13%) than the proportion of patients with a prolonged hospitalization period (10.2%). There were significant differences in the CIRS scores between patients who died and those who survived; the CIRS is thus potentially a useful tool in predicting this outcome [17]. In our univariate analysis, high CIRS scores were associated with death during hospitalization, with death rate differing by a factor of six between patients with the highest and lowest scores. These results confirmed those of Salvi et al. [18] that previously demonstrated the CIRS's ability to predict 18-month mortality and rehospitalization in a cohort of 387 patients aged 65 and older from an acute internal medicine ward. One advantage of the CIRS is its suitability for use in common clinical practice: it is based on measures of clinically relevant physiological systems and uses a clear and clinically sound ranking of severity. Given its validity and reliability, the CIRS seems to provide a very useful measure of comorbidity for clinical research. This index appears to be sufficiently reliable because it allows all the comorbid diseases from clinical examinations and medical files to be taken into account in a comprehensive manner [19]. The CIRS, however, has some limitations and improvements are needed, such as the inclusion of psychiatric disturbances, which are highly prevalent in the elderly. Such limitations may explain why, when all variables were included in the model, only the GIC class 3 and 4 scores remained statistically significant for the prediction of death during hospitalization.

Similarly, previous studies confirmed the impact of the GIC index on the prediction of 6-month survival in a population of 1,402 hospitalized elderly patients (age 80.1 ± 7.1 years; 68% female) with chronic disability consecutively admitted to an acute care unit in Italy. As observed in our study, patients with GIC class 1 and 2 scores were scarce in this acute geriatric ward. In a Cox regression analysis, adjusting for factors associated with mortality in univariate models (low levels of serum albumin and cholesterol, anemia, dementia, chronic obstructive pulmonary disease, coronary heart disease, renal diseases, gastrointestinal diseases, and advanced cancer) and taking class 2 as a reference, patients with GIC scores in class 4 had a risk of death three times higher than patients with the lowest scores [9].

The CDS was the poorest predictor for all the adverse outcomes considered. This is consistent with other previous studies. The low predictive value of this medication-based score for short-term outcomes may be because of the use of preventive treatments or treatment for benign conditions in healthier patients. For example, elderly women who are generally healthy and aware of health risks are likely to take lipid-lowering drugs and hormone replacement therapy. Such patients are likely to fare better than patients whose primary diagnosis has a poor short-term prognosis that may deter treatment of secondary conditions. This is consistent with earlier findings that sicker patients are less likely to be treated for comorbid conditions [20], particularly if these conditions are not immediately life threatening; additionally, medication for treating these conditions has preventive effects, for example, oral antidiabetic agents [21] or lipid-lowering drugs [22]. Users are thus often healthier than would be suggested by their medication-based scores. Although these findings are yet to be confirmed in other populations, they suggest that medication-based scores should be

used only in situations when the available data on the medication taken by the patients are of much better quality than the diagnostic data, or are the only source of information.

The CCI was not predictive of institutionalization at all and performed more poorly than the ICED or Kaplan scale for predicting prolonged hospitalization and death during hospitalization. The CCI is the most extensively studied CI for predicting mortality [2]. It was designed and scaled to predict mortality rather than functionally relevant comorbidity. This index does not take into account the severity of certain major diseases but only the presence of the disease. For example, in the case of congestive heart failure, patients with either a mild or a severe form of the disease will be assigned a score of 1. This index may therefore fail to identify important diseases, or their severity, in the elderly, which may otherwise act as predictors of adverse outcomes. The CCI has previously been found to be limited in determining the full range of diseases in elderly patients [19]. For this reason, some studies tried to outperform the CCI comparing the predictive capacity on mortality, readmission, and length of stay of the original CCI with a new CI regarding a larger range of diseases. Their results favor the utilization of newly developed indices [23,24]. On the contrary, Buntinx et al. [25], in a large cohort of 2,624 institutionalized elderly people, showed that the CCI is a predictor of short-term mortality and, to a lesser extent, also of hospitalization. In addition, the CCI has been shown to predict costs of chronic disease in primary care patients and in consequence being useful to predict resource utilization [26].

The GIC classifies patients based on increasing somatic comorbidity and takes into account disease severity. This probably explains why, when including all variables in the model, this index remained statistically significant and the best predictor for death during hospitalization in these elderly patients with acute disease. In the logistic regression model, the ICED also remained statistically, but weakly, significant. A distinct advantage of the ICED is that this index includes information on physical impairment in the assessment of comorbidity. Physical impairment is considered to be an additional dimension of comorbidity [27], reflecting symptomatic, uncontrolled, or advanced stages of disease. The ICED is the only one of these measures studied that has a 2-dimensional structure, measuring both the severity and extent of the disability associated with pathophysiologic disease. This could be particularly useful in studies assessing mortality and disability as outcomes of interest [2].

The Kaplan index performed well in our univariate analyses but lost all significance when all variables were controlled for. This index was specifically developed for use in diabetes research and contains clinically relevant information. It distinguishes between vascular and nonvascular comorbidity and uses severity rankings based on parameters derived from common clinical practice. The validity of this test makes the Kaplan scale a useful CI for clinical diabetes research [2] but probably less useful for assessing comorbidity in the elderly.

Currently, there is no accepted standardized method for measuring and quantifying the prognostic value of comorbid conditions in hospitalized elderly patients with acute disease. Our results showed that it is unlikely that any one particular index can be used to predict a variety of relevant outcomes. According to our results, the choice of measures will depend on the outcomes of interest as previously stated by Byles et al. [28]. We can recommend more usefully the GIC in predicting vital outcomes because of its link to physiological aspects of diseases, whereas the CIRS captures more comorbidity information related to the care because of its link to functional aspects of diseases. These findings have widespread implications for improved planning of the hospitalization period through the discharge of very ill elderly patients with acute disease.

The ways that health researchers have measured comorbidity has advanced our understanding in aging population but an important issue in geriatrics remains the need for new and better measures of the health status of elderly individuals that summarize the complex disorders that burdened them. Studies contrasting multimorbidity, which is defined—following van den Akker et al. study [29,30]—as the co-occurrence of two or more diseases in one person, without defining an index disease and comorbidity, corresponding to additional diseases to one index disease are needed. It would be essential to take into account not only the number of comorbid conditions and an index weighted by the severity of the comorbid conditions but also the associations among diseases.

Acknowledgments

The authors thank the teams of Mrs. O. Baumer, L. Humblot, and M. Cos for their technical assistance. This work was supported by grant 3200B0-102069 from the Swiss National Science Foundation.

References

[1] Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. J Clin Epidemiol 2001;54:661−74.

[2] de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: a critical review of available methods. J Clin Epidemiol 2003;56:221−9.

[3] Karlamangla A, Tinetti M, Guralnik J, Studenski S, Wetle T, Reuben D. Comorbidity in older adults: nosology of impairment, diseases, and conditions. J Gerontol A Biol Sci Med Sci 2007;62:296−300.

[4] Rozzini R, Sabatini T, Barbisoni P, Trabucchi M. How to measure comorbidity in elderly persons. J Clin Epidemiol 2004;57:321−2.

[5] Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373−83.

[6] Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the cumulative illness rating scale in a geriatric residential population. J Am Geriatr Soc 1995;43:130−7.

[7] Greenfield S, Sullivan L, Dukes KA, Silliman R, D'Agostino R, Kaplan SH. Development and testing of a new measure of case-mix for use in office practice. Med Care 1995;33:AS47−55.
[8] Kaplan MH, Feinstein A. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 1974;27:387−404.
[9] Rozzini R, Frisoni GB, Ferrucci L, Barbisoni P, Sabatini T, Ranieri P, et al. Geriatric index of comorbidity: validation and comparison with other measures of comorbidity. Age Ageing 2002;31:277−85.
[10] Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992;45:197−203.
[11] Bravo G, Dubois MF, Hébert R, De Wals P, Messier L. A prospective evaluation of the Charlson Comorbidity Index for use in long-term care patients. J Am Geriatr Soc 2002;50:740−5.
[12] Di Bari M, Virgillo A, Matteuzzi D, Inzitari M, Mazzaglia G, Pozzi C, et al. Predictive validity of measures of comorbidity in older community dwellers: the Insufficienza Cardiaca negli Anziani Residenti a Dicomano Study. J Am Geriatr Soc 2006;54:210−6.
[13] Zekry D, Herrmann FR, Grandjean R, Vitale AM, De Pinho MF, Michel JP, et al. Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients. Int J Geriatr Psychiatry 2008;37:83−9.
[14] Folstein MF, Folstein SE, MacHugh PR. Mini Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189−98.
[15] Solomon PR, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux RD, et al. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998;55:349−55.
[16] Robert PH, Schuck S, Dubois B, Olié JP, Lépine JP, Gallarda T, et al. Screening for Alzheimer's disease with the short cognitive evaluation battery. Dement Geriatr Cogn Disord 2003;15:92−8.
[17] Nagaratnam N, Gayagay G. Validation of the cumulative illness rating scale (CIRS) in hospitalized nonagenarians. Arch Gerontol Geriatr 2007;44:29−36.
[18] Salvi F, Miller MD, Grilli A, Giorgi R, Towers AL, Morichi V, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56(10):1926−31.
[19] Harboun M, Ankri J. Comorbidity indexes: review of the literature and application to studies of elderly population. Rev Epidemiol Sante Publique 2001;49:287−98.
[20] Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. N Engl J Med 1998;21:1516−20.
[21] Glynn RJ, Monane M, Gurwitz JH, Choodnovskiy I, Avorn J. Aging, comorbidity, and reduced rates of drug treatment for diabetes mellitus. J Clin Epidemiol 1999;52:781−90.
[22] Glynn RJ, Knight EL, Levin R, Avorn J. Paradoxical relations of drug treatment with mortality in older persons. Epidemiology 2001;12:682−9.
[23] Martins M, Blais R. Evaluation of comorbidity indices for inpatient mortality prediction models. J Clin Epidemiol 2006;59:665−9.
[24] Holman CD, Preen DB, Baynham NJ, Finn JC, Semmens JB. A multipurpose comorbidity scoring system performed better than the Charlson index. J Clin Epidemiol 2005;58:1006−14.
[25] Buntinx F, Niclaes L, Suetens C, Jans B, Mertens R, Van den Akker M. Evaluation of Charlson's comorbidity index in elderly living in nursing homes. J Clin Epidemiol 2002;55:1144−7.
[26] Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care. J Clin Epidemiol 2008;61:1234−40.
[27] Iezzoni LI. Dimensions of risk. In: Iezzoni LI, editor. Risk adjustment for measuring health outcomes. Ann Arbor, MI: Health Administration Press; 1994. p. 1−29.
[28] Byles JE, D'Este C, Parkinson L, O'Connell R, Treloar C. Single index of multimorbidity did not predict multiple outcomes. J Clin Epidemiol 2005;58:997−1005.
[29] Van den Akker M, Buntinx F, Roos S, Knottnerus JA. Problems in determining occurrence rates of multimorbidity. J Clin Epidemiol 2001;54:675−9.
[30] Van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: what's in a name? A review of literature. Eur J Gen Pract 1996;2:65−70.

PAPER 3

Prospective comparison of 6 comorbidity indices as predictors of 1-year post-hospital discharge institutionalization, readmission, and mortality in elderly individuals

Dina Zekry, Bernardo Hermont Loures Valle, Christophe Graf,
Jean-Pierre Michel, Gabriel Gold, Karl-Heinz Krause, François R. Herrmann

Journal of American Medical Directors Association 2011 Jan 8

In this paper, we intended to compare the same 6 comorbidity scores, studied in the previous paper, predicting the risk of rehospitalization, institutionalization and death one-year after discharge.

The predictive values of the CIRS and the GIC were also confirmed to medium term survival. After 1 year of discharge, approximately 50% of the high-score patients were already deceased, compared with <5% in the lowest scores. The best multiple regression model retained the CIRS quartile 4 followed by the GIC class 4 as the strongest risk predictors of death one-year after discharge.

Of the 6 indices, the GIC explained the greatest amount of variability of 2 of the studied outcomes (one-year death and one-year institutionalization), and its scores alone were the only ones associated with institutionalization. The specificity of this index for this outcome was very high (99.7%) with a positive predictive value of 50.0% and a negative predictive.

Prospective Comparison of 6 Comorbidity Indices as Predictors of 1-Year Post-Hospital Discharge Institutionalization, Readmission, and Mortality in Elderly Individuals

Dina Zekry, MD, PhD, Bernardo Hermont Loures Valle, MD, Cristophe Graf, MD, Jean-Pierre Michel, MD, Gabriel Gold, MD, Karl-Heinz Krause, MD, and François R. Herrmann, MD, MPH

Background: Older patients often suffer from multiple comorbid conditions. Few comorbidity indices are valid and reliable in the elderly and were rarely compared.

Objective: To compare the performance, relevance, and ability of 6 widely used and validated comorbidity indices—Charlson Comorbidity Index, Cumulative Illness Rating Scale–Geriatrics, Index of Coexistent Diseases, Kaplan, Geriatric Index of Comorbidity (GIC), and Chronic Disease Score—to predict adverse outcomes after discharge (1-year risk of rehospitalization, institutionalization, and death).

Design, setting, and participants: Prospective study with 1-year follow-up, between January 2004 and December 2005 in 444 elderly patients (mean age, 85; 74% female) discharged from acute geriatric hospital, Geneva University Hospitals.

Results: In univariate analyses, Cumulative Illness Rating Scale–Geriatrics and GIC were the predictors with the largest coefficient of determination for mortality with (R^2 of 9.3%, respectively 8.8%). GIC was also the only significant predictor of institutionalization (R^2 = 6.0%). Higher risk of readmission was significantly associated with GIC (R^2 = 14.0%), Cumulative Illness Rating Scale–Geriatrics (R^2 = 5.6%), Charlson Comorbidity Index (R^2 = 3.1%), and Chronic Disease Score (R^2 = 1.7).

Conclusions: Understanding how to efficiently predict these adverse outcomes in hospitalized elders is important for a variety of clinical and policy reasons. GIC and Cumulative Illness Rating Scale–Geriatrics may improve hospital discharge planning in a geriatric hospital treating very old patients with acute disease. **(J Am Med Dir Assoc 2011; ■: ■–■)**

Keywords: Comorbidity scores; 1-year mortality; rehospitalization; institutionalization

Elderly patients often suffer from multiple chronic conditions that individually and jointly affect their quality of life, use of health services, morbidity, and mortality.[1] Old persons with chronic, progressive, and disabling illnesses often require hospitalization, leading to further functional decline and morbidity.[2,3] Hospitalization therefore may present a key trigger point for identifying persons at greatest risk of adverse outcomes like mortality, institutionalization, and readmission in the ensuing year after discharge.[4] Hospital discharge planning and prognosis can help physicians and family members plan for the care of patients who may be at an increased risk of adverse outcomes in the coming year, especially regarding goals of care, advance planning, and clinical therapeutic options.[5–7]

There are some prognostic indices available for predicting mortality after discharge in older hospitalized adults. Some existing models are only applicable to specific patient populations and particular disease states.[8–10] Other models require the use of more lengthy formulas based on laboratory data and functional status,[11–13] or based on common geriatric syndromes.[14] Recently, a multidimensional prognostic index based on the comprehensive geriatric assessment has been used to predict mortality.[15] Although these tools have been

Rehabilitation and Geriatrics Department, Geneva University Hospitals and University of Geneva, Thônex, Switzerland (D.Z., C.G., J.-P.M., G.G., F.R.H.); Pathology and Immunology Department, Geneva University Hospitals and University of Geneva, Geneva, Switzerland (K.-H.K.); Clementino Fraga Filho Hospital, Rio de Janeiro Federal University, Rio de Janeiro, Brazil (B.H.L.V.).

This work was supported by grants from the Swiss National Science Foundation (SNF) (3200B0–102069) and from the Swiss Foundation for Ageing Research (AETAS).

Address correspondence to Dina Zekry, MD, PhD, Rehabilitation and Geriatrics Department, Geneva University Hospitals, 3, chemin du Pont-Bochet, Thônex, Switzerland. E-mail: dina.zekry@hcuge.ch

DOI:10.1016/j.jamda.2010.11.011

developed to target high-risk patients, their use has not been incorporated into routine medical practice. For screening to be effective, predictive variables should be readily available and easily measurable soon after admission.

The aim of this prospective study was to compare the performance and the value of 6 validated and widely used comorbidity indices predicting adverse hospitalization outcomes 12 months after discharge, including rehospitalization, institutionalization and mortality. We also aimed to identify an easy and accurate predictive index that could be used by clinicians to plan patient discharge and improve prevention of these adverse outcomes. The study population was derived from a cohort study of very elderly, acutely ill geriatric inpatients.

METHODS

Patients and Data Collection

We carried out a prospective study in a 300–acute bed geriatric hospital (HOGER) where 22.7% were direct admission from the community, 54.0% were referred by the emergency unit, and 23.3% were transferred from other divisions of Geneva University Hospitals, Switzerland. Patients and data collection have been described elsewhere.[16–18] Briefly, a representative sample of all patients aged 75 years and older, consecutively admitted between January 2004 and December 2005 were selected by randomization, with a sampling fraction of 30% using a computer-generated randomization table. The local ethics committee approved the protocol, and patients, their families, or legal representatives provided signed written informed consent. Demographic data for the patients studied did not significantly differ from data for all patients admitted to HOGER in 2004–2005. Our sample was therefore representative of all patients admitted to this hospital, demonstrating the reliability of the randomization procedure used in this study.

Medical history was recorded on a standardized form and the same geriatrician carried out a comprehensive geriatric assessment of all patients. A follow-up with a similar assessment was done 1 year after. Information on length of stay in the acute geriatric hospital and indication for hospitalization, as well as the location of discharge was described previously.[18]

Sociodemographic Data

The data recorded included age, sex, native language, marital status, living arrangements, and educational level.

Assessment of Comorbidity

We chose the 6 validated comorbidity indices most widely used to assess elderly comorbidity.[19,20] They are described in detail in Table 1: Charlson Comorbidity Index (CCI),[21] Cumulative Illness Rating Scale–Geriatrics (CIRS),[22] Index of Coexistent Diseases (ICED),[23] Kaplan scale,[24] Geriatric Index of Comorbidity (GIC),[25] and Chronic Disease Score (CDS).[26] The same geriatrician calculated all 6 scores for each patient, via an extensive review of the patient's medical records and administrative data for diagnoses established at or before enrollment in this study and by standardized interviews with patients and surrogates.

Adverse Outcomes

The adverse outcomes, coded as dichotomous data, included the following: institutionalization defined as being permanently admitted to a long-term care institution, rehospitalization and mortality 12 months after discharge. Information regarding the outcomes was obtained through phone calls to the patient, family, and/or general practitioner. Mortality data was also confirmed through access to the population registrar of the State of Geneva.

Statistical Methods

We checked for the normal distribution of continuous scores (CCI, CIRS, Kaplan, and CDS) using skewness and kurtosis tests, and carried out standard transformations to normalize non-Gaussian variables. As it was not possible to normalize these scores, they were categorized into quartiles to facilitate comparison with the 4 predefined classes of the other 2 indices, ICED and GIC. Data for continuous variables are presented as means $\pm$ 1 standard deviation. Collinearity among the 6 indices was checked using Spearman's rank correlation coefficient. First, we measured the univariate relationship between each index of comorbidity to the 3 outcomes using logistic or Cox regression models and computed pseudo R-squared (R^2) which provides information on the amount of variance explained by the model. For mortality only, we used Cox proportional hazards models to take into account the time to the event. Odds ratios (OR) and hazard ratios (HR) along with their 95% confidence intervals (CI) were calculated. Statistical analyses were performed with Stata software version 10.1 (College Station, TX).

RESULTS

Characteristics of Participants

Of the 1854 eligible patients, 556 were randomized, 523 were successfully enrolled, and 496 survived to hospital discharge (27 died during the hospitalization). The 1-year follow-up was not done in 52 patients (10.5%): 12 patients had moved abroad from Switzerland and the assessment was refused in 30 cases by the patient and in 10 cases by the family. Then 444 patients were successfully followed for 12 months and had full data for these analyses (mean age 85.3 $\pm$ 6.7; 74% women). Table 2 summarizes the frequency distribution of patients according to each comorbidity score. As there were no patients in ICED classes 1 and 2, we considered only classes 3 and 4 coded as binary data for the analyses. Likewise, only 2% of the patients were classified as class 1 by the GIC, allowing us to combine classes 1 and 2 for the analysis. Spearman rho values among the 6 indices ranged between 0.038 and 0.548, which does not meet the criteria for colinearity usually set at 0.900 or more.

Adverse Outcomes

Institutionalization

Twelve months after discharge, 124 (27.9%) patients were residents in a nursing home. Interestingly, univariate analysis revealed that the highest GIC score was significantly associated with a double risk of institutionalization accounting

Table 1. *Details of Scoring of the 6 Comorbidity Scores Studied*

Index Name	Number/Nature of Items	Item Score	Index Total Score (Range)
Charlson Comorbidity Index[21]	19 medical conditions	Derived from the relative risk of death in a cohort of cancer patients, are fixed for each diagnosis and range from: ➢ **1:** for conditions such as myocardial infarction or mild liver disease, with a relative risk ≥ 1.2 and < 1.5 ➢ to **6:** assigned to metastatic, cancer, AIDS, with a relative risk ≥ 6	Summing of the weight assigned to each disease (0–38)
Cumulative Illness Rating Scale–Geriatrics[22]	14 medical conditions	➢ **0:** no problem affecting that system or past problem without clinical relevance; ➢ **1:** current mild problem or past significant problem; ➢ **2:** moderate disability or morbidity and/or requires first-line therapy; ➢ **3:** severe problem and/or constant and significant disability and/or hard to control chronic problems (complex therapeutic regimen); ➢ **4:** extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment	Summing of the weight assigned to each disease (0–56)
Index of Coexistent Diseases[23]	15 Medical conditions plus 12 physical impairment	**IDS:** ➢ **0:** disease is absent; ➢ **1:** asymptomatic; ➢ **2:** symptoms are mild and controlled by treatment; ➢ **3:** symptoms are severe; ➢ **4:** disease is life-threatening or has the last level of severity **PIS:** ➢ **0:** absent; ➢ **1:** mild to moderate; ➢ **2:** moderate to severe	Based on an algorithm combining both indices (4 classes) **Class I:** IDS 0, PIS 0 or 1, **Class II:** IDS 1 or 2, PIS 0 **Class III:** IDS 1 or 2, PIS 1 **Class IV:** IDS 3 or plus, and PIS 0–2 / IDS 0–4, and PIS 2
Kaplan[24]	14 medical conditions	➢ **0:** comorbidity is absent or easy to control; ➢ **1:** mild; ➢ **2:** moderate; ➢ **3:** recent full decompensation of comorbid disease	Summing of the weight assigned to each disease (0–42)
Geriatric Index of Comorbidity[25]	15 medical conditions	**Disease score**: based on the number of diseases **IDS:** ➢ **0:** disease is absent; ➢ **1:** asymptomatic; ➢ **2:** symptoms are mild and controlled by treatment; ➢ **3:** symptoms are severe; ➢ **4:** disease is life-threatening or has the last level of severity	Based on an algorithm combining both indices (IDS) and the disease score (4 classes) **Class I:** no disease IDS >1, **Class II:** 1 or more conditions IDS = 2, **Class III:** only 1 condition IDS = 3, **Class IV:** at least 2 conditions IDS = 3 or at least 1 condition IDS = 4
Chronic Disease Score[26]	30 classes of medication	Depends on the weight and on the severity of a given disease, for example: ➢ **0:** no treatment; ➢ **1:** anticholesterol, glaucoma, ulcer disease; ➢ **2:** only 1 class of treatment to asthma, chronic obstructive pulmonary disease; ➢ **3:** L-dopa for Parkinson disease, 2 or more classes of treatment for respiratory illness; only 1 class for heart disease ➢ **4:** 2 classes for heart disease ➢ **5:** 3 classes for heart disease	Summing of the weight assigned to each category of treatment (0–37)

IDS, Individual Disease Severity; PIS, Physical Impairment Severity.

Table 2. *Quartile Range and Frequency of 6 Comorbidity Scores*

Level/ Classes*	CCI		CIRS		ICED*	Kaplan		GIC*	CDS	
	Quartile Range Score	N (%)	Quartile Range Score	N (%)	N (%)	Quartile Range Score	N (%)	N (%)	Quartile Range Score	N (%)
1	0–3	165 (37)	0–11	121 (27)	0	0–2	128 (29)	9 (2)	0–3	122 (28)
2	4	91 (20)	12–14	107 (24)	0	3–4	156 (35)	34 (8)	4–6	117 (26)
3	5–6	91 (20)	15–18	119 (27)	93 (21)	5	55 (12)	310 (70)	7–8	109 (24)
4	7–14	97 (23)	19–30	97 (22)	351 (79)	6–16	105 (24)	91 (20)	9–15	96 (22)

Data are expressed as number of cases (%).
CCI, Charlson Comorbidity Index; CDS, Chronic Disease Score; CIRS, Cumulative Illness Rating Scale–Geriatrics; GIC, Geriatrics Index of Comorbidity; ICED, Index of Coexistent Diseases; Kaplan, Kaplan scale.
* Quartile ranges do not apply to ICED and GIC, as these indices are predefined into 4 classes.

for only 2% of the variability of this outcome (OR = 1.84, 95% CI = 1.04–3.27, $P < .001$). The specificity of this index for this outcome was very high (99.7%) with a positive predictive value of 50.0% and a negative predictive value of 72.2%. Age, sex, and all 5 other scores were not statistically significantly associated with institutionalization.

Rehospitalization

Twelve months after discharge, 136 (30.6%) patients were rehospitalized (Table 3); 82 (18.5%) once and 54 (12.1%) 2 or more times. In the univariate analysis, being male and high scores for the CIRS, CCI, and CDS indices were found to be independent predictors. This model explained between 0% and 14% of the variance of this outcome.

Death during the first year after discharge

Among the 444 patients, 97 died during the first year after discharge (22%) (Table 4). In univariate analysis, mortality was not significantly associated with sex, but was significantly associated with age (HR = 1.08). The best prognostic

Table 3. *Univariate Logistic Regression Predicting Rehospitalization at 12 months after Discharge (n = 444)*

Outcomes	Independent Variables	Crude OR	95% CI	*P*	R^2 (%)
Rehospitalization (n = 136)					
	Age	0.99	0.97–1.02	.521	0.0
	Male vs female	**1.46**	1.03–2.08	**.035**	0.6
	CCI				3.1
	Quartile 1	1.00	—	—	
	Quartile 2	1.13	0.59–2.15	.714	
	Quartile 3	1.88	0.94–3.77	.076	
	Quartile 4	**2.22**	1.40–3.54	**<.001**	
	CIRS				5.6
	Quartile 1	1.00	—	—	
	Quartile 2	1.22	0.78–1.94	.378	
	Quartile 3	**1.82**	1.16–2.85	**.009**	
	Quartile 4	**2.52**	1.69–3.75	**<.001**	
	ICED				0.4
	Class 1+2+3	1.00	—	—	
	Class 4	1.43	0.95–2.13	.083	
	Kaplan				0.5
	Quartile 1	1.00	—	—	
	Quartile 2	0.97	0.44–2.15	.938	
	Quartile 3	1.30	0.75–2.29	.352	
	Quartile 4	1.49	0.71–3.11	.294	
	GIC				14.0
	Class 1+2	1.00	—	—	
	Class 3	1.57	0.92–2.71	.099	
	Class 4	1.71	0.88–3.35	.114	
	CDS				1.7
	Quartile 1	1.00	—	—	
	Quartile 2	0.97	0.59–1.60	.904	
	Quartile 3	**1.71**	1.10–2.64	**.017**	
	Quartile 4	**1.79**	1.14–2.82	**.012**	

Bold entries = relevant results.
CCI, Charlson Comorbidity Index; CDS, Chronic Disease Score; CI, confidence interval; CIRS, Cumulative Illness Rating Scale–Geriatrics; GIC, Geriatrics Index of Comorbidity; ICED, Index of Coexistent Diseases; Kaplan, Kaplan scale; OR, odds ratio.

Table 4. *Univariate Cox Regression Predicting 1-Year Mortality (n = 444)*

Outcome	Independent Variables	Crude HR	95% CI	*P*	R^2 (%)
Death at 12 months (n = 97)					
	Age	**1.08**	1.04–1.15	**<.001**	4.6
	Male vs female	1.33	0.87–2.05	.189	0.3
	CCI				1.9
	Quartile 1	1.00	—	—	
	Quartile 2	1.68	0.88–3.21	.116	
	Quartile 3	1.74	0.92–3.28	.086	
	Quartile 4	**2.49**	1.34–4.60	**.004**	
	CIRS				9.3
	Quartile 1	1.00	—	—	
	Quartile 2	1.61	0.71–3.62	.250	
	Quartile 3	**3.70**	1.82–7.53	**<.001**	
	Quartile 4	**6.33**	3.17–12.65	**<.001**	
	ICED				2.0
	Class 1+2+3	1.00	—	—	
	Class 4	**2.58**	1.34 – 4.96	**.005**	
	Kaplan				4.1
	Quartile 1	1.00	—	—	
	Quartile 2	1.54	0.84–2.84	.165	
	Quartile 3	**2.47**	1.22–4.99	**.012**	
	Quartile 4	**3.45**	1.92–6.19	**<.001**	
	GIC				8.8
	Class 1+2	1.00	—	—	
	Class 3	**8.15**	1.13–58.91	**.038**	
	Class 4	**27.6**	3.80–200.51	**.001**	
	CDS				0.2
	Quartile 1	1.00	—	—	
	Quartile 2	1.04	0.59–1.82	.885	
	Quartile 3	1.20	0.68–2.16	.442	
	Quartile 4	1.24	0.71–2.13	.544	

Bold entries = relevant results.

CCI, Charlson Comorbidity Index; CDS, Chronic Disease Score; CI, confidence interval; CIRS, Cumulative Illness Rating Scale–Geriatrics; GIC, Geriatrics Index of Comorbidity; HR, hazard ratio; ICED, Index of Coexistent Diseases; Kaplan, Kaplan scale.

predictor was CIRS with an R^2 of 9.3%, followed by GIC (R^2 = 8.8%), Kaplan scale, ICED, and CCI. The CDS was not a predictor of this outcome.

DISCUSSION

This article examines the relationship between a variety of comorbidity indices and a number of health outcomes (rehospitalization, institutionalization, and death) in hospitalized elderly. Of the 6 indices, the GIC explained the greatest amount of variability of 2 of the studied outcomes in univariate analysis, and its scores alone were the only ones associated with institutionalization. One of the main strengths of this study was the prospective, comprehensive assessment of the presence and the extent of comorbidity: the same geriatrician scored the 6 comorbidity indices for all patients. This is the first prospective study comparing at the same time the use of 6 comorbidity indices for the prediction of 3 adverse outcomes 1 year after discharge in elderly patients with acute disease. Previous studies, as described above, have used only 1 comorbidity score and have been done in a community-dwelling population, and only a few of them present the coefficient of determination (R^2) of their model.[20,25,27]

In our prospective study, excluding the CDS, the other 5 comorbidity indices in the univariate analysis were significantly associated with death 1 year after discharge. However, the CIRS and the GIC better explained the prediction of this outcome. This is probably because the GIC and the CIRS assume that the impact of all diseases is cumulative. The Kaplan index assumes that the single most severe illness will determine the prognosis; the ICED allows a high score in functional status severity to override a high disease severity score and the CCI weights the severity categories that have an impact on the patient's health differently. The type of scoring system based on cumulative effects is probably more appropriate to the elderly population.[28] As suggested by Fried et al,[29] some diseases or conditions, in addition to having greater or lesser likelihoods of co-occurrence, may be synergistic in their effects. For example, Ettinger et al[30] have shown that, during the development of mobility disability, the risks posed by heart disease alone (OR = 2.3) and the risks posed by osteoarthritis alone (OR = 4.3) are considerably less than those posed by the combination of the two (OR = 13.6). Currently, none of the existing indices consider the impact of specific combinations of comorbid illnesses.

The GIC was the only predictor for institutionalization and explained the largest percentage of variability for 1-year mortality in the univariate regression model. The GIC scores take into account disease severity and categorize patients based on increasing somatic comorbidity. In addition, this score targets functional status. This probably explains why this index

predicts institutionalization while others did not in these elderly patients with acute disease. Similarly, previous studies have confirmed the impact of the GIC index in predicting 6-month survival in a population of 1402 hospitalized elderly patients (age 80.1 ± 7.1 years; 68% female) with chronic disability who were subsequently admitted to an acute care unit in Italy. As observed in our study, patients with GIC class 1 and 2 scores were few in this acute geriatric ward. In a multiple Cox regression analysis adjusted for factors associated with mortality in univariate models (low levels of serum albumin and cholesterol, anemia, dementia, chronic obstructive pulmonary disease [COPD], coronary heart disease, renal diseases, gastrointestinal diseases, advanced cancer) and where class 2 is used as the reference, patients with GIC scores in class 4 had a risk of death 3 times higher than patients with the lowest scores.[20]

In our study, the CIRS was also significantly associated with 1-year mortality and was the best predictor of readmission. These results are consistent with other studies. Salvi et al[31] previously demonstrated the CIRS's ability to predict 18-month mortality and rehospitalization in a cohort of 387 patients aged 65 years and older in an acute internal medicine ward. Parmelee et al[22] showed a significant association between the CIRS and mortality, acute hospitalization, medication usage, laboratory test results, and functional disability among frail elderly institutionalized patients. One advantage of the CIRS is its suitability for use in common clinical practice: it is based on measurements of clinically relevant physiological systems and uses a clear and clinically sound ranking of severity. This index appears to be sufficiently reliable because it allows all comorbid diseases from clinical examinations and medical files to be taken into account in a comprehensive manner.[27] The CIRS was based on the mortality of a series of men in a southeastern US veterans' hospital in 1964. At the start, the CIRS was designed to estimate the total medical burden and the capacity for elderly patients to survive.[32] It has been converted into a comorbidity index by removing the disease of interest.

The CDS only predicted 1-year readmission, but not institutionalization or mortality. This is consistent with previous studies. The low predictive value of this medication-based index for short-term outcomes may be attributable to the use of preventive treatment or treatment for benign conditions in healthier patients. For example, elderly women who are generally healthy and aware of health risks are likely to take lipid-lowering drugs and hormone replacement therapy. These patients are likely to fare better than patients whose primary diagnosis has a poor short-term prognosis, which may deter the treatment of secondary conditions. This is consistent with earlier findings that sicker patients are less likely to be treated for comorbid conditions, particularly if these conditions are not immediately life threatening.[33–35]

The CCI was a significant but poor predictor of both 1-year mortality and rehospitalization. The CCI is the most extensively studied comorbidity index. It was designed and scaled to predict mortality based on the mortality of 607 patients admitted to a general internal medicine service in a single New England hospital during a single month in 1984.[21] This index does not take into account the severity of certain major diseases but only the presence of the disease. For example, in the case of congestive heart failure, patients with either a mild or a severe form of the disease will be assigned a score of 1. This index may therefore fail to identify important diseases, or their severity in the elderly, which may otherwise act as predictors of adverse outcomes. The CCI has previously been found to be limited in determining the full range of diseases in elderly patients.[27] By contrast, another previous study examined the prognostic value of the CCI in predicting 3-year mortality and functional decline in patients receiving long-term care from 88 residential care facilities in Quebec, Canada (291 dependent elderly adults with a mean age of 83 years). The CCI performed well in predicting both outcomes.[36]

The ICED and the Kaplan index performed well in our univariate analysis of 1-year mortality. The Kaplan was specifically developed for use in diabetes research and has been mostly used in oncology. The ICED has been mostly used in renal disease. Both of these scores appear to be less useful for assessing comorbidity in the elderly.

Our study has some limitations. First, because it focused on hospitalized elderly patients, it is likely that it is difficult to generalize its conclusions to all institutionalized and community-dwelling subjects. Second, only one center was involved, so the results have to be confirmed in other centers. Third, the enrolled patients were very old, acutely ill, and had a high burden of comorbidities. Thus, the indices might behave differently in other patient groups with characteristics different from these. Moreover, some indices seem less appropriate in very old acutely ill patients, because no patients were found in the lowest classes of comorbidities, such as in the ICED. Finally, the regression models explained only a limited amount of the variance of each outcome. Thus, comorbidity alone is insufficient to explain the variation of theses adverse outcomes and other predictor variables have to be included to increase the prediction accuracy, such as socioeconomic and postdischarge environmental factors,[37] or poor functional status. [38] In addition, for the most part, each index had a quite different view of comorbidity. Some incorporated severity, whereas others did not. In several cases, although these indices are titled comorbidity indices, they seem to be more indices of functional status, as key elements of the index focus more on the functional impact of disease like the CIRS.

In summary, the GIC index provides the most accurate method for identifying older patients at high risk of 1-year mortality after a hospital stay; the CIRS is the next best method for predicting this outcome. The GIC also accurately predicts 1-year institutionalization and the CIRS accurately predicts 1-year rehospitalization. Both indices are prognostic predictors and could be useful in guiding clinicians toward improvement in care and in making decisions at discharge. The use of measurements of comorbidity is also becoming more common in clinical research, but researchers are faced with a wide range of options, with surprisingly little information on the relative strengths and weaknesses of those options.[39] In the elderly population there is no accepted

standardized method for assessing and quantifying the prognostic value of comorbid conditions. Our results showed that it is unlikely that the same index can be used to predict different outcomes. According to our results, the choice of measures will depend on the outcomes of interest. Given their validity and reliability, the GIC and the CIRS seem to provide very useful measurements of comorbidity for clinical research. They may thus also assist researchers in selecting an effective index when studying specific outcomes of interest.

ACKNOWLEDGMENTS

We thank the teams of Mrs. O. Baumer, L. Humblot, and M. Cos for technical assistance.

REFERENCES

1. Gijsen R, Hoeymans N, Schellevis FG, et al. Causes and consequences of comorbidity: A review. J Clin Epidemiol 2001;54:661–674.
2. Covinsky KE, Palmer RM, Fortinsky RH, et al. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: Increased vulnerability with age. J Am Geriatr Soc 2003;51: 451–458.
3. Lunney JR, Lynn J, Foley DJ, et al. Patterns of functional decline at the end of life. JAMA 2003;289:2387–2392.
4. Levine SK, Sachs GA, Jin L, et al. A prognostic model for 1-year mortality in older adults after hospital discharge. Am J Med 2007;120:455–460.
5. Christakis NA. Death Foretold: Prophecy and Prognosis in Medical Care. 1st ed. Chicago, IL: The University of Chicago Press; 1999.
6. Lynn J. Serving patients who may die soon and their families: The role of hospice and other services. JAMA 2001;285:925–932.
7. Lynn J, Teno JM, Harrell FE. Accurate prognostications of death: Opportunities and challenges for clinicians. West J Med 1995;163:250–257.
8. Muers MF, Shevlin P, Brown J. Prognosis in lung cancer: Physicians' opinions compared with outcome and a predictive model. Thorax 1996;51:894–902.
9. Morita T, Tsunoda J, Inoue S, et al. Survival prediction of terminally ill cancer patients by clinical symptoms: Development of a simple indicator. J Clin Oncol 1999;29:156–159.
10. Fillenbaum GG, Pieper CF, Cohen HJ, et al. Comorbidity of five chronic health conditions in elderly community residents: determinants and impact on mortality. J Gerontol 2000;55:M84–89.
11. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. JAMA 2001;285:2987–2993.
12. Teno JM, Harrell FE, Knaus WA, et al. Prediction of survival for older hospitalized patients; The HELP survival model. J Am Geriatr Soc 2000;48:S16–S24.
13. Inouye SK, Peduzzi PN, Robison JT, et al. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 1998;279:1187–1193.
14. Anpalahan M, Gibson SJ. Geriatric syndromes as predictors of adverse outcomes of hospitalization. Int Med J 2008;38:16–23.
15. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. Rejuvenation Res 2008;11:151–161.
16. Zekry D, Herrmann FR, Grandjean R, et al. Demented versus nondemented very old inpatients: The same comorbidities but poorer functional and nutritional status. Age Ageing 2008;37:83–89.
17. Zekry D, Herrmann FR, Grandjean R, et al. Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients. Int J Geriatr Psychiatry 2009;24:283–291.
18. Zekry D, Loures Valle BH, Lardi C, et al. Geriatrics index of comorbidity was the most accurate predictor of death in geriatric hospital among six comorbidity scores. J Clin Epidemiol 2010;63:1036–1044.
19. de Groot V, Beckerman H, Lankhorst GJ, et al. How to measure comorbidity: A critical review of available methods. J Clin Epidemiol 2003;56: 221–229.
20. Rozzini R, Sabatini T, Barbisoni P, et al. How to measure comorbidity in elderly persons. J Clin Epidemiol 2004;57:321–322.
21. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–383.
22. Parmelee PA, Thuras PD, Katz IR, et al. Validation of the cumulative illness rating scale in a geriatric residential population. J Am Geriatr Soc 1995;43:130–137.
23. Greenfield S, Sullivan L, Dukes KA, et al. Development and testing of a new measure of case-mix for use in office practice. Med Care 1995; 33:AS47–AS55.
24. Kaplan MH, Feinstein A. The importance of classifying initial comorbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 1974;27:387–404.
25. Rozzini R, Frisoni GB, Ferrucci L, et al. Geriatric Index of Comorbidity: Validation and comparison with other measures of comorbidity. Age Ageing 2002;31:277–285.
26. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992;45:197–203.
27. Harboun M, Ankri J. Comorbidity indexes: Review of the literature and application to studies of elderly population. Rev Epidemiol Sante Publique 2001;49:287–298.
28. Wieland GD. From bedside to bench: Research in comorbidity and aging. Sci Aging Knowl Environ 2005;39:29–33.
29. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59:255–263.
30. Ettinger WH, Davis MA, Neuhaus JM, et al. Long-term physical functioning in persons with knee osteoarthritis from NHANES. I: Effects of comorbid medical conditions. J Clin Epidemiol 1994;47:809–815.
31. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926–1931.
32. Linn BS, Linn MW, Lee G. Cumulative Illness Rating Scale. J Am Geriatr Soc 1968;5:622–626.
33. Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. N Engl J Med 1998;21 (338):1516–1520.
34. Glynn RJ, Monane M, Gurwitz JH, et al. Aging, comorbidity, and reduced rates of drug treatment for diabetes mellitus. J Clin Epidemiol 1999;52:781–790.
35. Glynn RJ, Knight EL, Levin R, et al. Paradoxical relations of drug treatment with mortality in older persons. Epidemiology 2001;12:682–689.
36. Bravo G, Dubois MF, Hébert R, et al. A prospective evaluation of the Charlson Comorbidity Index for use in long-term care patients. J Am Geriatr Soc 2002;50:740–755.
37. Arbaje AI, Wolff JL, Yu Q, et al. Postdischarge environmental and socioeconomic factors and the likelihood of early hospital readmission among community-dwelling Medicare beneficiaries. Gerontologist 2008;48: 495–504.
38. Bellelli G, Magnifico F, Trabucchi M. Outcomes at 12 months in a population of elderly patients discharged from a rehabilitation unit. J Am Med Dir Assoc 2008;9:55–64.
39. Hall SF. A user's guide to selecting a comorbidity index for clinical research. J Clin Epidemiol 2006;59:849–855.

PAPER 4

Prospective comparison of six comorbidity indices as predictors of 5 years post hospital discharge survival in the elderly

Dina Zekry, Bernardo Hermont Loures Valle, Jean-Pierre Michel, Fabienne Esposito, Gabriel Gold, Karl-Heinz Krause, François R. Herrmann

Rejuvenation Research 2010;13:675-682

Due to the prospective design, it was possible to determine the accuracy of the same 6 comorbidity scores predicting long-term survival after discharge (five years mortality risk).

GIC class 4 and CIRS quartile 4 increased the risk of death by 4 and 3, respectively. After 5 years of discharge, approximately 80% of the high-score patients were already deceased, compared with <40% in the lowest scores.

When all variables were included in the full model while adjusting for age and sex, the CIRS quartile 4 (HR=2.00) remained the best predictor independently associated with 5-year mortality.

Our data suggests that the CIRS and the GIC are the best short term mortality predictors as well as long term mortality.

REJUVENATION RESEARCH
Volume 13, Number 6, 2010

DOI: 10.1089/rej.2010.1037

Prospective Comparison of Six Co-Morbidity Indices As Predictors of 5 Years Post Hospital Discharge Survival in the Elderly

Dina Zekry, M.D., Ph.D.,[1] Bernardo Hermont Loures Valle, M.D.,[1,3] Jean-Pierre Michel, M.D.,[1] Fabienne Esposito, M.S.,[1] Gabriel Gold, M.D.,[1] Karl-Heinz Krause, M.D.,[2] and François R. Herrmann, M.D., M.P.H.[1]

Abstract

Older patients often suffer from multiple co-morbid conditions. Few co-morbidity indices are valid and reliable in elderly patients and comparison between them is rare. Our objective was to compare the performance, relevance, and abilities of six widely used and validated co-morbidity indices—the Charlson Cumulative Illness Rating Scale–Geriatrics (CIRS), Index of Co-Existent Disease, Kaplan Scale, Geriatrics Index of Co-morbidity (GIC), and Chronic Disease Score—to predict 5 years of survival after hospital discharge. Data came from a prospective study with yearly follow up, conducted 2004–2009 in 444 patients (mean age 85 years; 74% female) discharged from the acute geriatric hospital of the Geneva University Hospitals. In univariate analysis, mortality was significantly associated with age; each supplementary year added 7% of additional risk; and with sex, being male increased the risk by 1.5-fold. The best prognostic predictor was the GIC class 4 followed by the CIRS quartile 4 multiplying the risk of death by 4 and 3, respectively. After 1 year of discharge, for both scores approximately 50% of the high-score patients were already deceased and 80% were deceased after 5 years, compared with <5% in the lowest scores after 1 year and <40% after 5 years. When we entered all of the significant independent variables in a stepwise backward analysis, the best multiple regression model retained the CIRS quartile 4 as the strongest risk predictor followed by the GIC class 4. We conclude that the CIRS and the GIC may improve hospital discharge planning as being useful for clinical decision-making purposes and for clinical research in older patients.

Introduction

Co-morbidity, a measure of an individual's underlying health status, is a key variable and has an important role in health-care use, clinical management, treatment decisions, discharge plan, prognosis of adverse outcomes, and survival estimates.[1,2] As a consequence, co-morbidity indices could be useful for both clinical decision-making purposes and for clinical research.[3] Elderly patients often suffer from multiple chronic conditions that individually and jointly increase the use of health services like hospitalization, as well as morbidity and mortality.[4] Hospital discharge planning and prognosis can help physicians and family members plan for the care of patients who may be at increased risk of adverse outcomes in the coming years, especially regarding discussions of goals of care, treatment preferences, advance planning, and clinical therapeutic options.[5–7] Therefore, hospitalization may present a key trigger point for identifying persons at greatest risk for mortality on the ensuing years after discharge.[8] Older patients with higher life expectancy may be more likely to benefit from some disease screening, like cancer, because recent guidelines recommend that clinicians target screening in patients with life expectancies greater than 5 years.[5–8]

Although several co-morbidity indices have proven useful for both patient classification in clinical research and prognostication in medical care, only some of them are valid and reliable for use as a measure of co-morbidity in elderly patients.[9,10] In addition, clinicians and researchers are faced with a wide range of indices, with surprisingly little information on the relative strengths and weaknesses of these tools.[3] Publications comparing the predictive performance of these indices are rare, especially in the elderly.

[1]Department of Rehabilitation and Geriatrics, Geneva University Hospitals and University of Geneva, Thônex, Switzerland.
[2]Pathology and Immunology Department, Geneva University Hospitals and University of Geneva, Geneva, Switzerland.
[3]Clementino Fraga Filho Hospital, Rio de Janeiro Federal University, Rio de Janeiro, Brazil.

The aim of this prospective study was to compare the performance and the value of six validated, widely used co-morbidity indices predicting 5 years of mortality after discharge and to identify a practical and valuable risk-prediction tool that could be applied in routine clinical practice. The study population was derived from a cohort of very old, acutely ill geriatric inpatients.

Methods

Patients and data collection

We carried out a prospective study in a geriatric hospital with 300 acute beds that is a part of Geneva University Hospitals, Switzerland. Patients and data collection have been described elsewhere.[11,12] Briefly, patients were recruited by clinically trained staff. All patients over 75 years of age and consecutively admitted between January, 2004, and December, 2005, were included. We used a computer-generated randomization table to select daily a random sample of patients. The local ethics committee approved the protocol, and patients, their families, or legal representatives provided signed, written informed consent. Demographic data for the patients studied did not differ significantly from data for all patients admitted to the geriatric hospital in 2004–2005.[11] Therefore, our sample was representative of all patients admitted to this hospital, demonstrating the reliability of the randomization procedure used in this study.

Medical history was recorded on a standardized form, and the same geriatrician carried out a comprehensive geriatric assessment on all patients. Annual follow up was carried out with the same assessment over a 5-year period.

Sociodemographic data

The data recorded included age, sex, native language, marital status, living arrangement, and educational level.

Cognitive diagnosis

The same neuropsychologist assessed all subjects for clinical dementia. The Mini-Mental State Examination (MMSE)[13] (scores 0–30) and the Short Cognitive Evaluation Battery were used.[14,15] On the basis of screening results, the neuropsychologist then carried out a comprehensive standardized neuropsychological assessment to determine the etiology and severity of clinical dementia, as previously described.[11]

Assessment of co-morbidity

We chose the six validated co-morbidity indices that were most widely used to assess the elderly. At the baseline assessment, the same geriatrician calculated all six scores for each patient via an extensive review of the patient's medical records and administrative data for diagnoses established at or before enrollment in this study and by standardized interviews with patients and surrogates.

Charlson Co-morbidity Index (CCI)[16]. The CCI is a list of 19 conditions; each is assigned a weighting (1–6). Weightings reflect the ability of each condition to predict 1-year mortality, as originally reported for cancer patients. They are fixed for each diagnosis and range from 1 (for conditions, such as myocardial infarction or mild liver disease, with a relative risk $\geq$1.2 and $<$1.5) to 6 (assigned to metastatic cancer, with a relative risk $\geq$6). The CCI is the sum of the weightings for all conditions observed in a patient; higher scores indicated greater co-morbidity.

Cumulative Illness Rating Scale—Geriatrics (CIRS)[17]. The CIRS identifies 14 items, corresponding to different systems. Each system is scored as follows: 1 (none), no impairment to that organ/system; 2 (mild), impairment does not interfere with normal activity; treatment may or may not be required; prognosis is excellent; 3 (moderate), impairment interferes with normal activity, treatment is needed, prognosis is good; 4 (severe), impairment is disabling, treatment is urgently needed, prognosis is guarded; 5 (extremely severe), impairment is life-threatening, treatment is urgent or of no avail; poor prognosis. The Illness Severity Index (summary score based on the average of all CIRS items, excluding psychiatric/behavioral factors) and the co-morbidity index (summary score based on a count of organ system with moderate or greater impairment, excluding psychiatric/behavioral) can then be calculated using these scores.

Index of Coexistent Diseases (ICED)[18]. The ICED is based on the presence and severity of 19 medical conditions and 11 physical impairments, using two scales: the Index of Disease Severity (IDS) and the Index of Physical Impairment (IPI). The final ICED score is determined by an algorithm combining the peak scores for the IDS and IPI. The ICED score ranges from 0 to 3 (four classes), reflecting increasing severity.

Kaplan Scale[19]. This index uses two forms of classification, focusing on the type of co-morbidity and the pathophysiologic severity of the co-morbid conditions present, respectively. The type of co-morbidity can be classified as vascular (hypertension, cardiac disorders, peripheral vascular disease, retinopathy, and cerebrovascular disease) or nonvascular (lung, liver, bone, and nondiabetic renal diseases). Pathophysiologic severity is rated on a four-point scale, ranging from 0 (co-morbidity is absent or easy to control) to 3 (recent full decompensation of co-morbid disease). The rating of the most severe condition determines the overall co-morbidity score. Scores for vascular and nonvascular co-morbidity can be calculated, based on the most severe condition in each subscale.

Geriatric Index of Co-morbidity (GIC)[20]. In computing the GIC, each of the 15 more prevalent clinical conditions (ischemic or organic heart diseases, primary arrhythmias, heart diseases with a nonischemic or nonorganic origin, hypertension, stroke, peripheral vascular diseases, diabetes mellitus, anemia, gastrointestinal diseases, hepatobiliary diseases, renal diseases, respiratory diseases, parkinsonism and nonvascular neurologic diseases, musculoskeletal disorders, malignancies) is graded on a 0–4 disease severity scale on the basis of the following general framework 0 = absence of disease, 1 = asymptomatic disease, 2 = symptomatic disease requiring medication but under satisfactory control, 3 = symptomatic disease uncontrolled by therapy, and 4 = life-threatening or the most severe form of the disease. The GIC classifies patients into four classes of increasing somatic co-morbidity. Class 1 includes patients who have

one or more conditions with a disease severity grade equal to or lower than 1. Class 2 includes patients who have one or more conditions with a disease severity grade of 2. Class 3 includes patients who have one condition with a disease severity of 3, other conditions having a disease severity equal to or lower than 2. Class 4 includes patients who have two or more conditions with a disease severity of 3 or one or more conditions with disease severity of 4.

Chronic Disease Score (CDS)[21]. This is a measure of co-morbidity obtained from a weighted sum of scores based on the use of 30 different classes of medication. An integer weight between 1 and 5 is given to each of the selected classes of medication; the overall score is then the sum of the weightings.

Outcome

The outcome of interest was death by December 31, 2009, which means there was 60 months (5 years) of follow up.

Statistical methods

We checked for the normal distribution of continuous scores (CCI, CIRS, Kaplan, and CDS) using skewness and kurtosis tests, and carried out standard transformations to normalize non-Gaussian variables. Because it was not possible to normalize these scores, they were categorized into quartiles to facilitate comparison with the four classes of the two other indices, ICED and GIC. Co-linearity among the six indexes was checked using Spearman rank correlation coefficient. Cox proportional hazards regression models was then carried out to take into account the time to the event using age, sex, and the six co-morbidity scores as independent variables and 5-year mortality as the dependent variable to identify the best predicting score for the outcome while adjusting for all the others. Hazard ratio (HR) and 95% confidence intervals (CI) were calculated. We then entered all the significant independent variables in a stepwise backward analysis to develop the best predictor model. We also used Kaplan–Meier survival curves to examine the performance of the six co-morbidity indices over time. The Cuzick nonparametric test for trend in survival across quartile of the indices was applied. Statistical analyses were performed with Stata software version 11 (College Station, TX).

Results

We included 444 patients in this study (mean age 85.3 ± 6.7; 74% female). A large number of different reasons for hospitalization were recorded, the most prevalent being falls and or fracture (139, 31%), pulmonary infection (55, 12.4%), cardiac failure (45, 10%), and delirium (39, 8.8%). Table 1 summarizes the frequency distribution of patients according to each co-morbidity score. Because there were no patients in the ICED classes 1 and 2, we considered only classes 3 and 4, providing binary data for the analyses. Likewise, only 2% of the patients were classified as class 1 by the GIC and were combined with class 2 for the analysis. For the other four indices, the distribution was almost equal between the four quartile ranges, with approximately 25% of the patients per range.

Univariate and multiple Cox proportional hazards modeling

Of the 444 patients, 264 died during the 5 years after discharge (59.5%). We first carried out a univariate Cox proportional hazard modeling analyses including age, sex, and the six co-morbidity indices tested predicting 5-year mortality after discharge. We then tested full multiple Cox proportional hazards models containing all the variables (Table 2). The Cuzick nonparametric test results for trend in survival across quartile were statistically significant ($p < 0.001$) for all indices except the CDS ($p = 0.117$).

In univariate analysis, mortality was significantly associated with age, each supplementary year added 7% of additional risk of death (HR = 1.07; 95% CI, 1.05–1.09); with sex, being male increased the risk by 1.5 fold (95% CI, 1.17–1.98). The best prognostic predictor was the GIC class 4 (HR = 3.85; 95% CI, 2.29–6.47) followed by the CIRS quartile 4 (HR = 3.17; 95% CI, 2.24–4.48). The CIRS quartile 3 (HR = 2.01; 95% CI, 1.42–2.84); the Kaplan scale quartile 4 (HR = 2.46; 95% CI, 1.75–3.45) and quartile 3: HR = 2.04; 95% CI, 1.36–3.05); the ICED (HR = 1.71; 95% CI, 1.23–2.37); the GIC class 3 (HR = 1.63; 95% CI, 1.01–2.66) the CCI quartile 4 (HR = 1.69;

Table 1. Quartile Range and Frequency of Six Co-Morbidity Scores

	Quartile / Classes							
	1		*2*		*3*		*4*	
Indices	*Score*	n *(%)*	*Score*	n *(%)*	*Score*	n *(%)*	*Score*	n *(%)*
CCI	0–3	165 (37)	4	91 (20)	5–6	91 (20)	7–14	97 (23)
CIRS	0–11	121 (27)	12–14	107 (24)	15–18	119 (27)	19–30	97 (22)
ICED[a]		0		0		93 (21)		351 (79)
Kaplan	0–2	128 (29)	3–4	156 (35)	5	55 (12)	6–16	105 (24)
GIC[a]		9 (2)		34 (8)		310 (70)		91 (20)
CDS	0–3	122 (28)	4–6	117 (26)	7–8	109 (24)	9–15	96 (22)

[a]Quartile ranges do not apply to ICED and GIC, because these indices are predefined into four classes. Data are expressed as number of cases (%).

CCI, Charlson Co-morbidity Index; CIRS, Cumulative Illness Rating Scale–Geriatrics; ICED, Index of Coexistent Diseases; Kaplan, Kaplan Scale; GIC, Geriatrics Index of Comorbidity; CDS, Chronic Disease Score.

Table 2. Univariate and Stepwise Backward Multiple Cox Regression Predicting 5-Year Mortality ($n = 444$)

	Univariate Cox regression			*Multiple Cox regression (full model)*			*Stepwise multiple Cox regression*		
				Independent variables					
Outcome	*Crude HR*	*95% CI*	p	*Adjusted HR*	*95% CI*	p	*Adjusted HR*	*95% CI*	p
Death at 5 years									
Age	**1.07**	1.04–1.09	**<0.001**	**1.06**	1.04–1.09	**<0.001**	**1.06**	1.04–1.08	**<0.001**
Male vs female	**1.52**	1.17–1.98	0.020	**1.53**	1.16–2.02	**0.002**	**1.54**	1.17–2.01	**0.002**
CCI									
Quartile 1	1.00	—	—						
Quartile 2	1.14	0.81–1.62	0.447	0.71	0.49–1.03	0.070			
Quartile 3	1.46	1.05–2.04	0.024	0.79	0.54–1.16	0.228			
Quartile 4	**2.49**	1.23–2.32	**0.001**	0.94	0.64–1.38	0.771			
CIRS									
Quartile 1	1.00	—	—	1.00	—	—	1.00	—	—
Quartile 2	1.15	0.79–1.69	0.464	1.00	0.66–1.50	0.990			
Quartile 3	**2.01**	1.42–2.84	**<0.001**	1.47	0.98–1.20	0.063	**1.58**	1.17–2.12	**0.003**
Quartile 4	**3.17**	2.24–4.48	**<0.001**	**2.00**	1.27–3.15	**0.003**	**2.19**	1.59–3.01	**<0.001**
ICED									
Class 1 + 2 + 3	1.00	—	—	—	—				
Class 4	**1.71**	1.23–2.37	**0.001**	1.22	0.86–1.74	0.271			
Kaplan									
Quartile 1	1.00	—	—	1.00	—	—			
Quartile 2	1.36	0.98–1.89	0.068	1.06	0.74–1.52	0.748			
Quartile 3	**2.04**	1.36–3.05	**0.001**	1.31	0.82–2.12	0.259			
Quartile 4	**2.46**	1.75–3.45	**<0.001**	1.28	0.82–1.99	0.270			
GIC									
Class 1 + 2	1.00	—	—	1.00	—	—	1.00	—	—
Class 3	**1.63**	1.00–2.66	**0.047**	1.12	0.65–1.95	0.675			
Class 4	**3.85**	2.29–6.47	**<0.001**	1.75	0.93–3.28	0.082	**1.71**	1.27–2.31	**<0.001**
CDS									
Quartile 1	1.00	—	—						
Quartile 2	1.12	0.80–1.57	0.497	0.92	0.64–1.31	0.639			
Quartile 3	1.16	0.83–1.64	0.384	0.95	0.66–1.38	0.808			
Quartile 4	1.38	0.98–1.94	0.979	1.02	0.69–1.49	0.933			

Bold entries indicate relevant results.

HR, Hazard ratio; CI, confidence interval; CCI, Charlson Co-morbidity index; CIRS, Cumulative Illness Rating Scale–Geriatrics; ICED, Index of Coexistent Diseases; Kaplan, Kaplan Scale; GIC, Geriatrics Index of Co-morbidity; CDS, Chronic Disease Score.

95% CI, 1.23–2.32) and quartile 3 (HR = 1.46; 95% CI, 1.05–2.04) performed in a similar manner increasing the risk of mortality by 1.5- to 2-fold. The CDS was not predictor of the outcome.

Kaplan–Meier survival curves of the six co-morbidity indices are shown in Fig. 1. The GIC class 4 and the CIRS quartile 4 were the best prognostic predictor of 5-year mortality, multiplying the risk of death by 4 and 3, respectively. For these two scores, after 1 year of discharge, approximately 50% of the high-score patients were already deceased, compared with <5% in the lowest scores. After 5 years, approximately 80% of the high-score patients were already deceased, compared with less than 40% in the lowest scores.

When all variables were included in the full model while adjusting for age and sex, the CIRS quartile 4 (HR = 2.00; 95% CI, 1.27–3.15) remained the best predictor independently associated with 5-year mortality. However, when we removed all the nonsignificant variables in a stepwise backward analysis, the best reduced multiple regression model retained the CIRS quartile 4 (HR = 2.19; 95% CI, 1.60–3.00) as the strongest risk predictor followed by the GIC class 4 (HR = 1.71; 95% CI, 1.28–2.30), the CIRS quartile 3 (HR = 1.58; 95% CI, 1.17–2.12); age (HR = 1.54; 95% CI, 1.17–2.01), and sex (HR = 1.06; 95% CI, 1.04–1.08).

Discussion

One of the main strengths of this study was the comprehensive and detailed assessment of the presence and extent of co-morbidity: The same medical doctor scored the six co-morbidity indices for all patients to ensure a high accuracy of scoring. To our knowledge, we carried out, for the first time, a prospective study in a very selected population of very old acutely ill geriatric inpatients. We compared the use of six co-morbidity indices, most of which have been widely used and validated in elderly subjects, for the prediction of 5-year mortality after discharge with a yearly follow up

In our prospective study, excluding the CDS, the others five co-morbidity indices were significantly associated with 5-year mortality in the univariate analysis. The CIRS provided the most accurate risk for 5-year mortality in the univariate as well as in the multiple regression model followed by the GIC. These results are consistent with other studies. Salvi et al. previously demonstrated the CIRS's

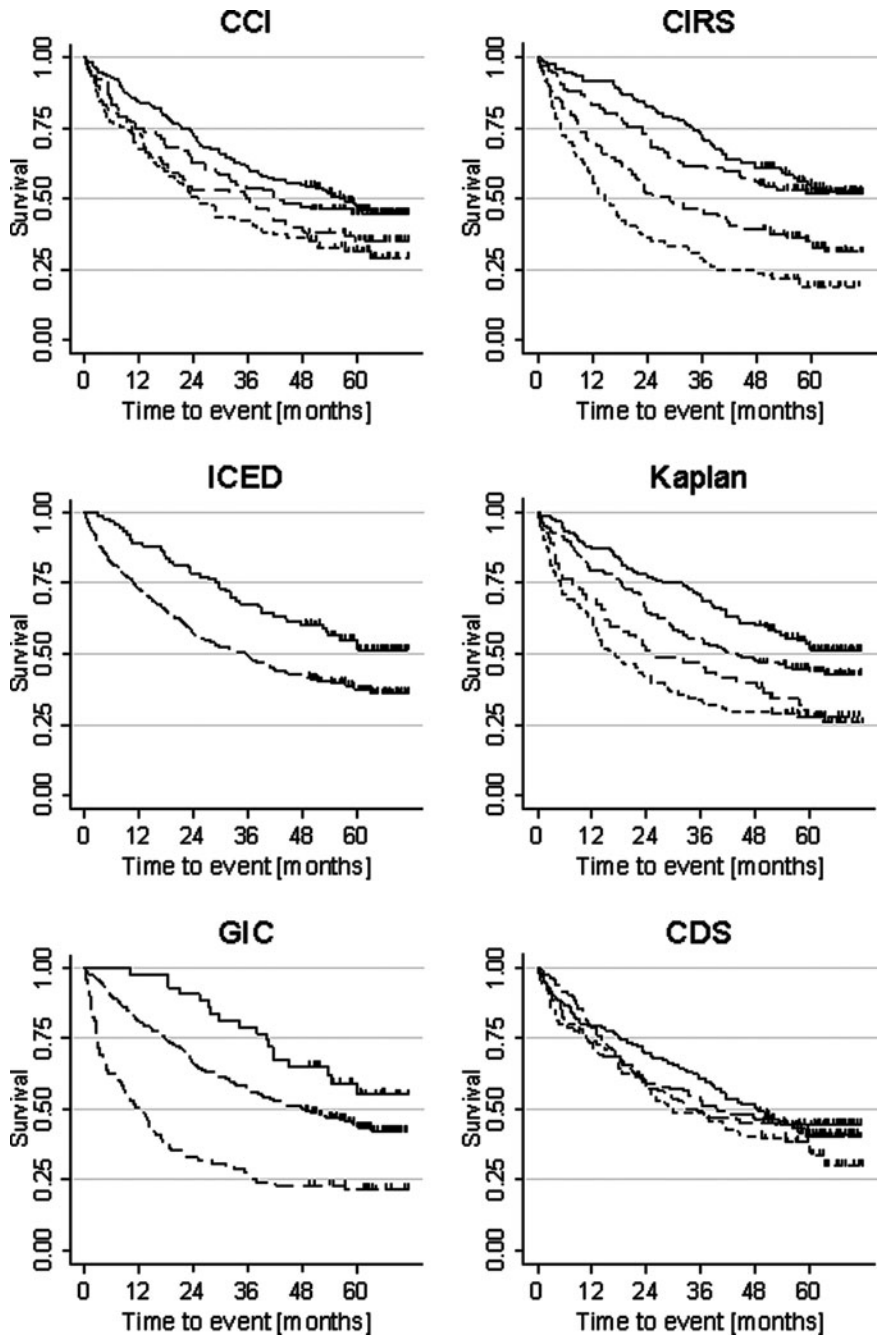


FIG. 1. Kaplan–Meier survival curves according to the six co-morbidity indices. Marks represent censored observations. CCI, Charlson Co-morbidity Index; CIRS, Cumulative Illness Rating Scale–Geriatrics; Kaplan, Kaplan Scale; CDS, Chronic Disease Score (quartile 1, black line; quartile 2, long dashed line; quartile 3, dashed line; quartile 4, short dashed line); ICED, Index of Coexistent Diseases (class 0, black line; 1, long dashed line; GIC, Geriatrics Index of Comorbidity (class 1–2, black line; 3, long dashed line; 4, dashed line).

ability to predict 18-month mortality and rehospitalization in a cohort of 387 patients aged 65 and older from an acute internal medicine ward.[22] Parmelee et al. showed a significant association between the CIRS and mortality, acute hospitalization, medication usage, laboratory test results, and functional disability among frail elderly institutionalized patients.[17] One advantage of the CIRS is its suitability for use in common clinical practice: It is based on measures of clinically relevant physiological systems and uses a clear and clinically sound ranking of severity. This index appears to be sufficiently reliable because it allows all of the co-morbid diseases from clinical examinations and medical files to be taken into account in a comprehensive manner.[23] The CIRS was based on the in-hospital mortality of a series of men in a southeastern U.S. veterans hospital in 1964. In the beginning, the CIRS was designed to estimate the total medical burden and survival capacity of elderly patients.[24] It has been converted to a co-morbidity index by removing the disease of

interest. On the other hand, the CIRS rates the severity of any given disease also on the basis of its impact on function and not exclusively on the basis of biological, clinical, or prognostic considerations. Thus, estimates of the severity of co-morbidity based upon CIRS are somewhat confounded by disability estimates, which is far from ideal in older patients, especially when assessing the impact of co-morbidity on new or worsening disability.

Similar to our results, previous studies confirmed the impact of the GIC index on the prediction of 6-month survival in a population of 1,402 hospitalized elderly patients (age 80.1 ± 7.1 years; 68% female) with chronic disability and consecutively admitted to an acute care unit in Italy.[20] As observed in our study, patients with GIC class 1 and 2 scores were not representative in this acute geriatric ward. In a Cox regression analysis, adjusting for factors associated with mortality in univariate models (low levels of serum albumin and cholesterol, anemia, dementia, chronic obstructive pulmonary disease, coronary heart disease, renal diseases, gastrointestinal diseases, advanced cancer) and taking class 2 as a reference, patients with GIC scores in class 4 had a risk of death three times higher than patients with the lowest scores.

The CCI was predictive of 5-year mortality only in the univariate analysis, losing its significance in the Cox regression model. The CCI is the most extensively studied co-morbidity index. It was designed and scaled to predict mortality based on the mortality of 607 patients admitted to a general internal medicine service in a single New England hospital during 1 month in 1984.[16] This index does not take into account the severity of certain major diseases, but only the presence of the disease. For example, in the case of congestive heart failure, patients with either a mild or a severe form of the disease will be assigned a score of 1. Therefore, this index may fail to identify important diseases, or their severity, in the elderly, which may otherwise act as predictors of adverse outcomes. On the contrary, certain pathological conditions, such as acquired immunodeficiency syndrome, are heavily weighted in the index yet rarely encountered in the elderly, whereas other highly elderly prevalent conditions, such as chronic heart failure, are probably underestimated. The CCI has previously been found to be limited in determining the full range of diseases in elderly patients, and very recently the CCI was not able to predict long-term mortality in elderly subjects with chronic heart disease.[23,25]

The ICED and the Kaplan index performed well in our univariate analyses for 5-year mortality, but lost all significance when all variables were controlled for. The Kaplan index was specifically developed for use in diabetes research and has been mostly used in oncology. The ICED was created to demonstrate that illness due to diseases other than the primary illness may affect the outcome of interest over the period of observation and has been applied in renal disease. Probably both these scores are less useful to assess co-morbidity in the elderly. The negative predictive value of the CDS, a medication-based score, is consistent with earlier findings and may be due to the use of preventive treatments or treatment for benign conditions in healthier patients. We have to point out that recently Johnson et al. updated and extended the CDS, now renamed the Rx-Risk-V, by adding 26 additional disease categories. This evolution of the basic score was specifically created for the elderly. In a large American national cohort of 260,321 outpatients, the pharmacy co-morbidity score further improved the prediction of 1-year mortality compared to the Deyo diagnosis-based co-morbidity index.[26]

Our data suggests that the CIRS and the GIC are the best 5-year mortality predictors. This is probably due to the fact that the CIRS as well as the GIC assumes that the impact of all diseases are additive. For these two scores, co-morbidity should take into account both the number of diseases and occurrence of very severe diseases as determinants of health.[20,22] The Kaplan Scale assumes that the single most severe illness will determine the prognosis. The ICED allows a high score in functional status severity to override a high disease severity score, and the CCI weights different severity categories having an impact on the patient's health. The type of scoring system based on additive effect is probably more appropriate to the elderly population.[27] As suggested by Fried, some diseases or conditions, in addition to having greater or lesser likelihoods of co-occurrence, may be synergistic in their effects.[28] Regarding the development of disability, Ettinger et al.[29] found that the risk posed by heart disease alone (odds ratio [OR] = 2.3) or by osteoarthritis alone (OR = 4.3) is considerably less than the risk posed by the combination of the two (OR = 13.6). Recently, the National Institute on Aging Comorbidity Task Force emphasized as central issues on co-morbidity tools on behalf of older persons the need to take into account coexisting and potentially synergistic diseases and their treatments, as well as the functional effect of each disease.[30–32] Currently, none of the existent indices consider the impact of specific combinations of co-morbid illnesses. There are few prognostic indices available combining co-morbid conditions and functional measures for predicting mortality after discharge in hospitalized older adults. Some existing models are applicable only to specific patient populations and specific diseases.[33–35] Others require the use of more lengthy formulas based on the knowledge of certain laboratory data and functional status,[36–38] are based on common geriatric syndromes,[39] or are a multidimensional prognostic index based on the comprehensive geriatric assessment.[40] Although these tools have been developed to target high-risk patients, their use has not been incorporated yet into routine medical practice.

This study has some limitations. First, subjects were assessed at a single site in a university hospital setting where we had no participant in ICED class 1 and 2 and in GIC class 1. This reflects a much compromised cohort of very ill inpatients. Second, patient co-morbidity data were collected only once during hospitalization at the beginning of the follow-up period, and the subject's status could have change over time but it is common practice to take advantage of this specific encounter of a person with the health-care system to collect data otherwise not available. Third, in this large patient cohort, there were different causes for patients' hospitalization, and each cause may vary in severity. As a consequence, these two factors could impact survival independently. Therefore, the generalizability of these results needs to be tested in other locations with different groups of patients and subgroups having more homogeneous hospitalization causes and severity. In addition, the co-morbidity indices tested do not include laboratory data or functional status. Functional status has been shown to be a formidable

predictor of health outcomes and a major health outcome by itself. Di Bari et al. have demonstrated in a longitudinal epidemiological survey in the entire population ($n = 633$) aged 65 and older living in Dicomano (mean age 74), a small rural town in Italy, that physical performance measures adds significantly to the prognostic value of any co-morbidity scale. They compared five different indices (four of which were the same as ours: CCI, ICED, GIC, and CDS), and all were shown to predict in these old community dwellers, although with different strengths, both incident disability (the original cohort was re-examined 4 years after the baseline) and mortality (9 years after the baseline by the city register office). The ICED performed better than the GIC and the CDS. The CIRS index was not applied in this study.[41]

In summary, the CIRS index provided an accurate method to identify older patients at high risk of 5-year mortality after a hospital stay followed by the GIC. Both indices are prognostic predictors and could be useful to guide clinicians regarding improvement on care and decisions at discharge. Given their validity and reliability, the GIC and the CIRS seem to provide useful measures of co-morbidity for clinical research and could assist researchers in selecting an effective index for the same outcome of interest.

Acknowledgments

We would like to thank the teams of Mrs. O. Baumer, L. Humblot, and M. Cos for technical assistance. This work was supported by grants from the Swiss National Science Foundation (3200B0-102069) and from the Swiss Foundation for Ageing Research (AETAS).

Author Disclosure Statement

No author received any consultancy fees or has any company holdings or patents. There are no conflicts of interest.

References

1. Guralnik JM. Assessing the impact of comorbidity in the older population. Ann Epidemiol 1996;6:376–380.
2. Boyd CM, Weiss CO, Halter J, Han KC, Ershler WB, Fried LP. Framework for evaluating disease severity measures in older adults with comorbidity. J Gerontol A Biol Sci Med Sci 2007;62:286–295.
3. Hall SF. A user's guide to selecting a comorbidity index for clinical research. J Clin Epidemiol 2006;59:849–855.
4. Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: A review. J Clin Epidemiol 2001;54:661–674.
5. Christakis NA. Death Foretold: Prophecy and Prognosis in Medical Care. University of Chicago Press, Chicago, 1999.
6. Lynn J. Serving patients who may die soon and their families: The role of hospice and other services. JAMA 2001; 285:925–932.
7. Lynn J, Teno JM, Harrell FE. Accurate prognostications of death: Opportunities and challenges for clinicians. West J Med 1995;163:250–257.
8. Levine SK, Sachs GA, Jin L, Meltzer D. A prognostic model for 1-year mortality in older adults after hospital discharge. Am J Med 2007;120:455–460.
9. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: A critical review of available methods. J Clin Epidemiol 2003;56:221–229.
10. Rozzini R, Sabatini T, Barbisoni P, Trabucchi M. How to measure comorbidity in elderly persons. J Clin Epidemiol 2004;57:321–322.
11. Zekry D, Herrmann FR, Grandjean R, Meynet MP, Michel JP, Gold G, Krause KH. Demented versus non-demented very old inpatients: The same comorbidities but poorer functional and nutritional status. Age Ageing 2008;37: 83–89.
12. Zekry D, Herrmann FR, Grandjean R, Vitale AM, De Pinho MF, Michel JP, Gold G, Krause KH. Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients. Int J Geriatr Psychiatry 2009;24:283–291.
13. Folstein MF, Folstein SE, MacHugh PR. Mini Mental State: A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
14. Solomon PR, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux RD, Pendlebury WW. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998;55:349–55.
15. Robert PH, Schuck S, Dubois B, Olié JP, Lépine JP, Gallarda T, Goni S, Troy S; Investigators' Group. Screening for Alzheimer's disease with the Short Cognitive Evaluation Battery. Dement Geriatr Cogn Disord 2003;15:92–98.
16. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
17. Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the cumulative illness rating scale in a geriatric residential population. J Am Geriatr Soc 1995;43:130–137.
18. Greenfield S, Sullivan L, Dukes KA, Silliman R, D'Agostino R, Kaplan SH. Development and testing of a new measure of case-mix for use in office practice. Med Care 1995;33:AS47–AS55.
19. Kaplan MH, Feinstein A. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 1974;27:387–404.
20. Rozzini R, Frisoni GB, Ferrucci L, Barbisoni P, Sabatini T, Ranieri P, Guralnik JM, Trabucchi M. Geriatric Index of Comorbidity: Validation and comparison with other measures of comorbidity. Age Ageing 2002;31:277–285.
21. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992;45:197–203.
22. Salvi F, Miller MD, Grilli A, Giorgi R, Towers AL, Morichi V, Spazzafumo L, Mancinelli L, Espinosa M, Rappelli A, Dessí-Fulgheri P. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926–1931.
23. Harboun M, Ankri J. Comorbidity indexes: Review of the literature and application to studies of elderly population. Rev Epidemiol Sante Publique 2001;49:287–298.
24. Linn BS, Linn MW, Lee G. Cumulative Illness Rating Scale. J Am Geriatr Soc 1968;5:622–626.
25. Testa G, Cacciatore F, Galizia G, Della-Morte D, Mazzella F, Russo S, Ferrara N, Rengo F, Abete P. Charlson Comorbidity Index does not predict long-term mortality in elderly subjects with chronic heart failure. Age Ageing 2009;38:734–740.
26. Johnson ML, El-Serag HB, Tran TT, Hartman C, Richardson P, Abraham NS. Adapting the Rx-Risk-V for mortality

prediction in outpatient populations. Med Care 2006;44: 793–797.
27. Wieland GD. From Bedside to Bench: Research in comorbidity and aging. Sci Aging Knowl Environ 2005;39: 29–33.
28. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G: Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004; 59:255–263.
29. Ettinger WH, Davis MA, Neuhaus JM, Mallon KP. Long-term physical functioning in persons with knee osteoarthritis from NHANES. I: Effects of comorbid medical conditions. J Clin Epidemiol 1994;47;809–815.
30. Yancik R, Ershler W, Satariano W, Hazzard W, Cohen HJ, Ferrucci L. Report of the national institute on aging task force on comorbidity. J Gerontol A Biol Sci Med Sci 2007; 62:275–280.
31. Lash TL, Mor V, Wieland D, Ferrucci L, Satariano W, Silliman RA. Methodology, design, and analytical techniques to address measurement of comorbid disease. J Gerontol A Biol Sci Med Sci 2007;62A:281–285.
32. Karlamangla A, Tinetti M, Guralnik J, Studenski S, Wetle T, Reuben D. Comorbidity in older adults: Nosology of impairment, diseases, and conditions. J Gerontol A Biol Sci Med Sci 2007;62A:296–300.
33. Muers MF, Shevlin P, Brown J. Prognosis in lung cancer: Physicians' opinions compared with outcome and a predictive model. Thorax 1996;51:894–902.
34. Morita T, Tsunoda J, Inoue S, Chihara S. Survival prediction of terminally ill cancer patients by clinical symptoms: Development of a simple indicator. J Clin Oncol 1999;29: 156–159.
35. Fillenbaum GG, Pieper CF, Cohen HJ, Cornoni-Huntley JC, Guralnik JM. Comorbidity of five chronic health conditions in elderly community residents: determinants and impact on mortality. J Gerontol 2000;55:M84–M89.
36. Walter LC, Brand RJ, Counsell SR, Palmer RM, Landefeld CS, Fortinsky RH, Covinsky KE. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. JAMA 2001;285:2987–2993.
37. Teno JM, Harrell FE, Knaus WA, Phillips RS, Wu AW, Connors A Jr, Wenger NS, Wagner D, Galanos A, Desbiens NA, Lynn J. Prediction of survival for older hospitalized patients; the HELP survival model. J Am Geriatr Soc 2000; 48(Suppl):S16–S24.
38. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 1998; 279:1187–1193.
39. Anpalahan M, Gibson SJ. Geriatric syndromes as predictors of adverse outcomes of hospitalization. Int Med J 2008;38: 16–23.
40. Pilotto A, Ferrucci L, Franceschi M, D'Ambrosio LP, Scarcelli C, Cascavilla L, Paris F, Placentino G, Seripa D, Dallapiccola B, Leandro G. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. Rejuvenation Res 2008;11:151–161.
41. Di Bari M, Virgillo A, Matteuzzi D, Inzitari M, Mazzaglia G, Pozzi C, Geppetti P, Masotti G, Marchionni N, Pini R. Predictive validity of measures of comorbidity in older community dwellers: The Insufficienza Cardiaca negli Anziani Residenti a Dicomano Study. J Am Geriatr Soc 2006;54:210–216.

Address correspondence to:
Dr. Dina Zekry
Department of Rehabilitation
and Geriatrics Geneva University Hospitals
3, chemin du Pont-Bochet
Thônex, Switzerland.

E-mail: dina.zekry@hcuge.ch

Received: February 10, 2010
Accepted: May 28, 2010

PAPER 5

Does dementia predict adverse hospitalization outcomes ? A prospective study in aged inpatients

Dina Zekry, François R. Herrmann, Raphael Grandjean, Ana-Maria Vitale,
Maria-Fatima De Pinho, Jean-Pierre Michel, Gabriel Gold, Karl-Heinz Krause

Int J Geriatr Psychiatry 2009;24:283-291

The aim of this paper was to evaluate, in the same population, the relative contributions of accurate diagnosis of dementia, its aetiology and severity, when taking into account comorbidity, functional and nutritional status to predict adverse hospitalization outcomes: death in hospital, longer length of stay, higher rates of institutionalization and increase formal home care needs.

Moderate and severe dementia and poor physical function strongly predicted longer hospital stay (> 32 days), institutionalization and greater home care needs in univariate analyses. Moreover, comorbidity score was the best single predictor, with a four-fold difference in mortality rates between the highest and lowest scores.

In multivariate analysis, dementia was the best predictor of institutionalization and, comorbid conditions, the best predictor of death in hospital. Comorbidity score and functional status were independent predictors of a longer stay in hospital, regardless of cognitive status. Functional status, regardless of cognitive status, was the best predictor of greater home care needs.

Dementia in very old medically ill inpatients was predictive only of discharge to a nursing home. We have demonstrated that higher levels of comorbidity and poor functional status were more predictive than dementia for intra-hospital death, longer hospitalization and increase of formal care needs.

INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2009; **24**: 283–291.
Published online 26 August 2008 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/gps.2104

Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients

Dina Zekry[1]*, François R. Herrmann[1], Raphael Grandjean[1], Ana-Maria Vitale[1], Maria-Fatima De Pinho[1], Jean-Pierre Michel[1], Gabriel Gold[1] and Karl-Heinz Krause[2]

[1]*Rehabilitation and Geriatrics Department, Geneva University, Thônex, Switzerland*
[2]*Pathology and Immunology Department, Geneva University, Geneva, Switzerland*

SUMMARY

Background Dementia is often considered a predictor of adverse hospitalization outcomes. However, the relative contributions of dementia and other risk factors remain unclear.

Objective To assess, in a prospective study, the relative value of dementia for predicting hospitalization outcomes, taking into account comorbidity, functional and nutritional status in 435 inpatients (age 85.3 ± 6.7; 207 cognitively normal, 48 with mild cognitive impairment and 180 demented) from the acute and rehabilitation geriatric hospital of Geneva. Hospitalization outcomes (death in hospital, length of stay, institutionalisation and formal home care needs) were predicted using logistic regression models with sociodemographic characteristics, cognitive status, comorbid Charlson index-CCI, functional and nutritional status as independent variables.

Results Moderate and severe dementia and poor physical function strongly predicted longer hospital stay, institutionalization and greater home care needs in univariate analyses. CCI was the best single predictor, with a four-fold difference in mortality rates between the highest and lowest scores. In multivariate analysis, the best predictor of institutionalisation was dementia, whereas the best predictor of death in hospital or longer hospital stay was higher comorbidity score, regardless of cognitive status. Functional status was the best predictor of greater home care needs.

Conclusions Dementia in very old medically ill inpatients was predictive only of discharge to a nursing home. Higher levels of comorbidity and poor functional status were more predictive than dementia for the other three hospitalization outcomes. Thus, comorbid medical conditions, functional and nutritional status should be considered, together with cognitive assessment, when predicting hospitalization outcome. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — dementia; Alzheimer's disease; aged; elderly; hospitalization outcomes

INTRODUCTION

In older people living at home, cognitive impairment is associated with adverse health outcomes (poor functional and nutritional status, lower survival rates and higher rates of institutionalization) (Aguero-Torres *et al*., 1998a,b; Ramos *et al*., 2001; Stump *et al*., 2001; Mehta *et al*., 2002; Soto *et al*., 2006). Cognitive impairment is also often used as a predictor of poorer hospitalization outcomes but without taking into account comorbid medical conditions, functional and nutritional status (Bertozzi *et al*., 1996; Inouye *et al*., 1998; Di Iorio *et al*., 1999; Fogel *et al*., 2000; Marengoni *et al*., 2004; Lang *et al*., 2006). In addition, in most of these studies, 'cognitive impairment' was defined based on MMSE score alone, with no accurate diagnosis of dementia, its etiology and severity (Folstein *et al*., 1975). Thus, the relative contributions of a full, accurate dementia diagnosis and of other risk factors to the prediction of adverse hospitalization outcomes remain unclear. We carried out a prospective study in a cohort of very old, acutely ill geriatric inpatients for whom accurate cognitive assessments were systematically carried out. This made it possible to evaluate the relative contributions of cognitive impairment, comorbidity, functional and nutritional

*Correspondence to: Dr. D. Zekry, Rehabilitation and Geriatrics Department Geneva University, 3, chemin du Pont-Bochet, Thônex, Switzerland. E-mail: dina.zekry@hcuge.ch

Received 18 February 2008
Accepted 17 July 2008

status to the prediction of adverse hospitalization outcomes.

METHODS

Patients and data collection

We carried out a prospective study in a 300 beds acute and rehabilitation geriatric hospital (HOGER) of the University Hospitals of Geneva, Switzerland. Patients and data collection have been described elsewhere (Zekry *et al*., 2008). Briefly, patients were recruited by clinically trained staff. All patients over the age of 75 years consecutively admitted on selected days between January 2004 and December 2005 were included. We selected a random sample of patients for each day, using a computer-generated randomization table. The exclusion criteria were disorders interfering with psychometric assessment (severe deafness or blindness, or major behavioral problems) and terminal illness. The local ethics committee approved the protocol and patients or their families or legal representatives gave signed written informed consent. The demographic data for the patients studied did not differ significantly from those for all patients admitted to the HOGER in 2004–2005. Our sample was therefore representative of all the patients admitted to this hospital, demonstrating the high quality of randomization in this study.

Medical history was recorded on a standardized form and the same geriatrician carried out physical examinations on all patients. Annual follow-up over a 4-year period, with the same assessment carried out each year, was planned in the study protocol.

Sociodemographic data

The data recorded included age, sex, native language, marital status, living conditions and educational level ($1 = \leq 11$; $2 = 12$–14; $3 \geq 15$ years of schooling).

Cognitive diagnosis

The same neuropsychologist assessed all subjects for clinical dementia, at least one week after admission, to avoid the effects of concomitant delirium. The MMSE (scores 0–30) and The Short Cognitive Evaluation Battery (Solomon *et al*., 1998; Robert *et al*., 2003) were used. Based on screening results, the same neuropsychologist carried out a comprehensive standardized neuropsychological assessment, to determine the etiology and severity of clinical dementia as previously described (Zekry *et al*., 2008). Dementia severity was assessed with the Clinical Dementia Rating (CDR) (Morris, 1993) (0.5 indicates mild cognitive impairment (MCI) (Petersen *et al*., 1999), 1, mild, 2, moderate and 3, severe dementia). The formal clinical criteria used for diagnosis were those of the DSM IV-TR (American Psychiatric Asoociation, 2000), NINCDS-ADRDA (Mckahnn *et al*., 1984), ADDTC (Chui *et al*., 1992) and NINDS-AIREN (Roman *et al*., 1993). Cerebral imaging was also carried out. Patients were then assigned to one of three groups: (i) normal cognition; (ii) MCI and (iii) dementia of various types.

Comorbidity

The Charlson Comorbidity Index (CCI) is a weighted index that takes into account the number and severity of comorbid conditions (Charlson *et al*., 1987). The same geriatrician calculated the CCI for each patient, by extensive review of the patient's medical records for diagnoses established at or before enrolment in this study. Higher scores indicated greater comorbidity. The aim was to assess the relative contribution of cognitive impairment to the prediction of adverse outcomes. For this reason, dementia was not included in the calculation of CCI or comorbidity.

Functionality

Base and Instrumental Activities of Daily Living (ADL, IADL) (Katz *et al*., 1963; Lawton and Brody, 1969) scores were determined as a function of patient status 2 weeks before admission, based on the patient's medical history or information supplied by an informal or formal carer. ADL assesses ability to manage activities such as bathing, dressing, going to the toilet, continence, feeding, and transfer (6 items). IADL assesses ability to use the telephone, to shop, to use transport, to cook, to do housework, to take medication and to handle finances (8 items). For both scales, 0 indicates total dependence and the maximum score (6 or 8) indicates total independence.

Nutritional assessment

Body mass index (BMI) was determined and the short version of the Mini Nutritional Assessment (MNA) (score ranging from 0–14, $\geq = 12$ normal) administered on admission, by the same nurse in each case (Rubenstein *et al*., 2001).

Hospitalization outcomes

Hospital stays greater than the median value, death in hospital, changes in living conditions at discharge

DOI: 10.1002/gps

(institutionalization), and an increase in formal home care were considered. Increase in formal home care was calculated based on the number of extra hours of formal help required each week (nurses, care assistants, cleaning ladies, meal deliveries).

Statistical methods

We checked the normality of the data by carrying out skewness and kurtosis tests, and carried out standard transformations to normalize non-Gaussian variables. Data for continuous variables are presented as means $\pm$ 1 standard deviation (SD) and as median $\pm$ inter quartile range (IQR).

Univariate analysis was performed to identify independent risk factors associated with each hospitalization outcome. Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated. The variables assessed as possible predictors included age, sex, cognitive diagnosis (normal, MCI, or dementia diagnosis and etiology), dementia severity, comorbidity, functional and nutritional status before admission (ADL, IADL and MNA scores) and BMI at admission. Multiple logistic regression analysis was then carried out to assess interactions between variables. Continuous variables were either included as such or dichotomized, using the lower cutoff value (ADL, IADL and MNA). Statistical analyses were performed with Stata software version 9.2.1.

RESULTS

In total, 49 of the 556 patients randomized (8.8%) were not eligible. Of these patients, 61 (10.9%) refused to participate (the patient in 58 cases and the family in three cases).

MCI was diagnosed in 48 of the 446 patients included, and dementia was diagnosed in 191: 77 cases of AD, 21 of vascular dementia (VaD), 82 of mixed dementia (MD), and 11 of other types of dementia. This last group was excluded from the analysis due to its heterogeneity and small size. Our analysis was therefore based on a cohort of 435 patients (mean age 85.3 $\pm$ 6.7; 74% women).

Table 1 summarizes demographic and pre-admission characteristics, and scores on admission and at discharge as a function of cognitive status. The groups compared were similar in age, sex and education level (demented patients were slightly older). Non demented patients were more likely to live alone, and demented patients were more likely to live in a nursing home ($p = 0.003$). Premorbid ADL, IADL and MNA scores and BMI on admission decreased with cognitive status. Patients with MCI had higher scores than demented patients and behaved more like non demented patients. CCI differed significantly between patients of different cognitive status. After Bonferroni correction for multiple comparisons, the demented group differed significantly from the others ($p = 0.029$). Hospital mortality rates were similar in all three groups. The duration of hospitalization and the likelihood of a change in living conditions (institutionalization rate) increased with cognitive impairment.

Table 2 shows demographic data for patients with the various types of dementia. Patients in the VaD group tended to be younger than other demented patients. They were also more likely to be male and had the highest average comorbidity score ($p < 0.001$) and BMI at admission ($p = 0.022$).

The prevalence of comorbid medical conditions was similar ($p = 0.173$) in patients with mild (mean 4.37 $\pm$ 2.4), moderate (mean 5.3 $\pm$ 3.0) and severe (mean 4.55 $\pm$ 2.1) dementia.

Univariate and multiple logistic regression analysis

Table 3 shows univariate and multiple logistic regression analyses, adjusted for age, sex and education level, including all the potentially predictive variables tested: presence or absence of dementia, dementia aetiology, dementia severity (treated as a dichotomous variable; CDR 0.5–1 = mild; CDR 2–3 = moderate to severe dementia), comorbidity score, functional scores and nutritional scores.

Length of stay (longer than the median = 32 days)

In univariate analysis, moderate and severe dementia, particularly of the AD or MD type, and poor physical function were found to be independent predictors of a longer stay in hospital (differences of two- to four-fold). The introduction of all variables eliminated this association, with only comorbidity score remaining statistically significant and accounting for 6% of the variability of this outcome.

Death in hospital

In univariate analysis, mortality was significantly associated (four-fold difference) with high CCI and poor nutritional status. Similar results were obtained if all variables were included in the model. Higher comorbidity scores and lower body mass index accounted for 19% of the variance of this outcome, and this relationship was independent of cognitive

DOI: 10.1002/gps

Table 1. Sociodemographic data, clinical features, hospitalization correlates and outcomes as a function of cognitive impairment diagnosis

Characteristics	Demented ($n=180$)		MCI ($n=48$)		Non-demented ($n=207$)		p-value*
Demographics and prehospitalization characteristics							
Age[a]	86.3	6.27	85.0	6.59	84.5	7.02	0.029
Female[b]	130	72.2%	40	83.3%	152	73.4%	0.286
Education (years)[b]							0.349
level 1	100	55.6%	31	64.6%	124	59.9%	
level 2	60	33.3%	10	20.8%	66	31.9%	
level 3	20	11.1%	7	14.6%	17	8.2%	
Prior living conditions[b]							0.003
Alone	98	54.4%	24	50.0%	133	64.2%	
With family	14	7.8%	5	10.4%	15	7.3%	
With spouse	45	25.0%	11	22.9%	46	22.2%	
Nursing home	15	8.3%	1	2.1%	2	1.0%	
In protected housing	8	4.4%	7	14.6%	11	5.3%	
Functional status[a]							
Premorbid ADL	4.51	1.31	4.99	1.14	5.27	0.86	<0.001
Premorbid IADL	3.47	2.26	4.60	2.02	5.33	2.01	<0.001
Assessment at admission							
BMI[a]	23.45	4.96	24.53	5.23	24.71	5.02	0.040
MNA[a]	8.72	2.66	9.19	2.95	9.72	2.77	0.002
CCI[a]	3.88	2.44	3.79	2.73	4.60	2.90	0.036
Hospitalization outcomes							
Institutionalization[b]	37	20.1%	4	8.3%	17	8.2%	0.001
Length of stay (days)[c]	41.50	45.0	31.0	23.0	29.0	29.0	<0.001
Death in hospital[b]	7	3.9%	3	6.3%	12	5.8%	0.641

[a]Data are expressed as means ± SD.
[b]number of cases (%).
[c]Data are expressed as median ± IQR.
*p-value of Kruskal Wallis tests or analysis of variance comparing three groups.
ADL = Activities of Daily Living (Katz *et al*., 1963); BMI = body mass index; CCI = The Charlson Comorbidity Index (Charlson *et al*., 1987); IADL = Instrumental Activities of Daily Living (Lawton *et al*., 1969); MCI = Mild cognitive impairment (Petersen *et al*., 1999); MNA = Mini Nutritional Assessment (Rubenstein *et al*., 2001).

status. CCI was the predictor most strongly associated with death in hospital, with a four-fold difference in adverse outcome rates between patients with the highest and lowest scores.

Institutionalization and changes in formal home care

Moderate to severe dementia, particularly of the AD or MD type, and dependence in base and instrumental activities of daily living were independent predictors of institutionalization and increase in formal home care. In the multivariate model, severely demented patients (regardless of aetiology) were four times more likely to be institutionalized. Patients with poor functional status (lowest base activities of daily living scores) were twice as likely to need an increase in formal home care or institutionalization.

DISCUSSION

This series of elderly inpatients (mean age of 85 years) was representative of the overall population of patients hospitalized in this geriatric hospital. The prevalence of dementia (44%) was very high. The prevalence of dementia in elderly inpatients (acute geriatric wards) has been reported to be between 20 and 30%. A previous study carried out 6 years ago in the same hospital reported a prevalence of 30%. The difference between these two studies in the same hospital is statistically significant ($p<0.001$) (Herrmann *et al*., 1999). These findings probably reflect the systematic and complete assessment of cognitive impairment in the random sample used to determine the prevalence of dementia. The inclusion of a large number of patients with dementia in this study was useful, as it made it possible to measure the impact of dementia on hospitalization outcomes.

One of the main strengths of this study is that the same neuropsychologist carried out a systematic and complete neuropsychological assessment of all patients, increasing the accuracy of cognitive diagnosis. In most studies of hospitalization outcomes in the elderly, cognition has been assessed with the MMSE alone. The MMSE is neither sensitive nor

DOI: 10.1002/gps

Table 2. Sociodemographic data, clinical features, hospitalization correlates and outcomes as a function of dementia etiology

Characteristics	Alzheimer's disease ($n=77$)		Mixed dementia ($n=82$)		Vascular dementia ($n=21$)		p-value*
Demographics and prehospitalization characteristics							
Age[a]	86.3	6.37	87.0	5.75	83.3	7.3	0.055
Female[b]	63	81.8%	59	72.0%	8	38.1%	<0.001
Education (years)[b]							0.435
level 1	45	58.4%	43	52.4%	12	57.1%	
level 2	20	26.0%	32	39.0%	8	38.1%	
level 3	12	15.6%	7	8.5%	1	4.8%	
Prior living conditions[b]							0.933
Alone	43	55.8%	45	54.9%	10	47.6%	
With family	4	5.2%	8	9.8%	2	9.5%	
With spouse	19	24.7%	20	24.4%	6	28.6%	
Nursing home	6	7.8%	7	8.5%	2	9.5%	
In protected housing	5	6.5%	2	2.4%	1	4.8%	
Functional status[a]							
Premorbid ADL	4.59	1.33	4.51	1.21	4.21	1.62	0.514
Premorbid IADL	3.57	2.30	3.29	2.20	3.05	2.50	0.642
Assessment at admission							
BMI[a]	23.5	4.57	22.73	4.92	26.07	5.78	0.022
MNA[a]	8.78	2.52	8.45	2.82	9.57	2.44	0.221
CCI[a]	3.22	2.40	4.15	2.30	5.29	2.43	<0.001
Hospitalization outcomes							
Institutionalization[b]	19	24.7%	14	17.1%	4	19.1%	0.487
Length of stay (days)[c]	37.0	37.0	47.5	53.0	36.0	29.0	0.457
Death in hospital[b]	1	1.3%	5	6.1%	1	4.8%	0.287

[a]Data are expressed as means ± SD.
[b]number of cases (%).
[c]Data are expressed as median ± IQR.
*p-value of Kruskal Wallis tests or analysis of variance comparing three groups.
ADL = Activities of Daily Living (Katz *et al*., 1963); BMI = body mass index; CCI = The Charlson Comorbidity Index (Charlson *et al*., 1987); IADL = Instrumental Activities of Daily Living (Lawton *et al*., 1969); MNA = Mini Nutritional Assessment (Rubenstein *et al*., 2001).

specific for detecting dementia in a very old population and, furthermore, does not distinguish between different types of dementia. We also studied a group of patients with MCI in addition to the demented and non demented groups. These patients behaved more like patients with normal cognition than demented patients.

In the univariate model, dementia was an independent predictor of longer stay in hospital, institutionalization and increase in formal home care. Taking the other covariables into account had two interesting effects. Firstly, moderate to severe dementia remained the best predictor for institutionalization. Sands *et al*. (2003) obtained similar results for a cohort of 2,557 patients from two teaching hospitals. They showed, in multivariate repeated measures analyses of basic and instrumental activities of daily living and mobility on admission, that patients with impaired cognitive performance were more likely to be admitted to a nursing home for the first time within 90 days of discharge. Secondly, comorbid medical conditions were the most predictive indicator of length of stay in hospital, regardless of cognitive status. Functional status was the best predictor of an increase in formal home care. Fogel *et al*. (2000) showed that functional variables were most predictive of the length of stay in hospital in a prospective cohort study of 322 hospitalized patients aged 65 years or older transferred from the emergency department to medical wards. In this study, the authors did not take into account comorbidity or nutritional status. Similarly, in a cohort of 1,745 elderly patients consecutively admitted to a geriatric ward, length of stay was not found to be related to severe cognitive impairment. However, this conclusion was drawn from the results of univariate analysis (Molaschi *et al*., 2001). Other studies have reported a relationship between cognitive impairment and length of stay in hospital (Di Iorio *et al*., 1999; Lang *et al*., 2006; Soto *et al*., 2006). However, cognitive impairment was assessed with the MMSE only and no account was taken of its aetiology or severity. In a prospective multicenter cohort study

DOI: 10.1002/gps

Table 3. Univariate and multivariate logistic regression including all variables for predictors of the 4 adverse hospitalization outcomes (length of stay greater than the median, in-hospital mortality, changes in living conditions and in formal home care ($n = 435$)

Outcomes	Characteristics	Univariate logistic regression				Multiple logistic regression			
		Crude OR	95% CI	*p*	pseudo R^2	Adjusted OR	95% CI	*p*	pseudo R^2
Length of stay									**0.057**
	Age[a]	1.03	0.99–1.06	0.063	0.006	1.02	0.99–1.05	0.253	
	Male *vs* female	0.98	0.64–1.50	0.942	0.000	0.90	0.56–1.42	0.626	
	Type of dementia				0.033				
	Normal cognition	1.00	—	—		1.00	—	—	
	MCI	1.31	0.70–2.48	0.395		0.60	0.20–1.82	0.366	
	AD	2.07	1.22- 3.53	**0.007**		0.93	0.33–2.66	0.898	
	VaD	2.53	1.00–6.37	**0.049**		*	*	*	
	MD	2.84	1.67–4.84	<**0.001**		1.16	0.41–3.28	0.777	
	Severity of dementia				0.029				
	Normal cognition	1.00	—	—		1.00	—	—	
	CDR 0.5–1	1.80	1.16–2.80	**0.008**		2.12	0.79–5.69	0.134	
	CDR 2–3	2.75	1.66–4.54	<**0.001**		2.15	0.75–6.22	0.156	
	CCI	1.30	0.99–1.70	**0.048**	0.006	1.36	1.01–1.83	**0.043**	
	ADL	0.53	0.36–0.80	**0.002**	0.015	0.78	0.48–1.25	0.303	
	IADL	0.49	0.33–0.70	<**0.001**	0.021	0.78	0.48 -1.28	0.328	
	BMI	1.01	0.97–1.05	0.610	0.000	1.03	0.98–1.08	0.169	
	MNA	0.95	0.89–1.02	0.136	0.004	0.96	0.89–1.04	0.333	
Death in hospital									**0.186**
	Age[a]	1.08	1.00–1.16	**0.029**	0.027	1.08	0.99–1.17	0.086	
	Male *vs* female	1.07	0.41–2.81	0.888	0.001	0.81	0.27–2.39	0.700	
	Type of dementia				0.021				
	Normal cognition	1.00	—	—		1.00	—	—	
	MCI	1.08	0.29–3.99	0.904		1.56	0.11–22.52	0.746	
	AD	0.21	0.03–1.67	0.142		0.20	0.01–3.81	0.286	
	VaD	0.81	0.10–6.58	0.846		*	*	*	
	MD	1.06	0.36–3.09	0.360		0.70	0.07–7.30	0.762	
	Severity of dementia				0.005				
	Normal cognition	1.00	—	—		1.00	—	—	
	CDR 0.5–1	0.63	0.22–1.83	0.396		0.83	0.07–9.59	0.884	
	CDR 2–3	0.91	0.31–2.67	0.868		1.28	1.12 -13.52	0.837	
	CCI	3.75	1.88–7.45	<**0.001**	0.090	3.93	1.86–8.29	<**0.001**	
	ADL	0.87	0.36–2.12	0.759	0.000	1.26	0.43 -3.70	0.672	
	IADL	0.55	0.23–1.30	0.179	0.010	0.58	0.20–1.70	0.323	
	BMI	0.87	0.79–0.97	**0.007**	0.042	0.88	0.78–0.99	**0.037**	
	MNA	0.90	0.77–1.05	0.174	0.011	1.00	0.84–1.20	0.985	
Institutionalization									**0.079**
	Age[a]	1.04	0.99–1.08	0.078	0.009	1.03	0.98–1.08	0.260	
	Male *vs* female	0.99	0.52–1.87	0.983	0.000	1.03	0.52–2.04	0.935	
	Type of dementia				0.044				
	Normal cognition	1.00	—	—		1.00	—	—	
	MCI	1.02	0.33–3.17	0.978		0.60	0.12–3.03	0.535	
	AD	3.66	1.79–7.50	<**0.001**		1.21	0.33–4.50	0.769	
	VaD	2.63	0.79–8.70	0.113		*	*	*	
	MD	2.30	1.08–4.92	**0.032**		0.69	0.19–2.57	0.582	
	Severity of dementia				0.056				
	Normal cognition	1.00	—	—		1.00	—	—	
	CDR 0.5–1	1.41	0.68–2.92	0.358		1.69	0.45–6.42	0.438	
	CDR 2–3	4.27	2.18–8.36	<**0.001**		4.17	1.07–16.26	**0.040**	
	CCI	0.98	0.67–1.45	0.934	0.000	1.06	0.69–1.63	0.782	
	ADL	0.41	0.23–0.72	**0.002**	0.028	0.50	0.26–0.99	**0.046**	
	IADL	0.56	0.32–0.98	**0.045**	0.012	1.38	0.67–2.86	0.385	
	BMI	0.98	0.93–1.04	0.581	0.000	0.99	0.93–1.06	0.824	
	MNA	0.97	0.88–1.08	0.632	0.000	1.02	0.90–1.15	0.736	

(*Continues*)

DOI: 10.1002/gps

Table 3. (Continued)

Outcomes	Characteristics	Univariate logistic regression				Multiple logistic regression			
		Crude OR	95% CI	*p*	pseudo R^2	Adjusted OR	95% CI	*p*	pseudo R^2
Change in formal care									**0.078**
	Age[a]	1.02	0.99–1.06	0.118	0.005	1.00	0.97–1.04	0.669	
	Male *vs* female	0.85	0.52–1.39	0.512	0.000	0.82	0.48–1.41	0.477	
	Type of dementia				0.052				
	Normal cognition	1.00	—	—		1.00	—	—	
	MCI	1.12	0.48–2.57	0.667		0.66	0.19–2.27	0.515	
	AD	3.80	2.05–7.15	**<0.001**		1.49	0.50–4.44	0.473	
	VaD	1.89	0.66–5.48	0.238		*	*	*	
	MD	2.51	1.34–4.68	**0.004**		0.91	0.31–2.69	0.867	
	Severity of dementia				0.053				
	Normal cognition	1.00	—	—		1.00	—	—	
	CDR 0.5–1	1.63	0.94–2.86	0.082		1.66	0.57–4.78	0.351	
	CDR 2–3	4.08	2.27–7.36	**<0.001**		2.63	0.86–8.02	0.090	
	CCI	1.01	0.75–1.36	0.950	0.000	1.13	0.80–1.57	0.477	
	ADL	0.39	0.25–0.60	**<0.001**	0.035	0.49	0.29–0.83	**0.008**	
	IADL	0.48	0.30–0.73	**<0.001**	0.022	0.92	0.53–1.59	0.759	
	BMI	0.99	0.95–1.03	0.57	0.000	0.97	0.92–1.02	0.301	
	MNA	1.02	0.95–1.10	0.597	0.000	1.10	1.00–1.21	0.055	

[a]Normalized by square root transformation.
*VaD dropped out from the model because of collinearity.
AD = Alzheimer's disease; ADL = Activities of Daily Living (Katz *et al*., 1963); BMI = Body Mass Index; CCI = The Charlson Comorbidity Index (Charlson *et al*., 1987); CDR = Clinical Dementia Rate (Morris *et al*., 1993); IADL = Instrumental Activities of Daily Living (Lawton *et al*., 1969); MCI = Mild cognitive impairment; MD = Mixed dementia; MNA = Mini Nutritional Assessment (Rubenstein *et al*., 2001); VaD = Vascular dementia.
Bold entries = relevant results.

of 908 hospital stays at nine hospitals in France, no association was found between the level of dependence and the length of stay in hospital. This lack of association led the authors to call into question the different methods used for ADL scoring. Continence was not included in the ADL score for this study, and the scores obtained were therefore based on a five-item rather than a six-item scale (Lang *et al*., 2006).

In our study, the CCI was the best predictor of death in hospital, followed by nutritional status, regardless of cognitive and functional status. Conversely, Rozzini *et al*. (2005), in a large cohort of 950 elderly patients living at home (mean age 78.4) and consecutively admitted to a geriatric ward showed that changes in function due to acute disease were independently associated with the six-month mortality rate. Once again, cognition was assessed solely with the MMSE in this study, and the six-month mortality rate was assessed rather than the rate of in-hospital mortality. Furthermore, functional status was assessed with the Barthel index score, a method different from that used in our study.

Our results show that, for the hospitalization outcomes considered, dementia in very old, medically ill inpatients is predictive only of discharge to a nursing home. In this context, the following question can be asked: why do demented patients get more institutionalised in nursing homes after physical illnesses compared to non-demented patients? Probably the strongest risk factor associated with nursing home admission in demented patients is behavioural disturbances which increase the caregiver burden (O'Donnell *et al*., 1992; Soto *et al*., 2006). Since behavioral disorders are potentially treatable aspects of dementia, their management should be a major focus of therapy in dementia. In addition, one study reveals a strong association between dementia severity variables and time to institutionalisation (Smith *et al*., 2001). Then, interventions designed to directly impact disease severity can be expected to produce also an impact on delay to nursing home admission.

Poor functional status and higher levels of comorbidity were more predictive than dementia for the other three hospitalization outcomes considered (longer stay in hospital, death in hospital and increase in formal care). Comorbid medical conditions, functional and nutritional status should therefore be considered together with cognitive assessment when trying to predict hospitalization outcome in very old medically ill inpatients.

DOI: 10.1002/gps

KEY POINTS

- The relative weight of dementia as a predictor of adverse hospitalization outcomes when other risk factors are taken into account remains unclear.
- In this prospective study, in a cohort of very old acutely ill geriatric inpatients, higher levels of comorbidity and poor functional status were more predictive than dementia for adverse hospitalization outcomes.

These findings have a global implication for a well-planned follow-up and home support after discharge (including medical and non-medical services) to possibly delay or prevent inappropriate institutionalisations.

CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

We would like to thank the teams of Mrs O. Baumer, L. Humblot and M. Cos for technical assistance. This work was supported by grant 3200B0–102069 from the Swiss National Science Foundation.

REFERENCES

Aguero-Torres H, Fratiglioni L, Guo Z, *et al.* 1998a. Dementia is the major cause of functional dependence in the elderly: 3-year follow-up data from a population-based study. *Am J Public Health* **88**: 1452–1456.

Aguero-Torres H, Fratiglioni L, Winblad B. 1998b. Natural history of Alzheimer's disease and other dementias: review of the literature in the light of the findings from the Kungsholmen Project. *Int J Geriatr Psychiatry* **13**: 755–766.

American Psychiatric Association. 2000. *Diagnostic and Statistical Manual of Mental Disorders, 4th edn, text revision (DSM IV-TR)*. American Psychiatric Association: Washington, DC.

Bertozzi B, Barbisoni P, Franzoni S, *et al.* 1996. Factors related to length of stay in a geriatric evaluation and rehabilitation unit. *Aging (Milano)* **8**: 170–175.

Charlson ME, Pompei P, Ales KL, Mackenzie CR. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* **40**: 373–383.

Chui HC, Victoroff JI, Margolin D, *et al.* 1992. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology* **42**: 473–480.

Di Iorio A, Longo A, Mitidieri Costanza A. 1999. Factors related to the length of in-hospital stay of geriatric patients. *Aging (Milano)* **11**: 150–154.

Fogel JF, Hyman RB, Rock B, Wolf-Klein B. 2000. Predictors of hospital length of stay and nursing home placement in an elderly medical population. *J Am Med Dir Assoc* **1**: 202–210.

Folstein MF, Folstein SE, MacHugh PR. 1975. 'Mini Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**: 189–198.

Herrmann F, Mermod J-J, Henderson S, *et al.* 1999. Epidemiology of dementia in Geneva. In *Management of Aging. The University of Geneva Experience*, Michel J-P (ed). Karger: Basel; 94–100.

Inouye SK, Peduzzi PN, Robison JT. 1998. Importance of functional measures in predicting mortality among older hospitalized patients. *JAMA* **279**: 1187–1193.

Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. 1963. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. *JAMA* **185**: 914–919.

Lang PO, Heitz D, Hedelin G, *et al.* 2006. Early markers of prolonged hospital stay in older people: a prospective, multicenter study of 908 inpatients in French acute hospitals. *J Am Geriatr Soc* **54**: 1031–1039.

Lawton MP, Brody EM. 1969. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**: 179–186.

Marengoni A, Agüero-Torres H, Cossi S, *et al.* 2004. Poor mental and physical health differentially contributes to disability in hospitalized geriatric patients of different ages. *Int J Geriatr Psychiatry* **19**: 27–34.

McKahnn G, Drachman D, Folstein M, *et al.* 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**: 939–944.

Mehta KM, Yaffe K, Covinsky KE. 2002. Cognitive impairment, depressive symptoms, and functional decline in older people. *J Am Geriatr Soc* **50**: 1045–1050.

Molaschi M, Ponzetto M, D'Agostino E, *et al.* 2001. Assessment of cognitive and functional status in hospitalized elderly. *Recenti Prog Med* **92**: 327–331.

Morris JC. 1993. The clinical dementia rating: Current version and scoring rules. *Neurology* **43**: 2412–2414.

O'Donnell BF, Drachman DA, Barnes HJ, *et al.* 1992. Incontinence and troublesome behaviors predict institutionalization in dementia. *J Geriatr Psychiatry Neurol* **5**: 45–52.

Petersen RC, Smith GE, Waring SC, *et al.* 1999. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* **56**: 303–308.

Ramos LR, Simoes EJ, Albert MS. 2001. Dependence in activities of daily living and cognitive impairment strongly predicted mortality in older urban residents in Brazil: a 2-year follow-up. *J Am Geriatr Soc* **49**: 1168–1175.

Robert PH, Schuck S, Dubois B, *et al.* 2003. Screening for Alzheimer's Disease with the Short Cognitive Evaluation Battery. *Dement Geriatr Cogn Disord* **15**: 929–928.

Roman GC, Tatemichi TK, Erkinjuntti T, *et al.* 1993. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology* **43**: 250–260.

Rozzini R, Sabatini T, Cassinadri A, *et al.* 2005. Relationship between functional loss before hospital admission and mortality in elderly persons with medical illness. *J Gerontol Med Sci* **6**: 1180–1183.

Rubenstein LZ, Harker JO, Salva A, *et al.* 2001. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol Med Sci* **56**: 366–372.

Sands LP, Yaffe K, Covinsky K, *et al.* 2003. Cognitive screening predicts magnitude of functional recovery from admission to 3 months after discharge in hospitalized elders. *J Gerontol Med Sci* **58**: 37–45.

Smith GE, O'Brien PC, Ivnik RJ, *et al.* 2001. Prospective analysis of risk factors for nursing home placement of dementia patients. *Neurology* **57**: 1467–1473.

Solomon PR, Hirschoff A, Kelly B, *et al.* 1998. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. *Arch Neurol* **55**: 349–355.

Soto ME, Andrieu S, Gillette-Guyonnet S, *et al.* 2006. Risk factors for functional decline and institutionalisation among community-dwelling older adults with mild to severe Alzheimer's disease: one year of follow-up. *Age Ageing* **35**: 308–310.

Stump TE, Callahan CM, Hendrie HC. 2001. Cognitive impairment and mortality in older primary care patients. *J Am Geriatr Soc* **49**: 934–940.

Zekry D, Herrmann FR, Grandjean R, *et al.* 2008. Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status. *Age Ageing* **37**: 83–89.

DOI: 10.1002/gps

PAPER 6

Mild cognitive impairment, degenerative and vascular dementia as predictors of intra-hospital, short- and long-term mortality in the oldest old

Dina Zekry, François R. Herrmann, Christophe E. Graf, Sandra Giannelli, Jean-Pierre Michel, Gabriel Gold, Karl-Heinz Krause

Aging Clinical Experimental Research 2011;23:60-66

In this study, we asked the question whether an accurate diagnosis of dementia is able to predict intra-hospital mortality; short and long-term mortality after discharge (one-year and 5-years). The data presented in this report, in a very old acutely ill population, clearly demonstrated that dementia (all aetiologies) is not predictive of short and either of long-term mortality.

Mortality was significantly associated with age, with each additional year increasing the risk of death by 7 to 8%. Being male increased the risk of death by a factor of 1.5 only for 5-year-mortality. For intra-hospital mortality, dementia of all etiologies and severities were not predictors of the outcome.

Dementia was associated with a significantly higher risk of 1-year-death than not being demented ($p=0.028$), increasing the risk by 50% although considering the group of MCI ($p=0.033$). This association disappeared when the outcome was the risk of 5-year death. VaD was the only type of dementia significantly associated with an increase of the risk of death (by a factor of two), one-year and 5-year risk. Severely demented patients (CDR 2-3; regardless of the aetiology), had a 100% higher risk of dying than non-demented controls when 1-year death was the outcome and a 50% higher risk of dying when 5-year death was the outcome. The introduction of all independent variables in a full logistic model eliminated the association of moderate and severe dementia. However, age and sex remained statistically associated with long-term survival.

Mild cognitive impairment, degenerative and vascular dementia as predictors of intra-hospital, short- and long-term mortality in the oldest old

Dina Zekry[1], François R. Herrmann[1], Christophe E. Graf[1], Sandra Giannelli[1], Jean-Pierre Michel[1], Gabriel Gold[1] and Karl-Heinz Krause[2]

[1]Rehabilitation and Geriatrics Department, Geneva University Hospitals and University of Geneva, Thônex, [2]Pathology and Immunology Department, Geneva University, Geneva, Switzerland

ABSTRACT. ***Background and aims:*** *The relative weight of various etiologies of dementia and mild cognitive impairment (MCI) as predictors of intra-hospital, short- and long-term mortality in very old acutely ill patients suffering from multiple comorbid conditions remains unclear. We investigated intra-hospital, 1- and 5-year mortality risk associated with dementia and its various etiologies in a very old population after discharge from acute care.* ***Methods:*** *Prospective cohort study of 444 patients (mean age 85 years; 74% female) discharged from the acute geriatric unit of Geneva University Hospital. On admission, each subject underwent standardized evaluation of cognitive and comorbid conditions. Patients were followed yearly by the same team. Predictive variables were age, sex, cognitive diagnosis, dementia etiology and severity. Survival during hospitalization, at 1- and 5-year follow-ups was the outcome of interest evaluated with Cox proportional hazard models.* ***Results:*** *Two hundred and six patients were cognitively normal, 48 had MCI, and 190 had dementia: of these, there were 75 cases of Alzheimer's disease (AD), 20 of vascular dementia (VaD), 82 of mixed dementia (MD) and 13 of other types of dementia. The groups compared were statistically similar in age, sex, education level and comorbidity score. After 5 years of follow-up, 60% of the patients had died. Regarding intra-hospital mortality, none of the predictive variables was associated with mortality. MCI, AD and MD were not predictive of short- or long-term mortality. Features significantly associated with reduced survival at 1 and 5 years were being older, male, and having vascular or severe dementia. When all the variables were added in the multiple model, the dementia effect completely disappeared.* ***Conclusions:*** *Dementia (all etiologies) is not predictive of mortality. The observed VaD effect is probably linked to cardiovascular risk comorbidities: hypertension, stroke and hyperlipidemia.*

(Aging Clin Exp Res 2011; 23: 60-66)

INTRODUCTION

Dementia is a serious health problem with a significant economic impact. Previous studies of population-based cohort type have evaluated survival in relation to dementia, most reporting that the risk of death is higher in the presence of dementia than in its absence (1-6). A recent Danish population-based cohort study (14 years of follow-up) involving 3065 non-demented (73.7±6.8 years) and 234 demented (83.3±7.0 years) subjects at baseline, showed that the hazard ratio (HR) of death increased from 1.82 for very mildly demented to 9.52 for severely demented subjects (7). However, most studies have analyzed mortality in patients with cognitive impairment as a global diagnosis (7) or only in patients with Alzheimer's disease (AD) (3, 5). Only a few rare studies have considered mortality in other types of dementia, such as mixed dementia (AD plus vascular), which is very frequent in the very old, or in mild cognitive impairment (MCI) (8, 9). In addition, the non-demented subjects in these studies are often significantly younger (2, 3) and have significantly fewer comorbid conditions than the group of demented patients. Also, there are only a few studies examining short-term (1-year) mortality and rare ones examining long-term (5-year) mortality in acutely ill very old patients after discharge from hospital, and information on the same population remains scarce.

Key words: Aged, Alzheimer's disease, dementia, long term mortality, short-term mortality.

Correspondence: Dr. Dina Zekry, Rehabilitation and Geriatrics Department, Geneva University, 3 Chemin du Pont-Bochet, Thônex, Switzerland.
E-mail: dina.zekry@hcuge.ch

Received February 14, 2011; accepted in revised form February 25, 2011.

We therefore studied the relationship between the various etiologies and severities of dementia and MCI and intra-hospital, short- and long-term mortality in a population of very old, acutely ill patients discharged from a geriatric hospital, in a prospective cohort study. We investigated the extent to which cognitive diagnosis was of greater added prognostic value in a population having the same number of other comorbid conditions.

METHODS

Patients and data collection

We carried out a prospective study in an acute 300-bed geriatric hospital (HOGER), in which 22.7% of patients are admitted directly from the community, 54.0% are referred by the emergency unit, and 23.3% are transferred from other divisions of the university hospitals of Geneva, Switzerland. The patients and data collection have been described elsewhere (10, 11). Briefly, a representative sample of all consecutive admissions of patients aged 75 years and over in 2004 was selected by randomization, with a sampling fraction of 30% and a computer-generated randomization table. Exclusion criteria were disorders interfering with psychometric assessment (severe deafness or blindness, or major behavioral problems) and terminal illness. The local Ethics Committee approved the protocol, and patients, their families or legal representatives gave their signed informed consent. Patients' demographic data did not significantly differ from that for all patients admitted to HOGER over the same period. Our sample was therefore representative of all patients admitted to this hospital, demonstrating the reliability and quality of the randomization procedure used.

Medical history was recorded on a standardized form and the same geriatrician carried out a comprehensive geriatric assessment of all patients. Annual follow-up was carried out by the same assessment procedure, over a 5-year period.

Socio-demographic data

Data recorded included age, sex, native language, marital status, living conditions and educational level (1=≤11; 2=12-14; 3=≥15 years of schooling).

Cognitive diagnosis

The same neuropsychologist assessed all subjects for clinical dementia, at least one week after admission, to avoid the effects of concomitant delirium. The Mini-Mental State Examination (MMSE) and the Short Cognitive Evaluation Battery (12) were used. According to screening results, the same neuropsychologist carried out a comprehensive standardized neuropsychological assessment, to determine the etiology and severity of clinical dementia, as previously described (10, 11). Briefly, the battery of neuropsychological tests included the following specific tests of cognitive function: the Mattis Dementia Rating Scale as a global scale; Buschke Double Memory Test (16 or 48 items according to education level), which assesses episodic memory and provides cognitive support for both encoding and retrieval, discriminating effectively between normal elderly subjects and subjects with mild dementia; Trail-Making Test, which measures mental flexibility, and Verbal Fluency Test, which investigates verbal incitement, both these tests assessing executive function; Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Figures, which measure visuospatial and construction abilities; Lexis or Bachy test for language, and Digit Symbol test for evaluating attention. Dementia severity was assessed on the Clinical Dementia Rating Scale (CDR) (13) [score 0.5 for MCI (14), score 1 for mild, score 2 for moderate and score 3 for severe dementia]. The formal clinical criteria used for diagnosis were those of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision (DSM IV-TR) (15), the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (16), and the National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neuroscience (NINDS-AIREN) (17). Brain imaging was also carried out and patients were then assigned to one of three groups: a) normal cognition, b) MCI, and c) dementia of various types: AD, vascular dementia (VaD), mixed dementia (MD), degenerative and vascular dementia in the same patient, and other types of dementia.

Comorbidity

From our previous work on this cohort (18), the best prognostic predictor of 5-year mortality was the Geriatric Index of Comorbidity (GIC) (19), class 4 multiplying the risk of death by 4, so we used this comorbidity score in this study. The same geriatrician calculated the score for each patient, *via* an extensive review of the patient's medical records and administrative data for diagnoses, established at or before enrolment in this study and by standardized interviews with patients and/or surrogates. In computing the GIC, each of the 15 most prevalent clinical conditions (ischemic or organic heart disease, primary arrhythmias, heart disease with a non-ischemic or organic origin, hypertension, stroke, peripheral vascular disease, diabetes mellitus, anemia, gastro-intestinal disease, hepatobiliary disease, renal disease, respiratory disease, parkinsonism and non-vascular neurologic disease, musculoskeletal disorders, malignancies) is graded on a 0 to 4 disease severity scale, according to the following general framework: 0 = absence of disease, 1 = asymptomatic disease, 2 = symptomatic disease requiring medication but under satisfactory control, 3 = symptomatic disease uncon-

trolled by therapy, and 4 = life-threatening or the most severe form of the disease. The GIC classifies patients into four classes of increasing somatic comorbidity. Class 1 comprises patients who have one or more conditions with a disease severity grade ≤1, class 2 patients who have one or more conditions with a disease severity grade of 2, class 3 patients who have one condition with a disease severity of 3, other conditions having a disease severity ≤2, and class 4 patients who have two or more conditions with a disease severity of 3 or one or more conditions with disease severity of 4. Only 2% of patients were classified as class 1, allowing us to combine classes 1 and 2 for purposes of analysis.

Outcomes

The outcomes of interest were intra-hospital mortality, death by December 31, 2005 for short-term mortality (1-year mortality) and December 31, 2009 for long-term mortality (5-year mortality). Information was obtained by yearly assessment, telephone calls to the patient, the patient's family and/or the patient's general practitioner. Mortality data were confirmed by the data of the population registry of the Canton of Geneva.

Statistical methods

We checked the normality of the data by carrying out skewness and kurtosis tests. Data for continuous variables are presented as means ± 1 standard deviation (SD). Kruskal-Wallis tests were performed to compare the data for the following groups: cognitively normal patients, patients with MCI, and demented patients. We first investigated the univariate relationship between each independent variable and intra-hospital, 1-year and 5-year mortality. We used Cox proportional hazards models to take into account the time to the event. The independent variables assessed as possible predictors included age, sex, cognitive diagnosis (normal, MCI, or dementia), dementia etiology (AD, VaD and MD; "other dementia" was excluded from the analysis due to its heterogeneity and small size) and dementia severity treated as a dichotomous variable (CDR 0.5-1 = mild; CDR 2-3 = moderate to severe dementia). We then entered all independent variables, together with intra-hospital, 1-year and 5-year mortality as the dependent variable, in multiple Cox models. The hazard proportional assumption was respected for each regression. HR and their 95% confidence intervals (CI) were calculated. Pseudo R-squared (R^2), which provides information about the proportion of the variance explained by the model, was computed with the Stata "str2ph" command, based on Royston's modification of O'Quigley, Xu & Stare's modification of Nagelkerke's R^2 statistic for proportional hazards models with censored survival data. Statistical analyses were performed with Stata software version 11.1, Texas, U.S.

Table 1 - *Number of intra-hospital deaths, after 1- and 5-year follow-ups, according to cognitive impairment diagnosis.*

	Intra-hospital		One year		Five years	
	n	%	n	%	n	%
Non-demented	12	54.5	39	37.5	115	43.7
MCI	3	13.6	10	9.6	27	10.3
Demented	7	31.9	55	52.9	121	46.0
AD	1	4.5	16	15.4	45	17.1
MD	5	22.7	27	26.0	50	19.0
VaD	1	4.5	7	6.7	17	6.5
Other types of dementia	0	-	5	4.8	8	3.0
Total number of deaths	22	100	104	100	263	100

MCI: mild cognitive impairment (14); AD: Alzheimer's disease; MD: mixed dementia; VaD: vascular dementia.

RESULTS

Of the 444 patients studied (mean age 85.3±6.7; 74.0% women), 206 were cognitively normal, 48 had MCI, and 190 had dementia: 75 cases of AD, 20 of VaD, 82 of MD, and 13 of other types of dementia (3 cases of dementia with Lewy bodies, 3 of Parkinson's disease with dementia, 1 of Creutzfeld-Jacob disease, 1 of cortico-basal dementia, 3 of fronto-temporal dementia, 1 of hydrocephaly with normal pressure, and 1 of alcohol-related dementia). Of the 444 patients, 22 (5%) died during hospitalization, 104 (23.4%) died during the first year after discharge, and 263 died during the 5 years after discharge (59.2%); 115 were cognitively normal (43.7%); 121 demented (46%) and 27 MCI (10.3%), with similar proportions for each group (p was not significant). Details are shown in Table 1.

The socio-demographic data and clinical features by cognitive impairment diagnosis have been published previously (11) (Table 2). Briefly, the groups compared (cognitively normal, MCI and demented) were similar in age, sex and education level. Patients without dementia were more likely to live alone (65%) than demented patients (50% of patients with MCI or dementia); 8% of demented patients were living in a nursing home, whereas this was the case for only 1% of non-demented patients. The GIC scores were very high; the majority of patients were assigned to GIC class 3 (n=310, 69.8%), followed by class 4 (n=91, 20.5%) and classes 1-2 (n=43, 9.7%) and GIC scores did not differ significantly between patients with different cognitive status.

Patients in the VaD group tended to be younger and were more likely to be male, although these trends were not statistically significant. They had higher average comorbidity scores, when compared with other demented patients, more frequent hypertension, stroke and hyperlipidemia. Comorbidity did not increase with dementia severity.

Table 2 - *Patients' socio-demographic and clinical variables according to cognitive status.*

Characteristics	Cognitively normal (n=206)		MCI (n=48)		Demented (n=190)		p-value[c]
Age[a]	84.5	±7.0	85.0	±6.6	86.1	±6.4	0.093
Female[b]	151	73.3%	40	83.3%	137	72.1%	0.278
Educational level[a]							0.408
1=≤11 years	123	59.7%	31	64.6%	103	54.2%	
2=12-14 years	66	32.0%	10	20.8%	66	34.7%	
3=≥15 years	17	8.3%	7	14.6%	21	11.1%	
Living conditions[a]							**0.002**
At home	204	99.0%	47	97.9%	175	92.1%	
Nursing home	2	1.0%	1	2.1%	15	7.9%	
GIC score[a]							0.290
Classes 1 and 2	20	9.7%	5	10.4%	18	9.5%	
Class 3	150	72.8%	35	72.9%	125	65.8%	
Class 4	36	17.5%	8	16.7%	47	24.7%	
Hypertension[b]	145	70.4%	28	58.3%	130	68.4%	0.271
Ischemic heart disease[b]	54	32.0%	13	31.7%	41	25.8%	0.442
Diabetes mellitus[b]	43	20.9%	10	20.8%	32	16.8%	0.567
Stroke[b]	20	11.8%	4	9.8%	33	20.8%	**0.047**
Known dyslipidemia[b]	27	16.0%	7	17.1%	23	14.5%	0.889

[a]Data are expressed as means±SD; [b]number of cases (%); [c]*p*-value, Kruskal-Wallis test. GIC score: Geriatric Index of Comorbidity (19). Entries in bold type: significant results.

Univariate and multiple Cox proportional hazard modeling (Table 3)

The following outcomes are shown in Table 3: intra-hospital mortality, mortality 1 year after discharge and 5 years after discharge, including all the potentially predictive variables tested: presence or absence of dementia, dementia etiology and dementia severity.

For the three outcomes, mortality was significantly

Table 3 - *Univariate Cox regression predicting intra-hospital, 1- and 5-year mortality (n=444).*

Characteristics	Intra-hospital				One-year mortality				Five-year mortality			
	Crude HR	95% CI	p	Pseudo R^2	HR	95% CI	p	Pseudo R^2	HR	95% CI	p	Pseudo R^2
Age[a]	1.08	1.00-1.16	**0.029**	0.027	1.07	1.04-1.15	**<0.001**	0.115	1.07	1.05-1.09	**≤0.001**	0.097
Male *vs* female	1.07	0.41-2.81	0.888	0.001	1.27	0.83-1.93	0.271	0.007	1.52	1.17-1.98	**0.002**	0.021
Demented *vs* normal	0.65	0.26-1.62	0.353	0.009	1.54	1.05-2.26	**0.028**	0.028	1.27	1.00-1.62	0.053	0.009
Demented *vs* MCI *vs* normal				0.005				0.088				0.009
Normal	1.00	-	-		1.00	-	-		1.00	-	-	
MCI	1.08	0.29-3.99	0.904		1.07	0.54-2.16	0.836		0.99	0.65-1.50	0.904	
Demented	0.66	0.25-1.71	0.389		1.56	1.04-2.35	**0.033**		1.27	0.98-1.64	0.068	
Type of dementia				0.021				0.143				0.016
Normal	1.00	-	-		1.00	-	-		1.00	-	-	
MCI	1.08	0.29-3.99	0.904		1.08	0.54-2.16	0.832		0.99	0.65-1.51	0.962	
AD	0.21	0.03-1.67	0.142		1.11	0.62-2.00	0.719		1.11	0.79-1.57	0.548	
VaD	0.81	0.10-6.58	0.846		1.96	0.87-4.37	**0.019**		2.00	1.18-3.33	**0.008**	
MD	1.06	0.36-3.09	0.360		1.80	1.10-2.94	0.102		1.22	0.87-1.70	0.247	
Severity of dementia				0.005				0.018				0.015
Normal	1.00	-	-		1.00	-	-		1.00	-	-	
CDR 0.5-1	0.63	0.22-1.83	0.396		1.14	0.71-1.83	0.879		1.04	0.78-1.39	0.772	
CDR 2-3	0.91	0.31-2.67	0.868		1.93	1.22-3.04	**0.005**		1.47	1.09-1.98	**0.011**	

[a]Normalized by square root transformation. MCI: mild cognitive impairment (14); AD: Alzheimer's disease; VaD: vascular dementia; MD: mixed dementia; CDR: Clinical Dementia Rate (13); HR: hazard ratio; CI: confidence interval. Entries in bold type: significant results.

associated with age, each additional year increasing the risk of death by 7-8%. Being male increased the risk of death by a factor of 1.5 only for 5-year mortality. For intra-hospital mortality, none of the independent variables was a predictor of the outcome. For this reason, we used only univariate models and not multiple models for this outcome. Dementia was associated with a significantly higher risk of 1-year death than not being demented (p=0.028), increasing the risk by 50%, although considering only the MCI group (p=0.033). This association disappeared when the outcome was the risk of 5-year death. VaD was the only type of dementia significantly associated with a double risk of death at 1- and 5-year follow-ups. MCI, AD and MD were not predictive of intra-hospital, short- or long-term mortality. Severely demented patients (CDR 2-3; regardless of etiology) had a 100% higher risk of dying than non-demented controls when 1-year death was the outcome and a 50% higher risk of dying when 5-year death was the outcome.

The introduction of all variables into the full model eliminated the association of moderate and severe dementia (HR=1.7, 95% CI=0.57-5.14, p=0.334) for 1-year and (HR=1.2, 95% CI=0.61-2.27, p=0.619) for 5-year mortality; particularly VaD: HR=1.3, 95% CI=0.44-4.02, p=0.615 for 1-year and HR=1.7, 95% CI=0.86-3.30, p=0.125 for 5-year mortality. Age remained significantly associated with 1-year mortality (HR=1.07, 95% CI=1.03-1.11, p<0.001), accounting for 12.5% of the variability of this outcome. Age (HR=1.08, 95% CI=1.05-1.10, p<0.001) and sex (HR=1.67, 95% CI=1.21-2.30, p=0.002) remained significantly associated with 5-year mortality, also accounting for 12.7% of the variability of this outcome.

DISCUSSION

This series of elderly inpatients (mean age 85 years) was representative of the overall population of patients in this geriatric hospital. The prevalence of dementia (43%) was very high; the prevalence of dementia in elderly inpatients (acute geriatric wards) has been reported to be between 20 and 30%. A previous study carried out in the same hospital reported a prevalence of 30%. The difference between these two studies in the same hospital is statistically significant (p=<0.001) (20). These findings probably reflect the systematic and complete assessment of cognitive impairment in the random sample used to determine the prevalence of dementia. The inclusion of a large number of patients with dementia in this study was useful, as it was possible to measure the impact of dementia on the outcomes of interest. In addition, comorbid scores were very high and similar in all three groups (cognitively normal, demented, MCI) allowing comparisons and then assessment of the influence of dementia among other comorbidities.

In our population of very old patients, the 5-year mortality rate was almost 60% after discharge. This rate is similar to that reported in previous studies. Age itself is a well-known negative prognostic risk factor for death, and this factor accounted for almost 10% of the variance of the outcome in this study in the univariate model. In addition, in the multiple regression analysis, age was the only remaining predictor for 1- and 5-year mortality risk.

For intra-hospital mortality, dementia, independent of etiology or severity, was not a predictor of death. Recently, a retrospective study based on hospital discharge database records in the period 1998-2003 from public hospitals in Andalusia, Spain, identified 40,482 cases of dementia, and reported that the intra-hospital mortality rate was greater (19.3 *vs* 8.7%) for patients with dementia compared with those without dementia. Dementia was an independent predictor of mortality [odds ratio (OR)=1.77; 95% CI=1.72-1.82] (21). This study was conducted in general hospitals, all ages confounded. In an Italian study of 923 patients at least 65 years old (mean age 78.7±7.2, 49% women) admitted to the acute care geriatric ward of an internal medicine department, in-hospital mortality was independently predicted by lower MMSE scores at hospital admission (OR=5.51, 2.34-12.9) (22). More recently, a study conducted in Iceland showed that moderate to severe cognitive problems predicted intra-hospital death but not death after 1 year of follow-up in a population of 749 patients discharged from an acute care hospital (23). In these studies, no complete systematic neuropsychological assessment was carried out, patients were classified with cognitive impairment as a global diagnosis, and etiology was not taken into account. In addition, the studied population was at least 10 years younger than ours.

In our study, MCI, AD and MD were not predictive of short- or long-term mortality. In contrast, many studies have investigated survival as a function of dementia, and most have reported that the risk of death is higher in patients with dementia than in those without (3-9, 24-26). Most of these studies were population-based and examined survival from the time of dementia diagnosis, whereas our study, which was not designed for exactly the same purpose, was based on a selected group in a clinical setting and 42% of the cohort had already been diagnosed with dementia at baseline. In some of the above studies, cognition was assessed with the MMSE alone. The MMSE is neither sensitive nor specific for detecting dementia in a very old population and, in addition, does not distinguish between different types of dementia. One of the main strengths of our study was its standardized comprehensive assessment: the same neuropsychologist carried out the same systematic, complete neuropsychological assessment of all study patients, which increased the accuracy of cognitive diagnosis and allowed us

to take the various etiologies and severity of dementia into account. Our study was also unusual in its inclusion of a group of patients with MCI in addition to the demented and non-demented groups. These patients behaved more like ones with normal cognition than demented patients. In addition, the same geriatrician scored the presence and extent of comorbidity in all patients.

In our study, features significantly associated with reduced survival at 1 and 5 years were being older, male, and having vascular or severe dementia. This effect can probably be explained by the higher average comorbidity scores in the VaD group compared with the AD and MD groups, especially more likely to be diagnosed as having cerebrovascular diseases such as stroke and cardiovascular risk factors like hypertension and high cholesterol. The multiple analyses confirmed these results: when all the variables were added in the multiple model, the effect of dementia severity and VaD completely disappeared, confirming that dementia (all etiologies) is not predictive of short- or long-term mortality, but the effect observed is probably linked to cerebro- and cardiovascular comorbidites (hypertension, stroke and hyperlipidemia).

Nonetheless, in the literature, higher comorbidity and poor functional status both had a negative effect on survival. Previous studies have also shown that poorer functional status before and at the time of hospital admission is associated with higher short- and long-term mortality and higher comorbidity scores (27-30).

Our study is subject to several limitations. First, as it focused on hospitalized elderly patients, it is difficult to generalize the conclusions drawn to all subjects, whether living in institutions or in the community. Second, this was a single-center study, and there is therefore a need to confirm the results obtained in other centers. Third, the enrolled patients were very old, acutely ill, and had a high burden of comorbidities.

In conclusion, we assessed intra-hospital, short-term and long-term mortality in acutely ill very old patients, with and without dementia. The groups with and without dementia were of similar age and had similar levels of comorbidity. MCI, AD and MD were not predictive of intra-hospital, short- or long-term mortality. Only VaD significantly predicted 1- and 5-year mortality. The VaD group had the highest comorbidity score. Comorbid medical conditions should therefore be considered more than cognitive impairment, when trying to predict intra-hospital, short- and long-term survival in very old medically ill inpatients. These findings have global implications for well-planned follow-up and home support after discharge, including medical and non-medical services.

ACKNOWLEDGEMENTS

We would like to thank the teams of Mrs. O. Baumer, L. Humblot and M. Cos for technical assistance. This work was supported by grant 3200B0-102069 from the Swiss National Science Foundation.

None of the authors received any consultancy fees or has any company holdings or patents. There are no conflicts of interest to report.

REFERENCES

1. Aevarsson O, Svanborg A, Skoog I. Seven-year survival rate after age 85 years: relation to Alzheimer disease and vascular dementia. Arch Neurol 1998; 55: 1226-32.
2. Bonsignore M, Heun R. Mortality in Alzheimer's disease. Dement Geriatr Cogn Disord 2003; 15: 231-6.
3. Larson EB, Shadlen MF, Wang L et al. Survival after initial diagnosis of Alzheimer disease. Ann Intern Med 2004; 140: 501-9.
4. Tschanz JT, Corcoran C, Skoog I et al. Cache County Study Group. Dementia: the leading predictor of death in a defined elderly population: the Cache County Study. Neurology 2004; 62: 1156-62.
5. Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer disease and mortality: a 15-year epidemiological study. Arch Neurol 2005; 62: 779-84.
6. Rait G, Walters K, Bottomley C, Petersen I, Iliffe S, Nazareth I. Survival of people with clinical diagnosis of dementia in primary care: cohort study. BMJ 2010; 341: c3584.
7. Andersen K, Lolk A, Martinussen T, Kragh-Sørensen P. Very mild to severe dementia and mortality: A 14-year follow-up - The Odense study. Dement Geriatr Cogn Disord 2010; 29: 61-7.
8. Koedam EL, Pijnenburg YA, Deeg DJ et al. Early-onset dementia is associated with higher mortality. Dement Geriatr Cogn Disord 2008; 26: 147-52.
9. Guehne U, Angermeyer MC, Riedel-Heller S. Is mortality increased in mildly cognitively impaired individuals? A systematic literature review. Dement Geriatr Cogn Disord 2006; 21: 403-10.
10. Zekry D, Herrmann FR, Grandjean R et al. Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status. Age Ageing 2008; 37: 83-9.
11. Zekry D, Herrmann FR, Grandjean R et al. Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients. Int J Geriatr Psychiatry 2009; 24: 283-91.
12. Robert PH, Schuck S, Dubois B et al; Investigators' Group. Screening for Alzheimer's disease with the short cognitive evaluation battery. Dement Geriatr Cogn Disord 2003; 15: 92-8.
13. Morris JC. The clinical dementia rating: Current version and scoring rules. Neurology 1993; 43: 2412-4.
14. Petersen RC, Smith GE, Waring SC, Ivik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56: 303-8.
15. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision (DSM IV-TR). Washington: American Psychiatric Association, 2000.
16. McKahnn G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939-44.
17. Roman GC, Tatemichi TK, Erkinjuntti T et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology 1993; 43: 250-60.
18. Zekry D, Hermont Loures Valle B, Esposito F et al. Prospective comparison of six comorbidity indices as predictors of 5 years post

hospital discharge survival in the elderly. Rej Res 2010; 13: 675-82.

19. Rozzini R, Frisoni GB, Ferrucci L et al. Geriatric Index of Comorbidity: validation and comparison with other measures of comorbidity. Age Ageing 2002; 31: 277-85.
20. Herrmann F, Mermod J-J, Henderson S et al. Epidemiology of dementia in Geneva. In Michel J-P, Ed. Management of Aging. The University of Geneva Experience. Basel: Ed. Karger, 1999: 94-100.
21. Guijarro R, San Román CM, Gómez-Huelgas R et al. Impact of dementia on hospitalization. Neuroepidemiology 2010; 35: 101-8.
22. Marengoni A, Cossi S, De Martinis M et al. Adverse outcomes in older hospitalized patients: the role of multidimensional geriatric assessment. Aging Clin Exp Res 2003; 15: 32-7.
23. Jónsson PV, Noro A, Finne-Soveri H et al. Admission profile is predictive of outcome in acute hospital care. Aging Clin Exp Res 2008; 20: 533-9.
24. Noale M, Maggi S, Minicuci N, et al; ILSA Working Group. Dementia and disability: impact on mortality. The Italian Longitudinal Study on Aging. Dement Geriatr Cogn Disord 2003; 16: 7-14.
25. Helmer C, Joly P, Letenneur L, Commenges D, Dartigues JF. Mortality with dementia: results from a French prospective community-based cohort. Am J Epidemiol 2001; 154: 642-8.
26. Wolfson C, Wolfson DB, Asgharian M et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med 2001; 344: 1111-6.
27. Covinsky KE, Justice AM, Rosenthal GE, Palmer R, Landefeld CS. Measuring prognosis and case mix in hospitalized elders: the importance of functional status. J Gen Intern Med 1997; 12: 203-8.
28. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 1998; 279: 1187-93.
29. Bertozzi B, Barbisoni P, Franzoni S, Rozzini R, Frisoni GB, Trabucchi M. Factors related to length of stay in a geriatric evaluation and rehabilitation unit. Aging Clin Exp Res 1996; 8: 170-5.
30. Minicuci N, Maggi S, Noale M et al. Predicting mortality in older patients. The VELCA Study. Aging Clin Exp Res 2003; 15: 328-35.

PAPER 7

High levels of comorbidity and disability cancel out the dementia effect in predictions of long-term mortality after discharge in the very old

Dina Zekry, François R. Herrmann, Christophe E. Graf, Ana Maria Vitale, Jean-Pierre Michel, Gabriel Gold, Karl-Heinz Krause

Dementia and Geriatric Cognitive Disorders 2011;32:103-10

Finally, by the means of a full multivariate Cox proportional hazards model, including all the independent variables: cognitive, functional and nutritional status; and comorbidity, we were able to answer our main research question:

"How cognitive, functional and nutritional status, and comorbidities; in a population of very old patients hospitalized in acute care, influence the adverse outcomes after discharge?"

Based in our own data, the GIC was the best predictor of short and long-term mortality among the others comorbidity scores. As a consequence, in this analysis, the GIC was the comorbidity score of choice.

The univariate model showed that being older and male, and having vascular or severe dementia, comorbidity and functional disability, were predictive of shorter survival.

However, in the full multivariate model adjusted for age and sex, the effect of dementia type or severity completely disappeared when all the variables were added.

In the multivariate model, higher GIC score, and dependence in instrumental activities of daily living remained significantly associated with 5-years mortality, accounting for 23% of the variability of this outcome.

This study demonstrated that the dementia effect in predictions of long-term mortality after discharge in the very old can be cancelled out when other important risk factors as high levels of comorbidity or disability are taken into account.

Original Research Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2011;32:103–110
DOI: 10.1159/000326950

Accepted: March 1, 2011
Published online: September 23, 2011

High Levels of Comorbidity and Disability Cancel Out the Dementia Effect in Predictions of Long-Term Mortality after Discharge in the Very Old

Dina Zekry[a] François R. Herrmann[a] Christophe E. Graf[a] Sandra Giannelli[a]
Jean-Pierre Michel[a] Gabriel Gold[a] Karl-Heinz Krause[b]

[a]Rehabilitation and Geriatrics Department, Geneva University, Thônex, and [b]Pathology and Immunology Department, Geneva University, Geneva, Switzerland

Key Words
Dementia · Alzheimer's disease · Aging · Long-term mortality · Functionality · Comorbidity

Abstract
Background/Aims: The relative weight of various etiologies of dementia as predictors of long-term mortality after other risk factors have been taken into account remains unclear. We investigated the 5-year mortality risk associated with dementia in elderly people after discharge from acute care, taking into account comorbid conditions and functionality. ***Methods:*** A prospective cohort study of 444 patients (mean age: 85 years; 74% female) discharged from the acute geriatric unit of Geneva University Hospitals. On admission, each subject underwent a standardized diagnostic evaluation: demographic variables, cognitive, comorbid medical conditions and functional assessment. Patients were followed yearly by the same team. Predictors of survival at 5 years were evaluated by Cox proportional hazards models. ***Results:*** The univariate model showed that being older and male, and having vascular and severe dementia, comorbidity and functional disability, were predictive of shorter survival. However, in the full multivariate model adjusted for age and sex, the effect of dementia type or severity completely disappeared when all the variables were added. In multivariate analysis, the best predictor was higher comorbidity score, followed by functional status (R^2 = 23%). ***Conclusions:*** The identification of comorbidity and functional impairment effects as predictive factors for long-term mortality independent of cognitive status may increase the accuracy of long-term discharge planning.

Introduction

In older people, cognitive impairment is associated with adverse health outcomes (poor functional and nutritional status, lower survival rates and higher rates of institutionalization) [1–4]. Many studies, mostly of the population-based cohort type, have evaluated survival in relation to dementia, with most reporting that the risk of death is higher in the presence of dementia than in its absence [5–10]. A recent Danish population-based cohort study (14 years of follow-up) involving 3,065 nondemented (73.7 ± 6.8 years) and 234 demented subjects (83.3 ± 7.0 years) at baseline showed that the hazard ratio (HR) of death increased from 1.82 for the very mildly demented to 9.52 for severely demented subjects [11]. However, most studies have analyzed mortality in patients with cognitive impairment as a global diagnosis

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–8008/11/0322–0103$38.00/0

Accessible online at:
www.karger.com/dem

Dr. Dina Zekry
Rehabilitation and Geriatrics Department Geneva University
3, chemin du Pont-Bochet
CH–1226 Thônex (Switzerland)
Tel. +41 22 305 6355, E-Mail dina.zekry@hcuge.ch

[11] or only in patients with Alzheimer's disease (AD) [7, 9]. Only a few rare studies have considered mortality for other types of dementia such as mixed dementia (AD plus vascular), which is highly prevalent in the very old, or mild cognitive impairment (MCI) [12, 13]. Furthermore, the nondemented subjects in these studies are often significantly younger [10, 11] and have significantly fewer comorbid conditions than the group of demented patients. Few studies have taken into account other risk factors such as comorbid medical conditions and functional status [14]. Information about long-term mortality in the acutely ill very old, taking into account the various etiologies of dementia and other potential predictors, remains scarce.

We therefore studied the relationship between the various etiologies of dementia and long-term mortality in a population of very old, acutely ill patients discharged from a geriatric hospital in a prospective cohort study. We investigated the extent to which cognitive diagnosis was of greater added prognostic value than other markers of risk of death such as comorbidity and functionality.

Methods

Patients and Data Collection

We carried out a prospective study in a 300-bed acute geriatric hospital (Hôpital de Gériatrie), in which 22.7% of patients are admitted directly from the community, 54.0% are referred by the emergency unit and 23.3% are transferred from other divisions of the university hospitals of Geneva, Switzerland. The patients and data collection have been described elsewhere [15–17]. Briefly, a representative sample of all consecutive admissions of patients aged 75 years and over in 2004 was selected by randomization, with a sampling fraction of 30% and a computer-generated randomization table. The exclusion criteria were disorders interfering with psychometric assessment (severe deafness or blindness, or major behavioral problems) and terminal illness. The local ethics committee approved the protocol, and patients, their families or legal representatives gave signed written informed consent. The demographic data for the patients studied did not significantly differ from that for all patients admitted to the Hôpital de Gériatrie over the same period [15]. Our sample was therefore representative of all patients admitted to this hospital, demonstrating the reliability and quality of the randomization procedure used in this study.

Medical history was recorded on a standardized form and the same geriatrician carried out a comprehensive geriatric assessment of all patients. Annual follow-up was carried out by the same assessment procedure over a 5-year period.

Sociodemographic Data

The data recorded included age, sex, native language, marital status, living conditions and educational level (1: ≤11 years; 2: 12–14 years; 3: ≥15 years of schooling).

Cognitive Diagnosis

The same neuropsychologist assessed all subjects for clinical dementia, at least 1 week after admission, to avoid the effects of concomitant delirium. The MMSE and the Short Cognitive Evaluation Battery [18, 19] were used. Based on screening results, the same neuropsychologist carried out a comprehensive standardized neuropsychological assessment to determine the etiology and severity of clinical dementia, as previously described [15]. Briefly, the battery of neuropsychological tests included the following specific tests of cognitive function: (1) the Mattis Dementia Rating Scale as a global scale; (2) the Buschke Double Memory Test (16 or 48 items according to educational level), which assesses episodic memory and provides cognitive support for both encoding and retrieval, discriminating effectively between normal elderly subjects and subjects with mild dementia due to an encoding specificity deficit in dementia that increases the difference in recall by cases and controls; (3) the trail-making test, which measures mental flexibility, and the verbal fluency test, which investigates verbal incitement, with both of these tests assessing executive function; (4) the Consortium to Establish a Registry for Alzheimer's Disease Figures, which measure visuospatial and construction abilities, and (5) the Lexis or Bachy test for language and the digit symbol test for evaluating attention. Dementia severity was assessed by the Clinical Dementia Rating Scale (CDR) [20] (score of 0.5 for MCI [21], score of 1 for mild, score of 2 for moderate, and score of 3 for severe dementia). The formal clinical criteria used for diagnosis were those of the DSM-IV-TR [22], of the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) for AD [23], and of the Alzheimer's Disease Diagnostic and Treatment Centers [24] and NINDS-AIREN (National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences) for vascular dementia (VaD) [25]. Brain imaging was also carried out. Based on the assessment described above, patients were then assigned to one of three groups: (i) normal cognition, (ii) MCI, and (iii) dementia of various types – AD, VaD, mixed dementia (MD) and others.

Comorbidity

Older patients often suffer from multiple comorbid conditions. Few comorbidity indices are valid and reliable in elderly patients, and few comparisons of these indices have been carried out. Based on our previous studies of this cohort comparing the performance of 6 comorbidity indices [26], the best prognostic predictor of 5-year mortality was considered to be the Geriatric Index of Comorbidity (GIC) [27], with class 4 multiplying the risk of death by 4. The GIC includes the 15 most prevalent clinical conditions (heart disease, hypertension, stroke, peripheral vascular diseases, diabetes mellitus, anemia, gastrointestinal, hepatobiliary, renal and respiratory diseases, parkinsonism, musculoskeletal disorders and cancers), with disease severity scored on a scale of 0–4 according to the following general framework: 0 = absence of disease; 1 = asymptomatic disease; 2 = symptomatic disease requiring medication but under satisfactory control; 3 = symptomatic disease not controlled by therapy, and 4 = life-threatening or the most severe form of the disease. The GIC classifies patients into 4 classes of increasing somatic comorbidity. Class 1 includes patients with 1 or more conditions with a disease severity grade no greater than 1. Class 2 includes patients with 1 or more conditions with a

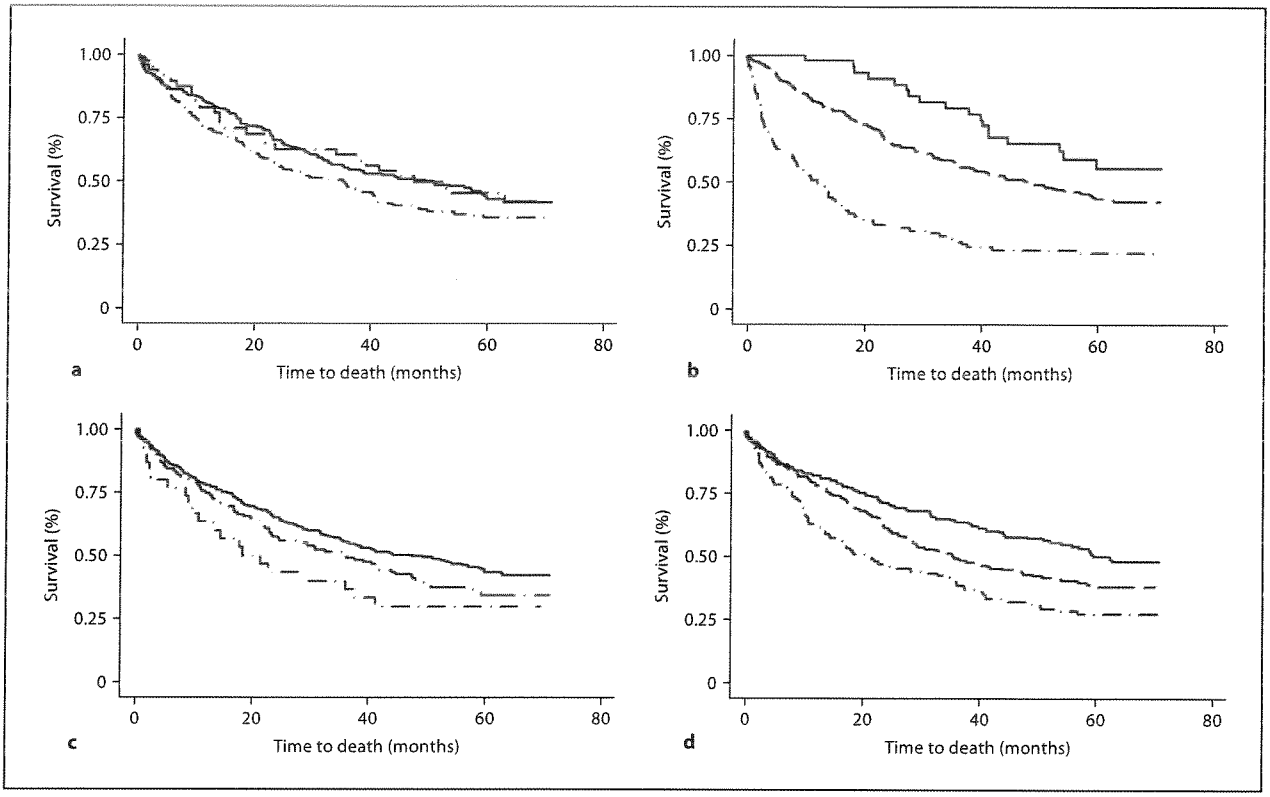


Fig. 1. Kaplan-Meier survival curves. **a** Cognitive status. Black line: normal. Long-dashed line: MCI [21]. Dashed line: demented. **b** GIC [27]. Black line: classes 1–2. Long-dashed line: class 3. Dashed line: class 4. **c** ADL [28]. Black line: index scores of 5–6. Long-dashed line: scores of 3–4. Dashed line: scores of 0–2. **d** IADL [29]. Black line: classes 6–8. Long-dashed line: classes 3–5. Dashed line: classes 0–2.

disease severity grade of 2. Class 3 includes patients with 1 condition with a disease severity of 3, their other conditions having a disease severity no greater than 2. Class 4 includes patients with 2 or more conditions with a disease severity of 3, or 1 or more conditions with a disease severity of 4. The same geriatrician calculated this score for each patient by an extensive review of the patient's medical records and administrative data on diagnoses established at or before inclusion in this study, and by standardized interviews with patients and their representatives (surrogates).

Functionality

Basic and instrumental activities of daily living (ADL, IADL) [28, 29] scores were determined as a function of the status of the patient 2 weeks before admission, based on the patient's medical history or information supplied by an informal or formal carer. ADL assesses the ability of the subject to carry out everyday activities such as bathing, dressing, going to the toilet, continence, feeding and transfer (6 items). IADL assesses the ability of the subject to use the telephone, to shop, to use means of transport, to cook, to do housework, to take medication and to handle finances (8 items). For both scales, a score of 0 indicates total dependence and the maximum score (6 or 8) indicates total independence.

Outcome

The outcome of interest was death by December 31, 2009, corresponding to a mean follow-up period of 60 months (5 years). Information was obtained via yearly assessment, telephone calls to the patient, the patient's family and/or the patient's general practitioner. Mortality data were confirmed by the data from the population registry of the Canton of Geneva.

Statistical Methods

We checked the normality of the data by carrying out skewness and kurtosis tests. Standard transformations were carried out to normalize non-Gaussian variables. Data for continuous variables are presented as means ± 1 SD. Kruskal-Wallis tests were performed to compare the data for the following groups: cognitively normal patients, patients with MCI and demented patients. We first investigated the univariate relationship between each independent variable and 5-year mortality. We used Cox proportional hazards models to take into account the time to the event. The independent variables assessed as possible predictors included: age; sex; cognitive diagnosis (normal, MCI or dementia); dementia etiology (AD, VaD and MD; 'other dementia' was excluded from the analysis due to its heterogeneity and

Table 1. Sociodemographic data and clinical features as a function of cognitive impairment diagnosis

	Nondemented (n = 206)	MCI (n = 48)	Demented (n = 190)	p
Age at inclusion, years	85.0 (7.02)	85.5 (6.59)	86.3 (6.27)	0.059
Female	152 (73.8%)	40 (83.3%)	130 (68.4%)	0.286
Education				
Level 1	124 (60.2%)	31 (64.6%)	110 (57.9%)	0.349
Level 2	66 (32.0%)	10 (20.8%)	60 (31.6%)	
Level 3	16 (7.8%)	7 (14.6%)	20 (10.5%)	
Prior living conditions				0.003
Alone	133 (64.6%)	24 (50.0%)	98 (51.6%)	
With family	15 (7.3%)	5 (10.4%)	21 (11.1%)	
With spouse	46 (22.2%)	11 (22.9%)	48 (25.2%)	
Nursing home	2 (1.0%)	1 (2.1%)	15 (7.9%)	
In protected housing	10 (4.9%)	7 (14.6%)	8 (4.2%)	
GIC class				0.291
Classes 1 + 2	20 (9.7%)	5 (10.4%)	18 (9.5%)	
Class 3	150 (72.8%)	35 (72.9%)	125 (65.8%)	
Class 4	36 (17.5%)	8 (16.7%)	47 (24.7%)	
Functional status, score				
ADL	5.27 (0.86)	4.99 (1.14)	4.51 (1.31)	<0.001
IADL	5.33 (2.01)	4.60 (2.02)	3.47 (2.26)	<0.001

Data are expressed as means with SD in parentheses, or as numbers of cases with percentages in parentheses. p values of Kruskal-Wallis tests or analyses of variance comparing 3 groups.

small size); dementia severity treated as a dichotomous variable (CDR score of 0.5–1 = mild; CDR score of 2–3 = moderate-to-severe dementia); functional status (ADL and IADL scores), and comorbidity score. The comorbidity score used, the GIC, is subdivided into 4 classes. As only 2% of the patients were assigned to GIC class 1, these patients were combined with those of class 2 to provide the reference group for the analysis. We also used Kaplan-Meier survival curves (fig. 1). We then entered all independent variables, together with 5-year mortality as the dependent variable, into multivariate Cox models. HR and their 95% confidence intervals (CI) were calculated. Pseudo R-squared (R^2), which provides information about the proportion of the variance explained by the model, was computed with the Stata 'str2ph' command, based on Royston's [30] modification of O'Quigley, Xu and Stare's modification of Nagelkerke's R^2 statistic for proportional hazards models with censored survival data. Statistical analyses were performed with Stata software version 11.

Results

Of the 444 patients studied (mean age: 85.3 ± 6.7 years; 74% women), 206 were cognitively normal, 48 had MCI, and 190 had dementia: 75 cases of AD, 20 of VaD, 82 of MD, and 13 of other types of dementia (3 cases of dementia with Lewy bodies, 3 of Parkinson's disease with dementia, 1 case of Creutzfeld-Jacob disease, 1 of corticobasal dementia, 3 cases of frontotemporal dementia, 1 case of hydrocephaly with normal pressure and 1 of alcohol-related dementia).

The sociodemographic data and clinical features are presented, by cognitive impairment diagnosis, in table 1. The groups compared were similar in age, sex and educational level. Patients without dementia were more likely to live alone (65%) than demented patients (50% of patients with MCI or dementia); 8% of demented patients were living in a nursing home, whereas this was the case for only 1% of nondemented patients. Comorbidity scores (GIC) did not differ significantly between patients with different cognitive statuses. Premorbid ADL and IADL scores on admission decreased with cognitive status. No significant differences were found between patients with the various types of dementia. Patients in the VaD group tended to be younger and were more likely to be male, although these trends were not statistically significant.

Of the 444 patients, 263 died during the first 5 years after discharge (59.2%); 142 were cognitively normal (54%) and 121 demented (46%), with similar proportions for each group (p was not significant).

Table 2. Univariate and full multiple Cox regression predicting 5-year mortality (n = 444)

	Univariate Cox regression (model 1)				Adjusted for age and sex (model 2)				Full multivariate Cox regression (model 3)			
	crude HR	95% CI	p	pseudo R^2	HR	95% CI	p	pseudo R^2	HR	95% CI	p	pseudo R^2
												0.229
Age[a]	1.07	1.05–1.09	*≤0.001*	0.097					1.06	1.05–1.09	*≤0.001*	
Male versus female	1.52	1.17–1.98	*0.002*	0.021					1.48	1.11–1.97	*0.007*	
Demented versus normal				0.009				0.131				
Normal	1.00	–	–		1.00	–	–					
Demented	1.27	1.00–1.62	0.053		1.18	0.92–1.50	0.191					
Demented versus MCI versus normal				0.009				0.131				
Normal	1.00	–	–		1.00	–	–					
MCI	0.99	0.65–1.50	0.904		1.05	0.69–1.60	0.815					
Demented	1.27	0.98–1.64	0.068		1.19	0.92–1.53	0.189					
Type of dementia				0.016				0.160				
Normal	1.00	–	–		1.00	–	–		1.00	–	–	
MCI	0.99	0.65–1.51	0.962		1.04	0.69–1.60	0.832		0.87	0.48–1.59	0.660	
AD	1.11	0.79–1.57	0.548		1.09	0.77–1.54	0.641		0.85	0.55–1.31	0.461	
VaD	2.00	1.18–3.33	*0.008*		1.87	1.11–3.14	*0.019*		1.13	0.62–2.09	0.686	
MD	1.22	0.87–1.70	0.247		1.06	0.76–1.49	0.712		0.76	0.50–1.16	0.201	
Severity of dementia				0.015				0.137				
Normal	1.00	–	–		1.00	–	–		1.00	–	–	
CDR score 0.5–1	1.04	0.78–1.39	0.772		1.02	0.77–1.36	0.879		1.16	0.77–1.74	0.480	
CDR score 2–3	1.47	1.09–1.98	*0.011*		1.37	1.02–1.85	*0.038*		1.19	0.79–1.85	0.504	
GIC				0.093				0.189				
Classes 1 + 2	1.00	–	–		1.00	–	–		1.00	–	–	
Class 3	1.63	1.01–2.66	*0.047*		1.45	0.89–2.36	0.137		1.43	0.86–2.39	0.168	
Class 4	3.85	2.29–6.47	*≤0.001*		3.03	1.79–5.12	*≤0.001*		2.74	1.58–4.89	*0.001*	
ADL	0.84	0.76–0.93	*0.001*	0.025	0.84	0.76–0.93	*0.001*	0.149	0.97	0.84–1.12	0.685	
IADL	0.87	0.82–0.92	*≤0.001*	0.061	0.89	0.85–0.94	*≤0.001*	0.161	0.93	0.86–1.00	*0.049*	

Significant p values are set in italics. [a] Normalized by square root transformation.

Univariate and Multivariate Cox Proportional Hazards Modeling

The following models are shown in table 2: the univariate model (model 1), the univariate model adjusted for age and sex (model 2), and the multivariate Cox proportional hazards model (model 3) including all the potentially predictive variables tested: presence or absence of dementia, dementia etiology, dementia severity, comorbidity and functional scores.

In univariate analysis (model 1), 5-year mortality was significantly associated with age, with each additional year increasing the risk of death by 7% (R^2 = 9.7%; HR = 1.07; 95% CI: 1.05–1.09). Being male increased the risk of death by a factor of 1.5 (R^2 = 2.1%; HR = 1.52; 95% CI: 1.17–1.98). Dementia was not associated with a significantly higher risk of death than not being demented, although a nonsignificant trend was observed for cognitive status (p = 0.053 for the comparison of nondemented controls with demented patients; p = 0.068 including the MCI group). VaD was the only type of dementia significantly associated with an increase in the risk of death (by a factor of 2). Severely demented patients (CDR score 2–3; regardless of etiology), had a 50% higher risk of dying than nondemented controls. The best prognostic predictor was GIC score, which accounted for 10% of the variability of outcome (R^2 = 9.3%) and was associated with a quadrupling of the risk of death (class 4 – HR = 3.85, 95% CI: 2.29–6.47; class 3 – HR = 1.63, 95% CI: 1.01–2.66). After 5 years, about 80% of the patients with the highest GIC scores had already died, versus less than 40% of those with the lowest scores. Poor functional status scores [lowest IADL (R^2 = 2.5%; HR = 0.84; 95% CI: 0.76–0.93) and ADL scores (R^2 = 6.1%; HR = 0.87; 95% CI: 0.82–0.92)] were found to be independent predictors of shorter long-term survival. Kaplan-Meier survival curves of the independent risk factors are shown in figure 1.

After adjustment for age and sex (model 2), GIC score was the predictor most strongly associated with death, with adverse outcome rates differing by a factor of 3 between the patients with the highest and lowest scores. Moderate-to-severe dementia, particularly VaD, and dependence in ADL and IADL remained independent predictors after adjustment for age and sex.

The introduction of all variables into the full model eliminated the association with 5-year mortality of both moderate and severe dementia, particularly VaD, and dependence in ADL. In this model (model 3), only comorbidity score and dependence in IADL remained significantly associated with 5-year mortality, accounting for 23% of the variability in this outcome.

Discussion

This study confirmed the importance of comorbidity and disability as specific independent predictors of long-term mortality in a very old population. In this study, there was only a trend for dementia to predict 5-year mortality (with dementia tending to yield higher mortality rates) in the univariate model. This trend disappeared completely when all the variables were integrated into the full model. Similarly, VaD and severe-to-moderate dementia were associated with a higher risk of long-term mortality in the univariate model, but this association disappeared when all the factors studied were taken into account in the multivariate model.

By contrast, many studies have investigated survival as a function of dementia, and most have reported that the risk of death is higher in patients with dementia than in subjects without dementia [7–14, 31, 32]. Most of these studies were population based and examined survival from the time of dementia diagnosis, whereas our study, which was not designed for exactly the same purpose, was based on a selected group in a clinical setting, and 42% of the cohort had already been diagnosed with dementia at baseline.

In our population of very old patients, the 5-year mortality rate was almost 60% after discharge. This rate is similar to that reported in previous studies. Age itself is a well-known negative prognostic risk factor for death, and this factor accounted for almost 10% of the variance of the outcome in this study. Nonetheless, higher comorbidity and poor functional status both had a negative effect on survival ($R^2 = 23\%$). The explained variance of the different variables studied here ranged between 10 and 20%; this is rather low, but it lends insight into their predictive values, knowing that a coefficient of determination (R^2) above 80% is needed to give a reliable individual prediction. Previous studies have also shown that poorer functional status before and at the time of hospital admission is associated with higher short- and long-term mortality [33, 34] and higher comorbidity scores. Cognitive impairment is also often used as a predictor of poorer hospitalization outcomes, including mortality in particular, but only a few studies have also taken comorbid medical conditions and functional status into account [34–37]. We assessed long-term mortality in acutely ill, very old patients with and without dementia. The groups with and without dementia were of similar age and had a similar level of comorbidity, and we took into account the various etiologies of dementia and other important potential predictors of mortality such as functional status. In some of these studies, cognition was assessed by the MMSE alone. The MMSE is neither sensitive nor specific to the detection of dementia in a very old population and, furthermore, does not distinguish between different types of dementia. One of the main strengths of this study was its standardized comprehensive assessment: the same neuropsychologist carried out the same systematic neuropsychological assessment of all the patients included, increasing the accuracy of cognitive diagnosis. The same geriatrician scored the presence and extent of comorbidity in all patients, and the same nurse obtained the scores for functional tools. Our study was also unusual in its inclusion of a group of patients with MCI in addition to the demented and nondemented groups. These patients behaved more like patients with normal cognition than demented patients.

This series of elderly inpatients (mean age of 85 years) was representative of the overall population of patients hospitalized in this geriatric hospital. The prevalence of dementia (44%) was very high. The prevalence of dementia in elderly inpatients (acute geriatric wards) has been reported to be between 20 and 30%. A previous study carried out 6 years ago in the same hospital had reported a prevalence of 30%. The difference between these two studies in the same hospital is statistically significant ($p \leq 0.001$) [38]. These findings probably reflect the systematic and complete assessment of cognitive impairment in the random sample used to determine the prevalence of dementia. In addition, a possible cohort effect due to a different referral policy to the hospital is not excluded. Furthermore, in our series, the prevalence of comorbid medical conditions was similar in demented patients, patients with MCI and patients with no cognitive impairment at the same age. The inclusion of a large

number of patients with dementia into this study was useful as it made it possible to measure the impact of dementia on long-term mortality in old patients with the same weight of comorbidities.

In the univariate model, VaD and moderate-to-severe dementia were independent predictors of long-term mortality. Taking the other covariates into account had two interesting effects. Firstly, the effect of dementia severity and VaD completely disappeared. Secondly, comorbid medical conditions remained the most predictive indicator, regardless of cognitive status, with functional status the next most useful predictive factor, but only considering IADL. No significant relationship with ADL was found in this model.

Our study is subject to several limitations. Firstly, as it focused on hospitalized elderly patients, it is difficult to generalize the conclusions drawn to all subjects, whether living in institutions or in the community. Secondly, this was a single-center study, and thus there is a need to confirm the results obtained in other centers. Thirdly, the enrolled patients were very old, acutely ill and had a high burden of comorbidities.

In conclusion, higher levels of comorbidity and poor functional status were more predictive of long-term mortality than dementia. Comorbid medical conditions and functional status should therefore be considered, together with cognitive assessment, when trying to predict long-term hospitalization outcome in very old, medically ill inpatients. These findings have global implications for well-planned follow-up and home support after discharge, including medical and nonmedical services.

Acknowledgments

We would like to thank the teams of Mrs. O. Baumer, L. Humblot and M. Cos for technical assistance. This work was supported by grant 3200B0-102069 from the Swiss National Science Foundation.

Disclosure Statement

None of the authors received any consultancy fees or has any company holdings or patents. There are no conflicts of interest to report.

References

1 Aguero-Torres H, Fratiglioni L, Winblad B: Natural history of Alzheimer's disease and other dementias: review of the literature in the light of the findings from the Kungsholmen Project. Int J Geriatr Psychiatry 1998; 13:755–766.

2 Mehta KM, Yaffe K, Covinsky KE: Cognitive impairment, depressive symptoms, and functional decline in older people. J Am Geriatr Soc 2002;50:1045–1050.

3 Ramos LR, Simoes EJ, Albert MS: Dependence in activities of daily living and cognitive impairment strongly predicted mortality in older urban residents in Brazil: a 2-year follow-up. J Am Geriatr Soc 2001;49:1168–1175.

4 Stump TE, Callahan CM, Hendrie HC: Cognitive impairment and mortality in older primary care patients. J Am Geriatr Soc 2001;49:934–940.

5 Ævarsson Ó, Svanborg A, Skoog I: Seven-year survival rate after age 85 years: relation to Alzheimer disease and vascular dementia. Arch Neurol 1998;55:1226–1232.

6 Bonsignore M, Heun R: Mortality in Alzheimer's disease. Dement Geriatr Cogn Didord 2003;15:231–236.

7 Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L, Kukull WA: Survival after initial diagnosis of Alzheimer disease. Ann Intern Med 2004;140:501–509.

8 Tschanz JT, Corcoran C, Skoog I, Khachaturian AS, Herrick J, Hayden KM, Welsh-Bohmer KA, Calvert T, Norton MC, Zandi P, Breitner JC, Cache County Study Group: Dementia: the leading predictor of death in a defined elderly population – the Cache County Study. Neurology 2004;62:1156–1162.

9 Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST: Alzheimer disease and mortality: a 15-year epidemiological study. Arch Neurol 2005;62:779–784.

10 Rait G, Walters K, Bottomley C, Petersen I, Iliffe S, Nazareth I: Survival of people with clinical diagnosis of dementia in primary care: cohort study. BMJ 2010;341:c3584. DOI: 10.1136/bmj.c3584.

11 Andersen K, Lolk A, Martinussen T, Kragh-Sørensen P: Very mild to severe dementia and mortality: a 14-year follow-up – the Odense study. Dement Geriatr Cogn Disord 2010;29:61–67.

12 Koedam EL, Pijnenburg YA, Deeg DJ, Baak MM, van der Vlies AE, Scheltens P, van der Flier WM: Early-onset dementia is associated with higher mortality. Dement Geriatr Cogn Disord 2008;26:147–152.

13 Guehne U, Angermeyer MC, Riedel-Heller S: Is mortality increased in mildly cognitively impaired individuals? A systematic literature review. Dement Geriatr Cogn Disord 2006;21:403–410.

14 Noale M, Maggi S, Minicuci N, Marzari C, Destro C, Farchi G, Scafato E, Baldereschi M, di Carlo A, Crepaldi G, ILSA Working Group: Dementia and disability: impact on mortality. The Italian Longitudinal Study on Aging. Dement Geriatr Cogn Didord 2003; 16:7–14.

15 Zekry D, Herrmann FR, Grandjean R, Meynet MP, Michel JP, Gold G, Krause KH: Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status. Age Ageing 2008;37:83–89.

16 Zekry D, Herrmann FR, Grandjean R, Vitale AM, de Pinho MF, Michel JP, Gold G, Krause KH: Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients. Int J Geriatr Psychiatry 2009;24:283–291.

17 Zekry D, Herrmann FR, Irminger-Finger I, Ortolan L, Genet C, Vitale AM, Michel JP, Gold G, Krause KH: Telomere length is not predictive of dementia or MCI conversion in the oldest old. Neurobiol Aging 2010;31:719–720.

18 Solomon PR, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux RD, Pendlebury WW: A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998;55:349–355.

19 Robert PH, Schuck S, Dubois B, Lépine JP, Gallarda T, Olié JP, Goni S, Troy S: Screening for Alzheimer's disease with the Short Cognitive Evaluation Battery. Dement Geriatr Cogn Disord 2003;15:92–98.
20 Morris JC: The Clinical Dementia Rating: current version and scoring rules. Neurology 1993;43:2412–2414.
21 Petersen RC, Smith GE, Waring SC, Ivik RJ, Tangalos EG, Kokmen E: Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
22 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4, text rev (DSM-IV-TR). Washington, American Psychiatric Association, 2000.
23 McKahnn G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
24 Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R: Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992;42:473–480.
25 Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al: Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260.
26 Zekry D, Hermont Loures Valle B, Esposito F, Michel JP, Gold G, Krause KH, Herrmann FR: Prospective comparison of six co-morbidity indices as predictors of 5 years post hospital discharge survival in the elderly. Rejuvenation Res 2010;13:675–682.
27 Rozzini R, Frisoni GB, Ferrucci L, Barbisoni P, Sabatini T, Ranieri P, Guralnik JM, Trabucchi M: Geriatric Index of Comorbidity: validation and comparison with other measures of comorbidity. Age Ageing 2002;31:277–285.
28 Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW: Studies of illness in the aged: the index of ADL – a standardized measure of biological and psychological function. JAMA 1963;185:914–919.
29 Lawton MP, Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179–186.
30 Royston P: Explained variation for survival models. Stata J 2006;6:83–96.
31 Helmer C, Joly P, Letenneur L, Commenges D, Dartigues JF: Mortality with dementia: results from a French prospective community-based cohort. Am J Epidemiol 2001;154: 642–648.
32 Wolfson C, Wolfson DB, Asgharian M, M'Lan CE, Ostbye T, Rockwood K, Hogan DB: A reevaluation of the duration of survival after the onset of dementia. N Engl J Med 2001;344:1111–1116.
33 Covinsky KE, Justice AM, Rosenthal GE, Palmer R, Landefeld CS: Measuring prognosis and case mix in hospitalized elders: the importance of functional status. J Gen Intern Med 1997;12:203–208.
34 Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J: Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 1998;279:1187–1193.
35 Bertozzi B, Barbisoni P, Franzoni S, Rozzini R, Frisoni GB, Trabucchi M: Factors related to length of stay in a geriatric evaluation and rehabilitation unit. Aging (Milano) 1996;8: 170–175.
36 di Iorio A, Longo A, Mitidieri Costanza A: Factors related to the length of in-hospital stay of geriatric patients. Aging (Milano) 1999;11:150–154.
37 Fogel JF, Hyman RB, Rock B, Wolf-Klein B: Predictors of hospital length of stay and nursing home placement in an elderly medical population. J Am Med Dir Assoc 2000;1: 202–210.
38 Herrmann F, Mermod J-J, Henderson S: Epidemiology of dementia in Geneva; in Michel J-P (ed): Management of Aging. The University of Geneva Experience. Basel, Karger, 1999, pp 94–100.

PAPER 8

Telomere length, comorbidity, functional, nutritional and cognitive status as predictors of 5 years post hospital discharge survival in the oldest old

Dina Zekry, Karl-Heinz Krause, Irmingard Irminger-Finger, Chantal Genet, Anna-Maria Vitale, Jean-Pierre Michel, Gabriel Gold, François R. Herrmann

The Journal of Nutrition, Health & Aging 2011 (in press)

There is no longitudinal data examining the prognostic value of a biomarker like leukocyte telomere length in the context of other health variables such as comorbidity, functional, nutritional and cognitive status as a predictor of survival.

In this study, telomere length and nutritional status (the body mass index (BMI), the mini nutritional assessment (MNA) and the albumin level) were added as independent variables on the univariate and multivariate Cox proportional hazards models.

The telomere length and the MNA score were not predictors of the outcome (5 years mortality). The albumin level (HR = 0.97) was negatively associated, that means lower albumin levels was associated with greater mortality. Each supplementary gram of albumin added 3% of additional protective risk against death. Curiously, obesity (BMI > 30, HR = 0.55) was significantly associated with a half lower mortality risk compared to BMI between 20 and 25 considered as the reference level.

In this study, it was hypothesized and confirmed that poor health variables exceed biological factors like telomere length measure predicting log-term mortality. When all variables were included in the full model while adjusting for age and sex, telomere length had no additive effect in the multivariate model compared to the previous study.

J Nutr Health Aging

THE JOURNAL OF NUTRITION, HEALTH & AGING©

TELOMERE LENGTH, COMORBIDITY, FUNCTIONAL, NUTRITIONAL AND COGNITIVE STATUS AS PREDICTORS OF 5 YEARS POST HOSPITAL DISCHARGE SURVIVAL IN THE OLDEST OLD

D. ZEKRY[1], K.H. KRAUSE[2], I. IRMINGER-FINGER[2], C. GENET[1], A.-M. VITALE[1], J.-P. MICHEL[1], G. GOLD1, F.R. HERRMANN[1]

1. Department of Rehabilitation and Geriatrics, Geneva University Hospitals and University of Geneva, Thônex, Switzerland; 2. Pathology and Immunology Department, Geneva University Hospitals and University of Geneva, Geneva, Switzerland. Corresponding author: Dr. Dina Zekry, Department of Rehabilitation and Geriatrics Geneva University Hospitals, 3, chemin du Pont-Bochet, Thônex, Switzerland. Telephone number: (0114122) 3056355 / Fax number: (0114122) 3056115, E-mail address: dina.zekry@hcuge.ch

Abstract: *Background:* Telomere length has been considered in many cross-sectional studies as a biomarker of aging. However the association between shorter telomeres with lower survival at advanced ages remains a controversial issue. This association could reflect the impact of other health conditions than a direct biological effect. *Objective:* To test whether leukocyte telomere length is associated with 5-year survival beyond the impact of other risk factors of mortality like comorbidity, functional, nutritional and cognitive status. *Design:* Prospective study. *Setting and participants:* A population representative sample of 444 patients (mean age 85 years; 74% female) discharged from the acute geriatric hospital of Geneva University Hospitals (January-December 2004), since then 263 (59.2%) had died (December 2009). *Measurements:* Telomere length in leukocytes by flow cytometry. Results: In univariate model, telomere length at baseline and cognitive status were not significantly associated with mortality even when adjusting for age (R^2=9.5%) and gender (R^2=1.9%). The best prognostic predictor was the geriatric index of comorbidity (GIC) (R^2=8.8%; HR=3.85) followed by more dependence in instrumental (R^2=5.9%; HR=3.85) and based (R^2=2.3%; HR=0.84) activities of daily living and lower albumin levels (R^2=1.5%; HR=0.97). Obesity (BMI>30: R^2=1.6%; HR=0.55) was significantly associated with a two-fold decrease in the risk of mortality compared to BMI between 20-25. When all independent variables were entered in a full multiple Cox regression model (R^2=21.4%), the GIC was the strongest risk predictor followed by the nutritional and functional variables. *Conclusion:* Neither telomeres length nor the presence of dementia are predictors of survival whereas the weight of multiple comorbidity conditions, nutritional and functional impairment are significantly associated with 5-year mortality in the oldest old.

Key words: Telomere, aging, biomarker, mortality, survival.

Introduction

Telomeres are repetitive structures at the end of mammalian chromosomes and together with associated proteins they protect chromosome ends (1). In normal cells, a progressive telomere shortening accompany each cycle of replication (2) and there is a well-established gradual loss of telomere length in human peripheral blood with increasing age (3-7). In addition, most (8-10) but not all studies (11, 12) have shown a positive association between telomere length and overall survival in humans. Evidence accumulates that telomere shortening reflects lifestyle and predicts remaining lifespan by a direct biological effect. More recent findings suggest that telomere length may not be a strong biomarker of survival in older individuals, but may be an informative biomarker of healthy aging (13). However, there are few longitudinal data examining the prognostic value of leukocyte telomere length in the context of other health variables such as comorbidity, functional, nutritional and cognitive status.

Thus, we sought to investigate the relationship between leukocyte telomere length and mortality among a population of very old, acutely ill patients discharged from a geriatric hospital in a prospective cohort study and to determine whether leukocyte telomere length provides incremental prognostic value beyond existing other markers of risk.

Methods

Patients and data collection

We carried out a prospective study in a 300-acute bed geriatric hospital (HOGER) where 22.7% are direct admission from the community, 54.0% are referred by the emergency unit and 23.3% are transferred from other divisions of Geneva University Hospitals, Switzerland. Patients and data collection have been described elsewhere (14-16). Briefly, a representative sample of all patients aged 75 years and over, consecutively admitted in 2004 were selected by randomization, with a sampling fraction of 30% using a computer generated randomization table. The local ethics committee approved the protocol, and patients, their families or legal representatives provided signed written informed consent. Demographic data for the patients studied did not significantly differ from all patients admitted to HOGER at the same period. Our sample was therefore representative of all patients admitted to this hospital, demonstrating the reliability of the randomization procedure used in this study.

Medical history was recorded on a standardized form and the same geriatrician carried out a comprehensive geriatric

assessment on all patients. Annual follow-up was carried out with the same assessment over a five-year period.

Sociodemographic data

The data recorded included age, sex, native language, marital status, living arrangement and educational level.

Telomere length measurements

Telomere length were determined as a function of fluorescence intensity, using an FITC-labeled peptide nucleic acid (PNA) probe (FITC-coupled) supplied with the telomere PNA /FITC for flow cytometry kit by DAKO (http://www.dakousa.com/prod_downloadpackageinsert.pdf?objectid=11479 1002).

In situ hybridization: Lymphocytes were prepared for hybridization in the presence of hybridization solution without probe or in hybridization solution containing fluorescein-conjugated PNA telomere probe, as described in Hultdin et al. (17). Flow cytometry: Labelled cells were analyzed by flow cytometry. Homogeneous lymphocyte subpopulations were identified. DNA was labelled with DAPI to identify cell populations with similar DNA content, with gating on the G1 population. FITC-labelled cells were counted in the gated population. As an internal control, telomere length was measured in a standard cell line (HL60), which allowed normalizing the flow cytometric measurements with respect to day to day variations. Image analysis was performed with the same flow cytometer (FACS, Fluorescence Activated Cell Sorting; Partec PAS Flow Cytometer Galaxy, USA) in each case. Mean telomere fluorescence intensity was calculated as the difference between the fluorescence signal obtained with samples hybridized with the Telomere PNA Probe/FITC and the fluorescence signal obtained with a sample of the same cells incubated with the hybridization solution without probe. Results are expressed as telomere length index, which is the fluorescent signal obtained in the patient cells divided by the fluorescent signal of the control HL-60 cells. Thus, a telomere length index of 1 indicates a telomere length in the patient sample identical to the one observed in HL-60 cells. The intra-assay coefficient of variance of this measurement was less than 2%.

Nutritional assessment

Body mass index (BMI kg/m^2) was determined and the short version of the Mini Nutritional Assessment (MNA) (score ranging from 0 to 14, ≥ 12 being normal) administered on admission, by the same nurse in each case (18). The reference period for the MNA was two weeks before admission. Albumin blood level (g/l) was measured by bromocresol purple dye-binding method.

Functionality

Base and Instrumental Activities of Daily Living (ADL, IADL) (19, 20) scores were determined as a function of patient status two weeks before admission, based on the patient's medical history or information supplied by an informal or formal carer.

Assessment of Comorbidity

From our previous work on this cohort (21) the best prognostic predictor of 5-year mortality was the Geriatric Index of Comorbidity (GIC) (22) class 4 multiplying the risk of death by 4, thus we used this comorbidity score in this study. The same geriatrician calculated this score for each patient, via an extensive review of the patient's medical records and administrative data for diagnoses established at or before enrolment in this study and by standardized interviews with patients and surrogates. The GIC classifies patients into four classes of increasing somatic comorbidity.

Cognitive diagnosis

The same neuropsychologist assessed all subjects for clinical dementia, The MMSE (23) and the Short Cognitive Evaluation Battery were used (24, 25). Based on screening results, the neuropsychologist then carried out a comprehensive standardized neuropsychological assessment to determine the etiology and severity of clinical dementia, as previously described (14, 15). The formal clinical criteria used for diagnosis were those of the DSM IV-TR (26), NINCDS-ADRDA (27) and NINDS-AIREN (28). Cerebral imaging was also carried out.

Outcome

The outcome of interest was death by December 31, 2009, that means an average 60 months (five years) of follow-up. This information was obtained through yearly phone calls to the patient, his family and/or his general practitioner. Mortality data was also confirmed through access to the population registrar of the State of Geneva.

Statistical methods

We checked the normality of the data distribution with skewness and kurtosis tests, and carried out standard transformations to normalise non-Gaussian variables. Data for continuous variables are presented as means ± 1 standard deviation (SD).

First, we measured the univariate relationship between each independent variable and 5-year mortality. We used Cox proportional hazards models to take into account the time to the event. The independent variables assessed as possible predictors included age, sex, telomere length, nutritional and functional status before admission (MNA, ADL and IADL scores), albumin level and BMI at admission, comorbidity score and cognitive diagnosis (normal or demented). We also used Kaplan-Meier survival curves to examine the performance of the independent variables over time. We then entered all independent variables and 5-year mortality as dependent variable in multivariate Cox regression. Hazards ratios (HR)

along with their 95% confidence intervals (CI) were calculated. Continuous variables were either included as such or dichotomized, using the lower cut-off value (MNA, ADL and IADL). As it was not possible to normalize telomere length and BMI scores, they were categorized into tertiles for telomere length (lower tertile ≤ 0.49 (95% CI 0.44-0.52), reference tertile: 0.49-0.77 and upper tertile > 0.77 (95% CI 0.72-0.82)) and quartiles for BMI (< 20 kg/m2, 20-25 kg/m^2 = reference, 25-30 kg/m^2 and > 30 kg/m^2). The proportional-hazards assumption was successfully tested for telomere length based on Schoenfeld residuals. Pseudo R-squared (R^2) which provides information on the amount of variance explained by the model were computed using the Stata "str2ph" command based on the Royston's modification of O'Quigley, Xu & Stare's modification of Nagelkerke's R^2 statistic for proportional-hazards models with censored survival data (29). The comorbidity score applied, the GIC is predefined into four classes. As there were only 2% of the patients classified as class 1 by the GIC, they were combined with class 2 for the analysis and considered as the standard. Statistical analyses were performed with Stata software version 11, TX, US.

Results

556 patients were randomized, 523 were successfully enrolled and 496 survived to hospital discharge (27 died during the hospitalization), 444 patients had full data and were included in this study (mean age 85.3 ± 6.7; 74 % women). Of the 444 patients, 263 died during the five years after discharge (59.2%). The distribution of patients according to sex, telomere length, BMI, MNA, albumin level, ADL, IADL, comorbidity score and cognitive function on baseline and those who died after 5 years of follow-up are described in Table 1.

Univariate and multiple Cox proportional hazards modeling (Table 2)

In univariate analysis, 5 year-mortality was significantly associated with age, each supplementary year added 7% to the risk of death (R^2 = 9.5%, HR = 1.07, 95% CI = 1.05 - 1.09); being a men increased the risk by 1.5 fold (R^2 = 1.9%, HR = 1.52, 95% CI = 1.17 - 1.98). The telomere length, the cognitive status and the MNA score were not predictor of the outcome.

The best prognostic predictor was the GIC class 4 (R^2 = 8.8%, HR = 1.07HR = 3.85, 95% CI = 2.29 - 6.47). After 5 years, approximately 80% of the high score patients were already deceased, compared with less than 40% in the lowest scores.

The albumin level (R^2 = 1.5%, HR = 0.97, 95% CI = 0.95 - 0.99); the ADL (R^2 = 2.3%, HR = 0.84, 95% CI = 0.76 - 0.93) and IADL (R^2 = 5.9%, HR = 0.87, 95% CI = 0.82 - 0.92) were negatively associated, that means lower albumin levels and more dependence in based and instrumental activities of daily living were associated with greater mortality. Each supplementary gram of albumin added 3% of additional protective risk against death. Curiously, obesity (BMI > 30: R^2 = 1.6%, HR = 0.55, 95% CI = 0.35 - 0.86) was significantly associated with a half lower mortality risk compared to BMI between 20 and 25 considered as the reference level. Kaplan-Meier survival curves of the independent risk factors are shown in figure 1.

Table 1

Distribution of patients according to sex, telomere length, BMI, MNA, albumin level, ADL, IADL, comorbidity score and cognitive function at baseline (n = 444) and those who died (n = 263) after 5 years of follow-up

	Patients included at baseline		**Patients dead after 5 years of follow-up**	
	N	**%**	**N**	**%**
Age (mean ± SD)	85.2 ± 6.7	-	86.8 ± 6.5	-
Female/Male	328/116	74.0/26.0	183/80	69.6/30.4
Telomere length (median ± iqr, 0.63 ± 0.49)				
lower tertile (≤ 0.49)	147	33.1	109	41.4
medium tertile (0.49-0.77)	147	33.1	87	33.1
upper tertile (> 0.77)	150	33.8	67	25.5
BMI (kg/m2)				
< 20	94	21.2	62	23.6
20-25	179	40.3	109	41.5
25-30	115	25.9	69	26.2
> 30	56	12.6	23	8.7
MNA				
< 12	337	75.9	200	76.0
≥ 12	107	24.1	63	24.0
Albumin level g/l (median ± iqr, 33 ± 8)				
≤ median	240	54.0	152	57.8
> median	204	46.0	111	42.2
ADL (median ± iqr; 5 ± 1)				
≤ median	106	23.9	75	28.5
> median	338	76.1	188	71.5
IADL (median ± iqr; 4 ± 3)				
≤ median	166	37.4	121	46.0
> median	278	62.6	142	54.0
GIC				
Class 1+2	43	9.7	18	6.8
Class 3	310	69.8	174	66.2
Class 4	91	20.5	71	27.0
Demented/cognitively normal	190/254	42.8/57.2	121/142	46.0/54.0

BMI = body mass index, MNA = mini nutritional assessment, ADL = base activities of daily living, IADL = instrumental activities of daily living, GIC = geriatrics index of comorbidity, SD = standard deviation, iqr = inter quartile range. Bold entries = relevant results.

When all variables were included in the full model while adjusting for age and sex (R2 = 21.4%), the GIC class 4 (HR = 2.45, 95% CI = 1.40 - 4.28) remained the best predictor independently associated with 5-year mortality followed by the IADL (HR = 0.91, 95% CI = 0.84 - 0.98), the albumin level (HR = 0.97, 95% CI = 0.95 - 1.00); the BMI > 30 (HR = 0.60, 95% CI = 0.37 - 0.98); age (HR = 1.06, 95% CI = 1.03 - 1.08) and sex (HR = 1.69, 95% CI = 1.27 - 2.24).

Discussion

The purpose of this paper was to evaluate the weight of a biological predictor (telomere length) alone and compared to other well known health predictors of 5-year mortality after discharge of very elderly patients hospitalized in acute care. It

Table 2

Univariate and full multiple Cox regression predicting 5-year mortality (n=444). All independent variables are continuous unless otherwise specified

Outcome	Independent variables	Univariate Cox regression				Full Multiple Cox regression			
		Crude HR	95% CI	p	R2 (%)	Adjusted HR	95% CI	p	R2 (%)
Death at 60 months (n=263)									21.4
	Age	1.07	1.05 - 1.09	<0.001	9.5	1.06	1.03 - 1.08	<0.001	
	Sex male	1.52	1.17 - 1.98	0.002	1.9	1.69	1.27 - 2.24	<0.001	
	Telomere length				0.2				
	lower tertile	1.04	0.76 -1.40	0.815		0.75	0.55 - 1.04	0.082	
	medium tertile	1.00	--	--					
	upper tertile	1.06	0.77 - 1.44	0.726		0.95	0.69 - 1.31	0.771	
	BMI (kg/m^2)				1.6				
	< 20	1.15	0.71 - 3.62	0.369		1.17	0.83 - 1.65	0.383	
	20-25	1.00	--	--		1.00	--	--	
	25-30	0.96	1.82 - 7.53	0.791		0.86	0.62 - 1.19	0.364	
	> 30	0.55	0.35 - 0.86	0.009		0.60	0.37 - 0.98	0.042	
	MNA				0.5				
		0.96	0.92 - 1.00	0.071		0.99	0.94 - 1.05	0.734	
	Albumin (g/l)				1.5				
		0.97	0.95 - 0.99	0.007		0.97	0.95 - 1.00	0.031	
	ADL				2.3				
		0.84	0.76 - 0.93	0.001		1.00	0.87 - 1.16	0.949	
	IADL				5.9				
		0.87	0.82 - 0.92	<0.001		0.91	0.84 - 0.98	0.015	
	GIC			8.8					
	Class 1+2	1.00	--	--					
	Class 3	1.64	1.01 - 2.66	0.047		1.24	0.75 - 2.06	0.389	
	Class 4	3.85	2.29 - 6.47	<0.001		2.45	1.40 - 4.28	0.002	
	Demented vs cognitively normal	1.27	1.00 - 1.62	0.053	0.6	0.88	0.66 - 1.16	0.365	

BMI = body mass index, MNA = mini nutritional assessment, ADL = base activities of daily living, IADL = instrumental activities of daily living, GIC = geriatrics index of comorbidity. Bold entries = relevant results.

was hypothesized that poor health variables exceed biological factors like telomere length measure. This study confirmed the importance of disability, comorbidity and malnutrition as specific independent predictors in a very old population. One of the main strengths of this study was the standardized comprehensive assessment: the same geriatrician scored the presence and the extent of comorbidity for all patients, the same neuropsychologist carried out a systematic, complete neuropsychological assessment of all the included patients, increasing the accuracy of cognitive diagnosis, the same nurse scored functional and nutritional tools and finally the same biologist assessed the leukocyte telomere length.

Several studies have examined telomere length as determinant of mortality in the elderly. There is considerable inconsistency in the current literature. Some reports have shown associations of shorter telomere length with lower survival: Cawthon and colleagues (9), in their study of individuals 60 years old or older, demonstrated that the overall mortality rate of persons with short telomeres was nearly double that of individuals with long telomeres; Bakaysa et al. (30) reported that twins with shorter telomere length have three times the risk of death compared with their co-twins with longer telomere length. In contrast other studies showed no association between leukocyte telomere length and survival in older individuals' aged more than 85 years (11, 12). More recently, Terry et al. had examined telomere length in centenarians in good health versus poor health. Healthy centenarians had significantly longer telomeres than did unhealthy centenarians ($p = 0.0475$) (31). They have demonstrated that investigations of the association between telomere length and exceptional longevity must take into account the health status of the individuals and have raised the possibility that perhaps it is not exceptional longevity but one's function and health that may be associated with telomere length. Our results confirmed this hypothesis.

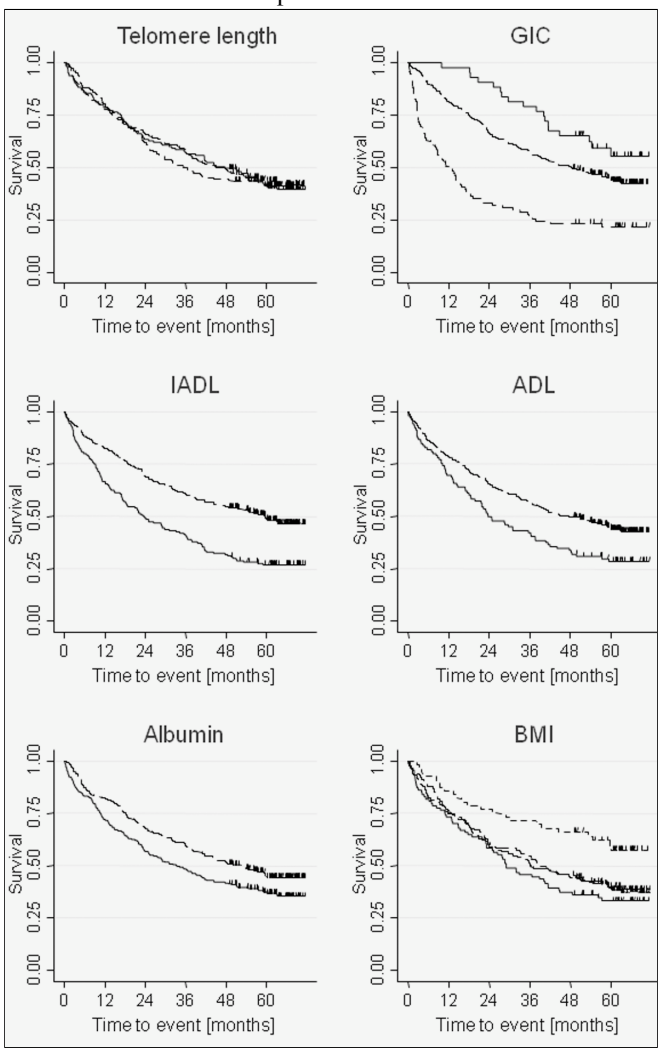
In our population of very old patients, a 5-year mortality rate of almost 60% was found after discharge. This rate was similar to that reported in previous studies. Age per se is a well-known negative prognostic risk factor for death and explained almost 10% of the variance of the outcome in this study. Nonetheless, higher comorbidity, poor functional and nutritional status were factors that negatively affected survival. Similarly to our results, previous studies have shown that worse functional status prior to and at hospital admission is associated with a higher short and long-term mortality (32, 33) as well as higher comorbidity scores and worse nutritional status (34, 35).

Curiously, in this study, the univariate model shows only a trend regarding dementia as a predictor of 5-year mortality. This trend had completely disappeared when all the variables were added in the full model. On the contrary, many studies have examined survival in relation to dementia and the majority has reported that dementia increases the risk of death compared

to no dementia (36, 37). Recently, a Danish population-based cohort study (14 years of follow-up) involving 3,065 nondemented and 234 demented at baseline , showed that the hazard ratio of death (95% confidence interval) increased from 1.82 (1.55-2.14) for the very mildly demented to 9.52 (6.60-13.74) for the severely demented subjects (38). The majority of these studies are population based and have examined survival from the time of diagnosis of dementia, whereas our study, which was not designed for this purpose, was based on a selected group in a clinical setting and 42% of the cohort had dementia diagnosis at baseline.

Figure 1

Kaplan-Meier survival curves according to the observed variables. Marks represent censored observations



Telomere length (lower tertile: black line; medium tertile: long dashed line; upper tertile: dashed line); GIC = geriatrics index of comorbidity (class 1-2: black line; 3: long dashed line; 4: dashed line); IADL = instrumental activities of daily living, ADL = base activities of daily living and Albumin = albumin level g/l (≤ median: black line; > median: long dashed line); BMI = body mass index (kg/m^2) (< 20: black line; 20-25: long dashed line; 25-30: dashed line; > 30 short dashed line).

Our study has some limitations. First, since it focused on hospitalized elderly patients, it is likely that it is difficult to generalize its conclusions to institutionalized and community dwelling subjects. Second, only one center was involved so the results have to be confirmed in others centers. Third the enrolled patients were very old, acutely ill, and had a high burden of comorbidities.

In conclusion, in this cohort of oldest old, neither leukocyte telomere length nor the presence of dementia are predictors of 5-year survival whereas the weight of multiple comorbidity conditions, nutritional and functional impairment are. Hospital discharge planning and prognosis can help physicians and family members plan for the care of patients who may be at increased risk of adverse outcomes in the coming years, especially regarding discussions of goals of care, treatment preferences, advance planning, and clinical therapeutic options. Hospitalization therefore may present a key trigger point to identify persons at greatest risk for mortality in the years following discharge.

Acknowledgments: We would like to thank the teams of Mrs. O. Baumer, L Humblot and M Cos for technical assistance.

Funding/Support: This work was supported by grants from the Swiss National Science Foundation (3200B0-102069) and from the Swiss Foundation for Ageing Research (AETAS).

Disclaimer: No author received any consultancy fees or has any company holdings or patents. There are no conflicts of interest.

References

1. Wong JM, Collins K. Telomere maintenance and disease. Lancet 2001; 362:983-988.
2. Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. Nature 1990; 345:458-460.
3. Slagboom PE, Droog S, Boomsma DI. Genetic determination of telomere size in humans: a twin study of three age groups. Am J Hum Genet 1994; 55: 876-882.
4. Martens UM, Brass V, Sedlacek L. Telomere maintenance in human B lymphocytes. Br J Haematol 2002; 119:810-818.
5. Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB et al. Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci USA 1992; 89:10114-10118.
6. Lindsey J, McGill NI, Lindsey LA, Green DK, Cooke HJ. In vivo loss of telomeric repeats with age in humans. Mutat Res 1991; 256:45-48.
7. Houben JM, Moonen HJ, van Schooten FJ, Hageman GJ. Telomere length assessment: biomarker of chronic oxidative stress? Free Radic Biol Med 2008; 44:235-246.
8. Njajou OT, Cawthon RM, Damcott CM, Wu SH, Ott S, Garant MJ et al. Telomere length is paternally inherited and is associated with parental lifespan. Proc Natl Acad Sci USA 2007; 104:12135-12139.
9. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. Lancet 2003; 361:393-395.
10. Bischoff C, Graakjaer J, Petersen HC, Hjelmborg JB, Vaupel JW, Bohr Vet al. The heritability of telomere length among the elderly and oldest-old. Twin Res Hum Genet 2005; 8:433-439.
11. Bischoff C, Petersen HC, Graakjaer J, Andersen-Ranberg K, Vaupel JW, Bohr VA et al. No association between telomere length and survival among the elderly and oldest old. Epidemiology 2006; 17:190-194.
12. Martin-Ruiz CM, Gussekloo J, van Heemst D, von Zglinicki T, Westendorp RG. Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: A population-based study. Aging Cell 2005; 4:287-290.
13. Njajou OT, Hsueh WC, Blackburn EH, Newman AB, Wu SH, Li R et al. Association between telomere length, specific causes of death, and years of healthy life in health, aging, and body composition, a population-based cohort study. J Gerontol A Biol Sci Med Sci 2009; 8:860-864.
14. Zekry D, Herrmann FR, Grandjean R, Meynet MP, Michel JP, Gold G, Krause KH. Demented versus non-demented very old inpatients: the same comorbidities but

poorer functional and nutritional status. Age Ageing 2008; 37:83-89.
15. Zekry D, Herrmann FR, Grandjean R, Vitale AM, De Pinho MF, Michel JP et al. Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients. Int J Geriatr Psychiatry 2009; 24:283-291.
16. Zekry D, Herrmann FR, Irminger-Finger I, Ortolan L, Genet C, Vitale AM et al. Telomere length is not predictive of dementia or MCI conversion in the oldest old. Neurobiol Aging 2010; 31:719-20.
17. Hultdin M, Grönlund E, Norrback K, Eriksson-Lindström E, Just T, Roos G. Telomere analysis by fluorescence in situ hybridization and flow cytometry. Nucleic Acids Res 1998; 26:3651-3656.
18. Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001; 56:366-372.
19. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. JAMA 1963; 185:914-919.
20. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179-186.
21. Zekry D, Hermont Loures Valle B, Esposito F, Michel JP, Gold G, Krause KH, Herrmann FR. Prospective comparison of six comorbidity indices as predictors of 5 years post hospital discharge survival in the elderly. Rej Res 2010; Sept 6, PMID: 20818930.
22. Rozzini R, Frisoni GB, Ferrucci L, Barbisoni P, Sabatini T, Ranieri P et al. Geriatric Index of Comorbidity: validation and comparison with other measures of comorbidity. Age Ageing 2002; 31:277-285.
23. Folstein MF, Folstein SE, MacHugh PR. Mini Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-198.
24. Solomon PR, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux RD, Pendlebury WW. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998; 55:349-355.
25. Robert PH, Schuck S, Dubois B, Olié JP, Lépine JP, Gallarda T et al. Screening for Alzheimer's Disease with the Short Cognitive Evaluation Battery. Dement Geriatr Cogn Disord 2003; 15: 92-98.
26. American Psychiatric Association. 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed Text Revision (DSM IV-TR). American Psychiatric Association: Washington, DC.
27. McKahnn G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939-944.
28. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology 1993; 43:250-260.
29. Royston P. Explained variation for survival models. The Stata Journal 2006; 6:83-96.
30. Bakaysa SL , Mucci LA , Slagboom PE , Boomsma DI, McClearn GE, Johansson B, Pedersen NL. Telomere length predicts survival independent of genetic influences. Aging Cell 2007; 6:769-774.
31. Terry DF, Nolan VG, Andersen SL, Perls TT, Cawthon R. Association of longer telomeres with better health in centenarians. J Gerontol A Biol Sci Med Sci 2008; 63:809-812.
32. Covinsky KE, Justice AM, Rosenthal GE, Palmer R, Landefeld CS. Measuring prognosis and case mix in hospitalized elders: the importance of functional status. J Gen Intern Med 1997; 12:203-208.
33. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 1998; 279:1187-1193.
34. Espaulella J, Arnau A, Cubí D, Amblàs J, Yánez A. Time-dependent prognostic factors of 6-month mortality in frail elderly patients admitted to post-acute care. Age Ageing 2007; 36:407-413.
35. Drame M, Jovenin N, Novella JL, Lang PO, Somme D, Laniece I et al. Predicting early mortality among elderly patients hospitalised in medical wards via emergency department: the SAFES cohort study. J Nutr Health Aging 2008; 12:599-604.
36. Tschanz JT, Corcoran C, Skoog I, Khachaturian AS, Herrick J, Hayden KM et al. Dementia: the leading predictor of death in a defined elderly population: the Cache County Study. Neurology 2004; 62:1156-1162.
37. Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer disease and mortality: a 15-year epidemiological study. Arch Neurol 2005; 62:779-784.
38. Andersen K, Lolk A, Martinussen T, Kragh-Sørensen P. Very mild to severe dementia and mortality: A 14-year follow-up - The Odense study. Dement Geriatr Cogn Disord 2010; 29:61-67.

PAPER 9

Telomere length is not predictive of dementia or MCI conversion in the oldest old

Dina Zekry, François R. Herrmann, Irmingard Irminger-Finger, Laura Ortolan, Chantal Genet, Anna-Maria Vitale, Jean-Pierre Michel, Gabriel Gold, Karl-Heinz Krause

Neurobiology of Aging 2010;31:719-720

Concerning the clinical implications of telomere biology, we performed this study to answer the following questions:

Does telomere shortening play a role in the mechanisms of dementia (VaD or AD)?

Does telomere length predict the risk of dementia and the risk of conversion of MCI to dementia in very elderly patients?

Does telomere length predict the degree of impairment or the severity of dementia?

Based on our results, there was no evidence that telomere length can be used to predict dementia, especially in very old subjects. In addition, telomere length cannot be used to distinguish between demented and non-demented patients, even if different types of dementia are assessed.

These negative results emanating from this prospective study, using a comprehensive standardized neuropsychological assessment and a yearly telomere length measure, gave solid arguments against the capacity of telomere length to predict dementia in the very old.

ELSEVIER

Neurobiology of Aging 31 (2010) 719–720

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Negative results

Telomere length is not predictive of dementia or MCI conversion in the oldest old

Dina Zekry [a,*], François R. Herrmann [a], Irmingard Irminger-Finger [b], Laura Ortolan [c], Chantal Genet [a], Anna-Maria Vitale [a], Jean-Pierre Michel [a], Gabriel Gold [a], Karl-Heinz Krause [b]

[a] *Department of Rehabilitation and Geriatrics, Geneva University Hospitals and University of Geneva, Switzerland*
[b] *Department of Pathology and Immunology, Geneva University Hospitals and University of Geneva, Switzerland*
[c] *Department of Psychiatry, Geneva University Hospitals and University of Geneva, Switzerland*

Received 13 February 2008; received in revised form 4 April 2008; accepted 18 May 2008
Available online 2 July 2008

Abstract

The contribution of telomere shortening to the onset of certain age-related diseases, such as dementia, and its role as a predictor of cognitive impairment remain unclear. We tested these hypotheses by analyzing telomere length in 449 inpatients in a large cohort of the oldest old (mean age 85 years) followed up yearly. No significant difference in telomere length was observed between cognitively normal patients (205), demented patients (195; 82 mixed dementia, 77 Alzheimer's disease and 21 vascular dementia) and patients (49) with mild cognitive impairment (MCI). Similarly, no significant differences in telomere length were found between patients with different etiologies or severities of dementia. Telomere length and change in cognitive status (from normal to MCI or dementia, or from MCI to dementia) were not associated after two years of follow-up. This longitudinal study in very old patients provided no evidence to suggest that telomere length could be used to distinguish between demented and non demented patients, regardless of the type of dementia, or to predict dementia or MCI conversion.

Keywords: Alzheimer's disease; Dementia; Aged; Telomere length

1. Introduction

Telomeres are short, repeated DNA sequences at the end of chromosomes. The telomere hypothesis of aging is based on telomere shortening with each cell division, and therefore with age, resulting in cell senescence and aging. Telomere length is considered as a potential biomarker of aging [8,12,15,18,19]. This leads to the hypothesis of whether telomere shortening contributes also to the genesis of certain age-related diseases, such as dementia. We carried out a prospective study in very elderly patients, with yearly follow-up, to determine whether telomere length predicted dementia or the conversion of mild cognitive impairment (MCI) to dementia.

2. Methods

Patients and data collection have been described elsewhere [44]. Briefly, we carried out a longitudinal study (cross-sectional study with yearly follow-up) of patients (aged 70 and above) from a randomized sample of the patients admitted to Geneva Geriatric Hospital over a two-year period. The same team carried out the same assessment yearly: a complete, systematic battery of neuropsychological tests, assessment of clinical criteria and scores for dementia etiology and severity, and measurement of telomere length in peripheral blood lymphocytes by flow cytometry (see supplementary data for details).

* Corresponding author at: Department of Rehabilitation and Geriatrics, Geneva University Hospitals and University of Geneva, 3, chemin du Pont-Bochet, Thônex, Switzerland. Tel.: +41 22 305 6355; fax: +41 22 305 6115.
E-mail address: dina.zekry@hcuge.ch (D. Zekry).

0197-4580/$ – see front matter © 2008 Published by Elsevier Inc.
doi:10.1016/j.neurobiolaging.2008.05.016

3. Results

The 449 patients (mean age 85.1 ± 6.8; 76% women) enrolled were assigned to three groups (supplementary Fig. 1): 205 cognitively normal, 49 with MCI [31] and 195 demented (77 with Alzheimer's disease (AD), 82 with mixed dementia and 21 with vascular dementia (VaD)). Mean age and sex ratio were similar for all groups.

3.1. Baseline results

No significant difference in telomere length was found between cognitively normal patients and those with dementia ($p = 0.443$), or between cognitively normal patients and patients with MCI or dementia ($p = 0.213$) (supplementary Fig. 2). Telomere length did not differ significantly with dementia etiology ($p = 0.769$) or severity ($p = 0.195$) (supplementary Figs. 3 and 4). In multiple linear regression analysis, age, sex and cognitive status were not predictive of telomere length ($p = 0.063$, 0.232 and 0.542, respectively; $r^2 = 2.1\%$) (supplementary Fig. 5).

3.2. Follow-up results (supplementary Fig. 1)

285 patients had one-year and 208 patients two-year assessments (63% and 46% of the included cohort). The incidence of dementia was 15% per year and that of MCI, 12% per year. The rate of MCI conversion was 50% per year. Telomere length was not associated with change in cognitive status from normal to dementia or MCI ($p = 0.764$), or from MCI to dementia ($p = 0.709$), from baseline to the first or second yearly assessment. Similarly, telomere length was not associated with dementia severity in demented patients during follow-up ($p = 0.791$).

3.3. Change in telomere length

Telomere length was measured three times for each individual. We therefore calculated the telomere length delta between baseline and first or second yearly follow-up, and between the two years of follow-up. The telomere length delta was not associated with change in cognitive status after one or two years of follow-up ($p = 0.934$).

4. Discussion

The first study to investigate the correlation between telomere length and dementia was a cross-sectional and had a strong selection bias for stroke and VaD inpatients. The authors compared patients with AD, VaD, stroke and/or other cardiovascular risk factors. The odds ratio for VaD was two times lower in individuals with long telomeres, increasing to more than three in patients with short telomeres [40]. Panoussian et al. using the MMSE as a marker of AD disease showed that telomere length and cognitive function were related [30]. These cross-sectional studies were carried out on small cohorts of younger elderly patients, using only the MMSE to assess cognitive function. In a larger study in an older population ($n = 598$, mean age 90 years), telomere length was not predictive of dementia incidence, again based on MMSE alone [23]. A recent study by this group on 195 non demented stroke survivors with a mean age of 80 years showed that telomere length was predictive of poststroke cognitive decline, dementia and death [24]. However, cognitive evaluation by MMSE alone is not sensitive or specific for detecting changes in a population of this great age (90 years for the first study), particularly after stroke (for the second study).

All these studies, including ours, measured telomere length in white blood cells. This is logical with respect to the accessibility of the patient material and previous studies, which suggest that telomere length in blood can be used as a surrogate marker for telomere length in other tissues [13].

The principal strength of our cohort is its clinically rich prospective data collection from a large group of elderly patients. In addition, the same neuropsychologist carried out the same systematic neuropsychological assessment at baseline and during the two years of follow-up, increasing the accuracy of cognitive diagnosis. This study is also the first of its type to consider a group of patients with MCI. This large longitudinal study in very old demented and non demented subjects followed up for two years provides no evidence that telomere length can be used to predict dementia or MCI conversion. It also shows that telomere length cannot be used to distinguish between demented and non demented patients, regardless of the type of dementia considered. In addition, repeated measures of telomere length in the same individual were not associated with change in cognitive status after one or two years of follow-up. More details of the methodology, raw data and references are provided in the supplementary data.

Acknowledgments

We would like to thank the teams of Mrs. O. Baumer, L. Humblot and M. Cos for technical assistance. This work was supported by grant 3200B0-102069 from the Swiss National Foundation. Actual or potential conflicts of interest are disclosed.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2008.05.016.

Supplementary data

1. Introduction

Telomeres are essential elements consisting of non coding repetitive DNA sequences and binding proteins, located at the ends of chromosomes [28,39]. The importance of telomeres lies in their multiple roles: they protect against degeneration, prevent chromosome fusion, cell death and neoplastic transformation, and are essential for chromosomal stability. DNA replication mechanisms result in the ends of chromosomes remaining single-stranded, leading to gradual telomere shortening. The critical shortening of telomeres leads to cell cycle arrest and cellular senescence, also known as replicative senescence [6,10]. Assuming that cells have a limited potential for proliferation, telomere length can be used as a marker of the biological age of a specific tissue. Telomere shortening during aging has been demonstrated *in vivo* and has been associated with DNA damage. Oxidative stress throughout the lifetime of a cell can lead to DNA damage, promoting telomere shortening. Telomere length therefore reflects not only biological age, but also stress management capacity. Telomere shortening may be a major determinant of human aging not only at the cellular level, but also at the organ and, perhaps, systemic levels. Telomere dysfunction is emerging as an important mechanism in vascular aging and, consequently, in the pathogenesis of hypertension, atherosclerosis, and heart failure [2,3,11,21,22,29]. These findings raise two questions concerning the clinical implications of telomere biology. Firstly, does telomere shortening play a role in the mechanisms of dementia (vascular dementia or Alzheimer's disease)? Secondly, is telomere length an independent predictor of the risk of dementia and the risk of conversion of MCI to dementia? We carried out a prospective study to test these hypotheses concerning the role of telomere shortening in a very elderly population, by means of a longitudinal study based on a standardized battery of detailed

neuropsychological tests.

2. Methods

2.1. Study population

A prospective study was carried out in the Geriatric Hospital (HOGER) of the University Hospitals of Geneva, Switzerland. Patients were recruited by staff with clinical training. The sampling frame consisted of a complete list of consecutive admissions of patients over 70 years old, on selected days between January 2004 and December 2005. A random sample was selected each day, using a computer-generated random table. The exclusion criteria were disorders interfering with psychometric assessment (severe deafness and blindness; and major behavioral disturbances, such as severe aggressiveness, psychotic or suicidal behavior), terminally illness with an expected survival time of less than 6 weeks and living outside the Canton of Geneva, due to difficulties following patients. Patients rather than admissions were used as the statistical units for randomization, so each individual patient could be selected no more than once. The local ethics committees approved the study protocol and signed written informed consent was obtained the patients or their families or legal representatives. We compared demographic data for the sample of patients included with data for all patients admitted to the HOGER in the same year and with data for patients who refused to participate in the study, to ensure that the study sample was representative of the whole hospital population. Patients who refused to participate in the study also underwent routine examination, including cognitive screening, making it possible to check for selection bias. No differences in demographic characteristics were found between the study sample and the entire population of patients admitted to the HOGER, or between the study sample and patients who were excluded or refused to participate. The homogeneity of the group of patients studied and the group consisting of all the patients admitted to the HOGER in the

same period shows that our sample was representative of the total population of patients admitted and demonstrates the quality of randomization in this study.

The patients' histories were recorded on a standardized form and physical examinations were performed by the same geriatrician (DZ). The study protocol included plans for four years of follow-up with a yearly visit consisting of the same assessment, as described below.

2.2. Measurements

Sociodemographic data

We recorded age, sex, first language, years of education, marital status and living conditions.

Cognitive diagnostic

The same neuropsychologist assessed all included subjects for possible clinical dementia, at least one week after inclusion, to reduce the possibility of concomitant delirium. The following neuropsychological screening battery was applied: the Mini mental state examination (MMSE) (scores 0-30) [13] and The Short Cognitive Evaluation Battery (SCEB) [32,34], which contains the clock-drawing test (Cdt) [36,43], the temporal orientation test [4], the 5-word test [17] and the semantic verbal fluency task [26]. The short version of the Geriatric Scale was used to screen for depression [38]. Based on this screening, a comprehensive standardized battery of neuropsychological tests used in routine clinical practice was carried out by the same neuropsychologist, with formal clinical criteria used to determine the etiology and severity of clinical dementia: The Mattis Dementia Rating Scale as a global scale [16], The Buschke Double Memory Test (16 or 48 items according to education level) [6,37], which assesses episodic memory and provides cognitive support for both encoding and retrieval, discriminating effectively between normal elderly subjects and subjects with mild dementia; The Trail-Making

Test [32], which measures mental flexibility, and The Verbal Fluency Test [7], which investigates verbal incitement, both of which assess executive function; The CERAD Figures [41], which measure visuospatial and construction abilities; The Lexis or Bachy test for language and The Digit Symbol test for evaluating attention [42]. Dementia severity was assessed with the Clinical Dementia Rating Scale (CDR) [27] (score 0.5 for MCI, score 1 for mild, score 2 for moderate and score 3 for severe dementia).

The formal clinical criteria used for diagnosis were those of the DSM IV-TR [1], NINCDS-ADRDA [25], ADDTC [10] and NINDS-AIREN [34]. Cerebral imaging was also carried out. Patients were assigned to three groups: i) cognitively normal, ii) patients with mild cognitive impairment (MCI) [30] and iii) patients with various types of dementia.

Telomere length measurements

Telomere length were determined as a function of fluorescence intensity, using an FITC-labeled peptide nucleic acid (PNA) probe (FITC-coupled) supplied with the telomere PNA /FITC for flow cytometry kit by DAKO (http://www.dakousa.com/prod_downloadpackageinsert.pdf?objectid=114791002). The method is ideal for estimating telomere length, as cell fluorescence intensity is directly correlated with telomere length and tightly correlated with the mean size of the terminal restriction fragments (TRF, expressed in kilobases, kb) obtained by Southern analysis.

In an initial pilot studies we have measured telomere length in 11 younger individuals (mean age 37.9 ± 10.4 y). In this population the telomere length index was 1.24 ± 0.58 [1.23 -- 0.61] (mean ± SD) [median -- IQR] as compared to 0.721 ± 0.507 [0.63 -- 0.49] in our study population ($p = 0.0148$ with unpaired t-test and $p = 0.0003$ with Mann-Withney two-sample Wilcoxon test). Thus,

as expected, there is an allover shorter telomere length in the geriatric population, as compared to young healthy individuals.

***In situ* hybridization:** Lymphocytes were prepared for hybridization in the presence of hybridization solution without probe or in hybridization solution containing fluorescein-conjugated PNA telomere probe, as described in Hultdin *et al*. [20]. Briefly, 6ml of blood taken in Vacutainer EDTA tubes are diluted to 10ml with PBS (phosphate buffer saline) and put on Ficoll (polymer of sucrose), then centrifuged. The ring of lymphocytes is then taken, washed with PBS, put in culture 2h at 37°C (5% CO_2) in culture medium (RPMI 1640). After that, lymphocytes are recovered and counted (1 M cells); then they are fixed (cytofix-cytoperm DAKO) 10 minutes in the dark, washed with PBS, denatured at 82°C for 5 minutes in a microcentrifuge tube either in the presence of hybridization solution without probe, or in hybridization solution containing fluorescein-conjugated PNA telomere probe. Then, hybridization takes place in the dark at room temperature overnight. After that, the cells are washed in wash solution and then resuspended in 250µl of the wash solution. The cells are ready for the passage with the flowcytometer.

Flow cytometry: Labeled cells were analyzed by flow cytometry. Homogeneous lymphocyte subpopulations were identified. DNA was labeled with DAPI to identify cell populations with similar DNA content, with gating on the G1 population. FITC-labeled cells were counted in the gated population. As an internal control, telomere length was measured in a standard cell line (HL60), which allowed normalizing the flow cytometric measurements with respect to day to day variations. Image analysis was performed with the same flow cytometer (FACS, Fluorescence Activated Cell Sorting) in each case. Mean telomere fluorescence intensity was calculated as the difference between the fluorescence signal obtained with samples hybridized with the Telomere

PNA Probe/FITC and the fluorescence signal obtained with a sample of the same cells incubated with the hybridization solution without probe. Results are expressed in telomere length index, which is the fluorescent signal obtained in the patient cells divided by the fluorescent signal of the control HL-60 cells. Thus, a telomere length index of 1 indicates a telomere length in the patient sample identical to the one observed in HL-60 cells. The intra-assay coefficient of variance of this measurement was less than 2%. In all cases, the dementia status of individuals within pairs was unknown at the time of analysis.

2.3. Statistical methods

We checked the normality of the data distribution, by skewness and kurtosis tests, and carried out standard transformations to normalize non Gaussian variables. Data for continuous variables are presented as means ± 1 standard deviation (SD).

ANOVA or Kruskal-Wallis tests were performed to compare data between the following groups: i) cognitively normal patients, patients with MCI and demented patients; ii) patients with dementia of different etiologies. Statistical analyses were performed with Stata version 9.2.1.

References

[1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed Text Revision (DSM IV-TR). Washington, DC: American Psychiatric Association, 2000.

[2] Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, Greider CW, Harley CB. Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci USA 1992;89:10114-8.

[3] Aviv A, Aviv H. Reflections on telomeres, growth, aging, and essential hypertension. Hypertension 1997;29:1067-72.

[4] Benton AL. Contributions to Neuropsychological Assessment. New York: Oxford University Press, 1983.

[5] Blackburn EH. Switching and signaling at the telomere. Cell 2001;106:661-73.

[6] Buschke H, Sliwinski MJ, Kuslansky G, Lipton RB. Diagnosis of early dementia by the Double Memory Test: encoding specificity improves diagnostic sensitivity and specificity. Neurology 1997;48:989-97.

[7] Butters N, Granholm E, Salomon DP, Grant I. Episodic and semantic memory: a comparison of amnesic and demented patients. J Clin Exp Neuropsychol 1987;9:479-97.

[8] Campisi J, Kim SH, Lim CS, Rubio M. Cellular senescence, cancer and aging: the telomere connection. Exp Gerontol 2001;36:1619-37.

[9] Chan SW, Blackburn EH. Telomerase and ATM/Tel1p protect telomeres from nonhomologous end joining. Mol Cell 2003;11:1379-87.

[10] Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992;42:473-80.

[11] Davis T, Kipling D. Telomeres and telomerase biology in vertebrates: progress towards a non-human model for replicative senescence and ageing. Biogerontology 2005;6:371-85.

[12] DePinho RA. The age of cancer. Nature. 2000;408:248-54.

[13] Friedrich U, Griese E, Schwab M, Fritz P, Thon K, Klotz U. Telomere length in different tissues of elderly patients. Mech Ageing Dev 2000;119:89-99.

[14] Folstein MF, Folstein SE, Mac Hugh PR. Mini Mental State: a practical method for grading the cognitive state of patients for the clinician. J Pychiatr Res 1975;12:189-98.

[15] Gasser SM. A sense of the end. Science 2000;288:1377-9.

[16] Gardner R, Oliver-Munoz S, Fisher L, Empting L. Mattis Dementia Rating Scale: Internal reliability study using a diffusely impaired population. J Clin Neuropsychol 1981;3:271-5.

[17] Grober E, Buschke H. Genuine memory deficits in dementia. Dev Neuropsychol 1987;3:13-35.

[18] Harley CB, Vaziri H, Counter CM, Allsopp RC. The telomere hypothesis of cellular aging. Exp Gerontol 1992;27:375-82.

[19] Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts, Nature 1990;345:458-60.

[20] Hultdin M, Grönlund E, Norrback K, Eriksson-Lindström E, Just T, Roos G. Telomere analysis by fluorescence in situ hybridization and flow cytometry. Nucleic Acids Res 1998;26:3651-6.

[21] Jeanclos E, Krolewski A, Skurnick J, Kimura M, Aviv H, Warram JH, Aviv A. Shortened telomere length in white blood cells of patients with IDDM. Diabetes 1998;47:482-6.

[22] Lindsey J, McGill NI, Lindsey LA, Green DK, Cooke HJ. In vivo loss of telomeric repeats with age in humans. Mutat Res 1991;256:45-8.

[23] Martin-Ruiz CM, Gussekloo J, van Heemst D, von Zglinicki T, Westendorp RG. Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: a population-based study. Aging Cell 2005;4:287-90.

[24] Martin-Ruiz C, Dickinson HO, Keys B, Rowan E, Kenny RA, Von Zglinicki T. Telomere length predicts poststroke mortality, dementia, and cognitive decline. Ann Neurol 2006;60:174-80.

[25] McKahn G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-44.

[26] Monsch AU, Bondi MW, Butters N, Salmon DP, Katzman R, Thal LJ. Comparison of verbal fluency tasks in detection of dementia of the Alzheimer type. Arch Neurol 1992;49:1253-7.

[27] Morris JC. The clinical dementia rating: Current version and scoring rules. Neurology 1993;43:2412-14.

[28] Nawrot TS, Staessen JA, Gardner JP, Aviv A. Telomere length and possible link to X chromosome. Lancet 2004;363:507-10.

[29] Oexle K, Zwirner A. Advanced telomere shortening in respiratory chain disorders. Hum Mol Genet 1997;6:905-8.

[30] Panossian LA, Porter VR, Valenzuela HF, Zhu X, Reback E, Masterman D, Cummings JL, Effros RB. Telomere shortening in T cells correlates with Alzheimer's disease status. Neurobiol Aging 2003;24:77-84.

[31] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303-8.

[32] Reitan RM. Validity of the Trail-Making Test as an indicator of organic brain damage. Percept Mot Skills 1958;8:271-6.

[33] Robert PH, Schuck S, Dubois B, Olie JP, Lepine JP, Gallarda T, Goni S, Troy S. Screening for Alzheimer's Disease with the short cognitive evaluation battery. Dement Geriatr Cogn Disord 2003;15:92-8.

[34] Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo J-M, Brun A, Hofman A, Moody DM, O'Brien MD, Yamaguchi T, Grafman J, Drayer BP, Bennet DA, Fisher M, Ogata J, Kokmen E, Bermejo F, Wolf PA, Gorelick PB, Bick KL, Pajeau AK, Bell MA, Decarli C, Culebras A, Korczyn AD, Bougousslavsky J, Hartmann A, Scheinberg P. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology 1993;43:250-60.

[35] Salomon PR, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux RD, Pendlebury WW. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998; 55: 349-55.

[36] Sunderland T, Hill JL, Mellow AM, Lawlor BA., Gundersheimer J. Clock drawing in Alzheimer's disease. A novel measure of dementia severity. J Am Geriatr Soc 1989;37:725-9.

[37] van der Linden M. Adaptation française de la procédure de Grober et Buschke. Marseille: Solal, 1999.

[38] van Marwijk HW, Wallace P, de Bock GH, Hermans J, Kaptein AA, Mulder JD. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. Br J Gen Pract 1995;45:195-9.

[39] Vaziri H, Benchimol S. From telomere loss to p53 induction and activation of a DNA-damage pathway at senescence: the telomere loss/DNA damage model of cell aging. Exp Gerontol 1996;31:295-301.

[40] von Zglinicki T, Serra V, Lorenz M, Saretzki G, Lenzen-Grossimlighaus R, Gessner R, Risch A, Steinhagen-Thiessen E. Short telomeres in patients with vascular dementia: an indicator of low antioxidative capacity and a possible risk factor? Lab Invest 2000;80:1739-47.

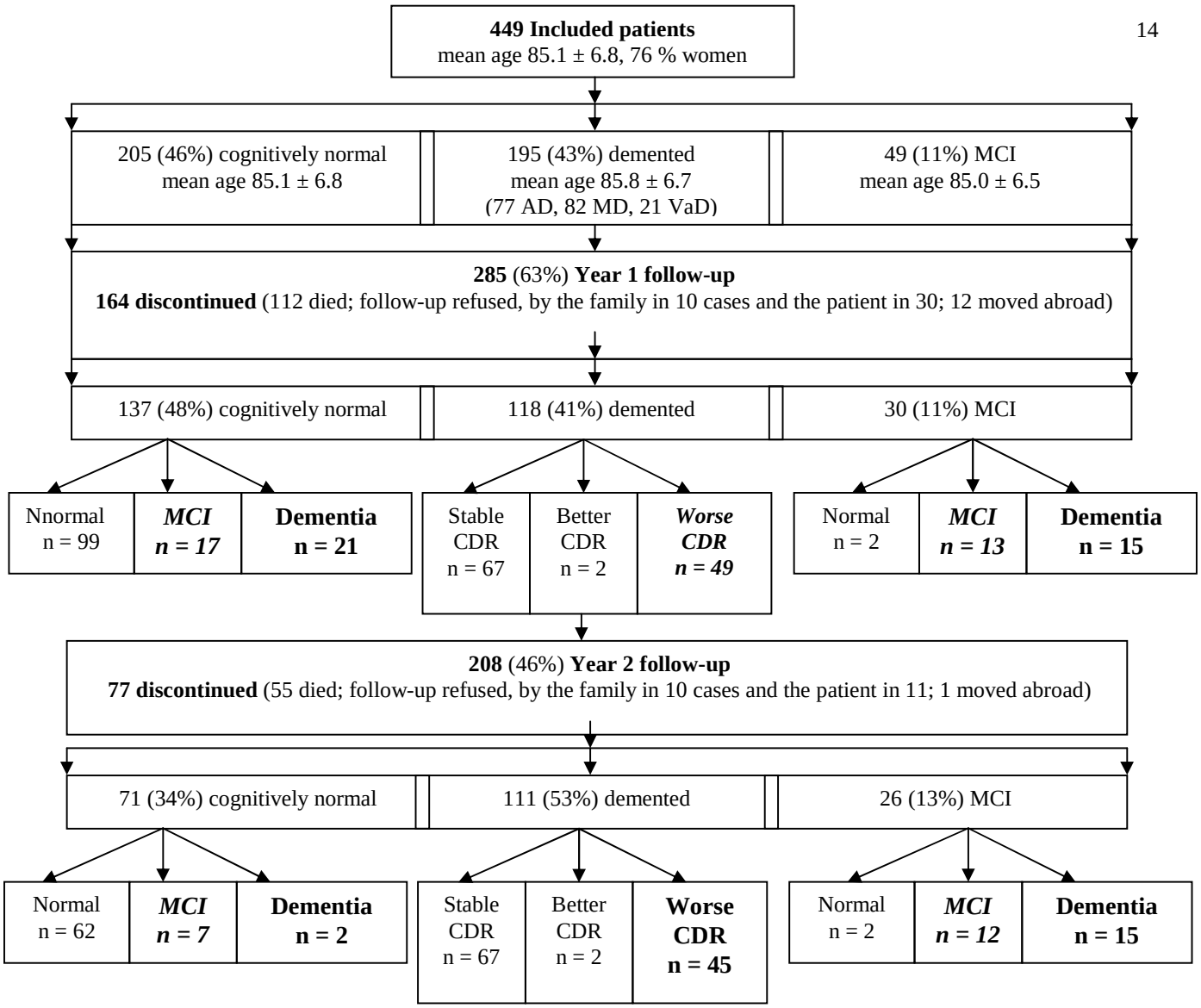
[41] Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, Heyman A. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Neurology 1994; 44: 609-14.

[42] Wechsler D: Wechsler Adult Intelligence Scale, Revised (WAIS-R). New York: Psychological Corporation, 1981.

[43] Wolf-Klein GP, Silverstone FA, Levy AP, Brod MS. Screening for Alzheimer's disease by clock drawing. J Am Geriatr Soc 1989;37:730-4.

[44] Zekry D, Herrmann FR, Grandjean R, Meynet MP, Michel JP, Gold G, Krause KH. Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status. Age Ageing. 2008;37:83-9.

Figure 1. ***Schematic diagram of baseline and follow-up of the included patients***



AD = Alzheimer's disease, MD = mixed dementia, VaD = vascular dementia, MCI = mild cognitive impairment, CDR = clinical dementia rate [26]

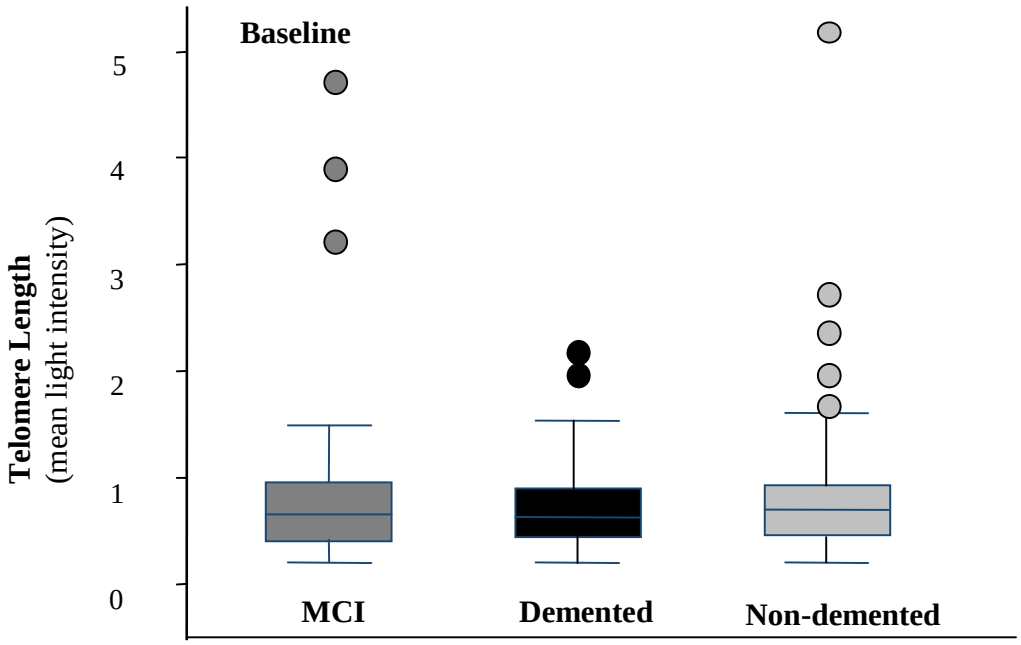


Fig. 2. No significant difference in telomere length was found between cognitively normal patients and patients with MCI or dementia (p = 0.213)

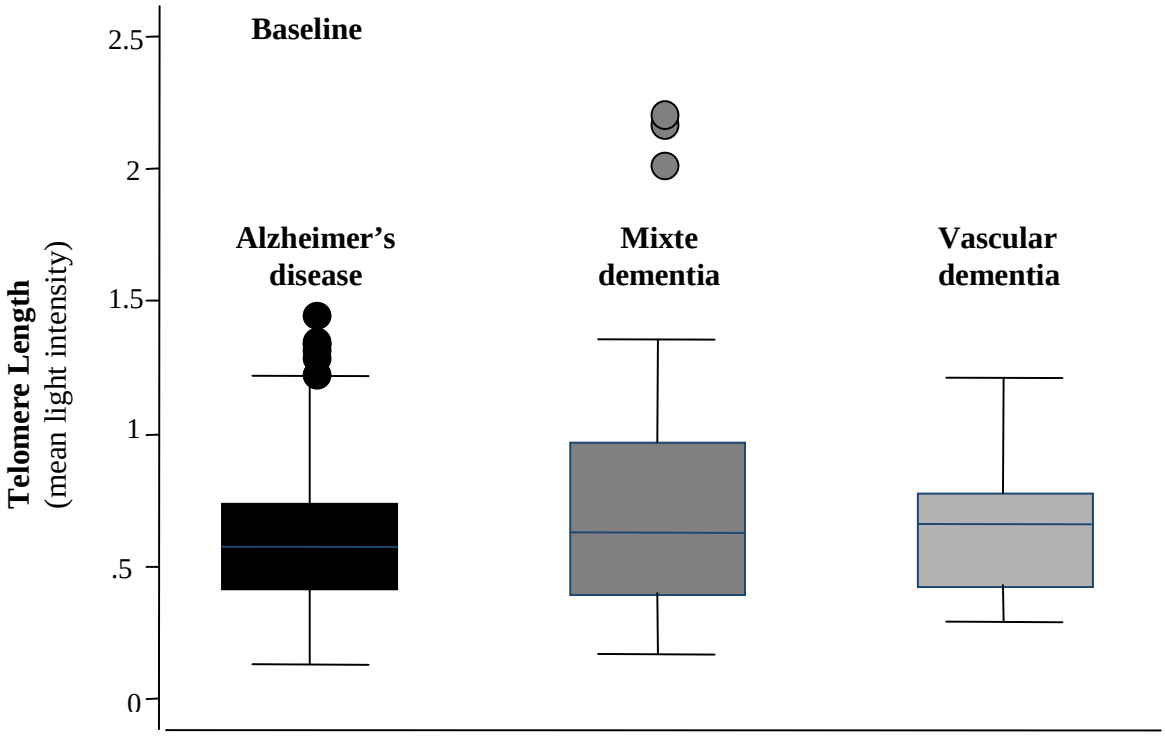


Fig. 3. Telomere length did not differ significantly according to the etiology of dementia (p = 0.769).

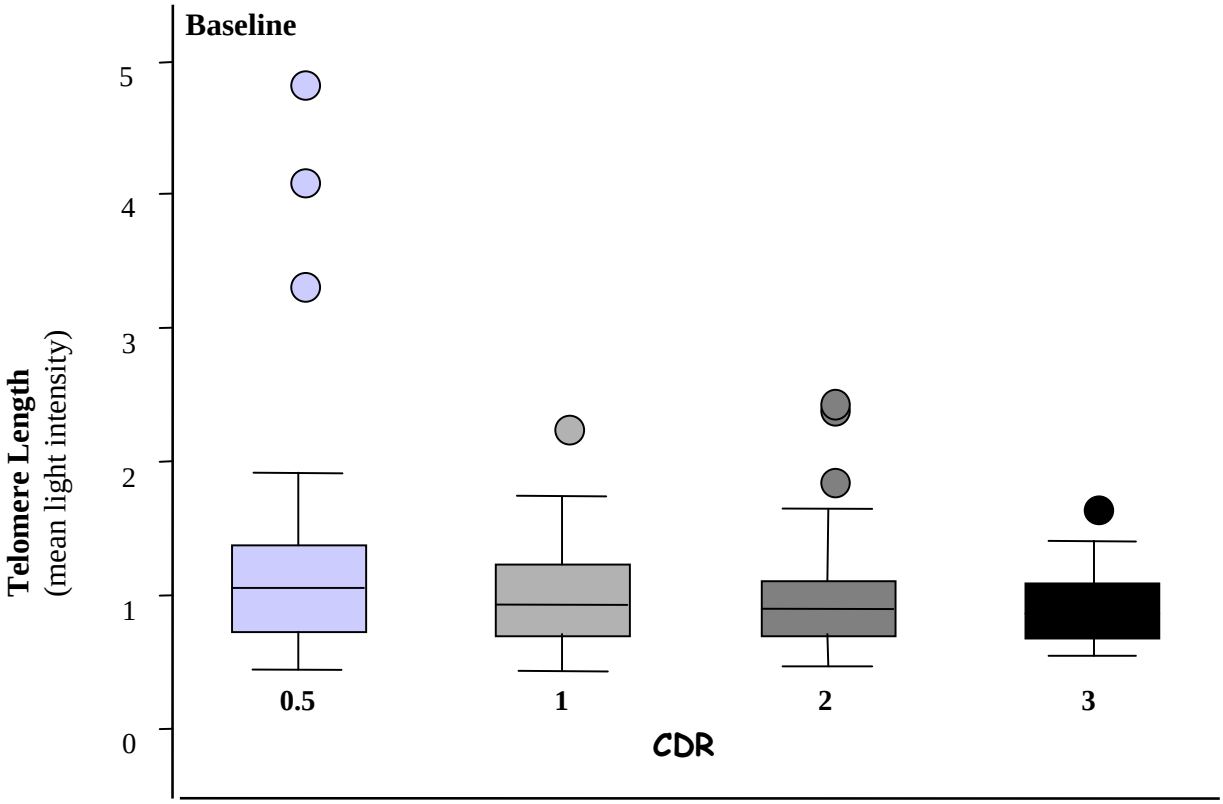


Fig. 4. Telomere length did not differ significantly according to the different degrees of dementia severity ($p = 0.195$) (according to clinical dementia rating scores) [26].

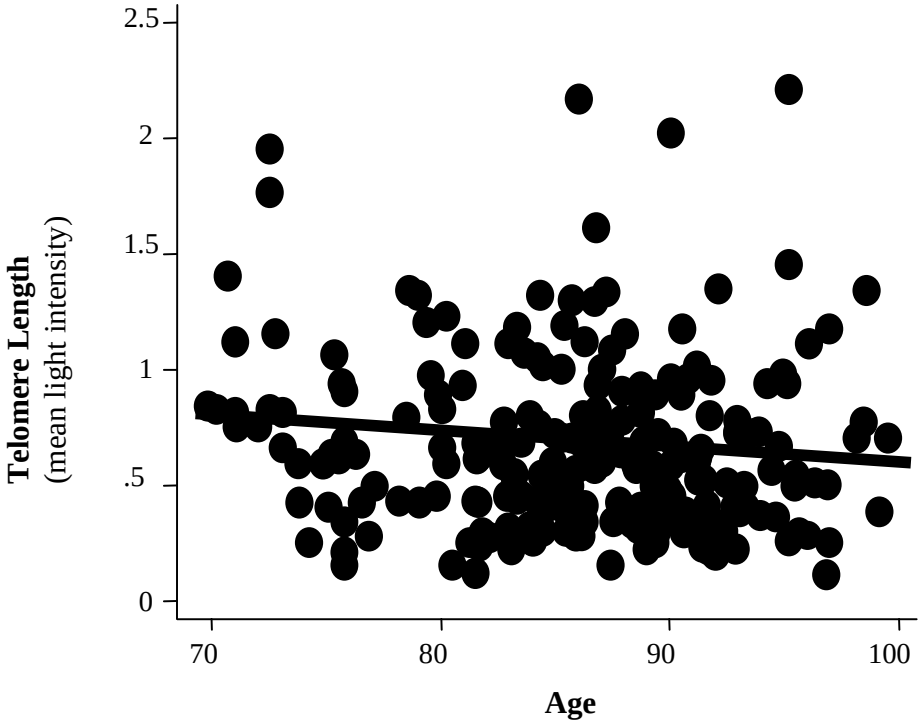


Fig. 5. In a multiple linear regression analyses, age, sex and cognitive status do not predict telomere length (p=0.063, 0.232 and 0.542 respectively; r-squared = 2.1%)

PAPER 10

Telomere length and ApoE polymorphism in mild cognitive impairment, degenerative and vascular dementia

Dina Zekry, François R. Herrmann, Irmingard Irminger-Finger, Christophe Graf, Chantal Genet, Anna-Maria Vitale, Jean-Pierre Michel, Gabriel Gold, Karl-Heinz Krause

The Journal of the Neurological Sciences 2010;299:108-111

In addition to telomere length, we have simultaneously analyzed the impact of ApoEε4 polymorphism; which is the best known genetic risk factor strongly associated with old age dementia; on the prevalence of dementia in very old subjects, in diagnosing MCI and in differentiating AD from VaD and mixed dementia (MD).

ApoEε4 was statistically associated with patients with dementia compared to cognitively normal or MCI patients. On the contrary, the frequencies of the ApoE polymorphism did not differ significantly among the various aetiologies of dementia (AD, VaD and MD).

In ordered logistic regression analysis, age and ApoEε4 were predictive of dementia. Each supplementary year added 3% of additional risk of being demented (OR=1.03). Patients carrying at least one allele of ApoEε4 doubled their risk of dementia as compared to normal or MCI patients (OR=2.12) but telomere length did not reach statistical significance.

Our study in very old demented and non demented subjects shows that telomere length, alone or combined with the ApoE polymorphism cannot be used to distinguish between demented and non demented patients, regardless of the type of dementia considered or MCI.

Journal of the Neurological Sciences 299 (2010) 108–111

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Telomere length and ApoE polymorphism in mild cognitive impairment, degenerative and vascular dementia

Dina Zekry [a,*], François R. Herrmann [a], Irmgard Irminger-Finger [b], Cristophe Graf [a], Chantal Genet [a], Anna-Maria Vitale [a], Jean-Pierre Michel [a], Gabriel Gold [a], Karl-Heinz Krause [b]

[a] Geneva University, Rehabilitation and Geriatrics Department, Thônex, Switzerland
[b] Geneva University, Department of Pathology and Immunology, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 6 April 2010
Accepted 27 July 2010
Available online 14 August 2010

Keywords:
Vascular dementia
Alzheimer's disease
Mixed dementia
MCI
Aged
Telomere length

ABSTRACT

Background: Clarifying the aetiology of dementia is of crucial importance in the management of patients as well as for research purposes but it is not always possible clinically. Therefore the identification of biological markers should complement clinical approaches. Telomere shortening is emerging as an important mechanism in vascular aging and the pathogenesis of hypertension and atherosclerosis. Thus, telomere length could be a potential candidate to accurately separate vascular from degenerative cognitive impairment.

Objectives: To evaluate the usefulness of telomere length alone or combined with ApoE polymorphism in diagnosing mild cognitive impairment (MCI) and in differentiating Alzheimer's disease (AD) from vascular (VaD) and mixed dementia (MD).

Methods: Telomere length in peripheral blood lymphocytes was performed by flow cytometry in 439 patients (mean age, 85.1 years): 204 cognitively normal, 187 demented patients: 80 AD, 86 MD, and 21 with VaD; and 48 patients with MCI. Simple and multiple ordered logistic regressions were used to predict the risk of dementia from telomere length, ApoE polymorphism and age.

Results: ApoEε4 was statistically associated with patients with dementia ($p<0.001$) compared to cognitively normal or MCI patients; but not with the aetiologies of dementia (AD, VaD and MD) ($p=0.385$). No significant differences in telomere length were found among patients with different aetiologies or severities of dementia. In the global model, the combination of telomere length and ApoE polymorphism did not confer a significantly higher dementia risk (OR=0.95, 95% CI=0.69–1.32; $p=0.784$) than APOEε4 alone (OR=2.12, 95% CI=1.15–3.9; $p=0.016$).

Conclusion: This longitudinal study in very old patients provided no evidence suggesting that telomere length alone could be used to distinguish between the different types of dementia or MCI, nor combined with the ApoE polymorphism.

1. Introduction

Distinguishing accurately among different types of dementia, especially from degenerative and vascular origin is not always possible on purely clinical ground. The identification of biological markers could complement clinical approaches facilitating risk prediction, early and accurate diagnosis, and monitoring newly developed treatments [1]. Telomere length is emerging as an important mechanism in vascular aging and, consequently, in the pathogenesis of hypertension, atherosclerosis, and heart failure [2–7] and represents a potential biomarker. Telomeres are essential elements consisting of non coding repetitive DNA sequences and binding proteins, located at the ends of chromosomes [8,9]. The importance of telomeres lies in their multiple roles: they protect against degeneration, prevent chromosome fusion, cell death and neoplastic transformation, and are essential for chromosomal stability. DNA replication mechanisms result in the ends of chromosomes remaining single-stranded, leading to gradual telomere shortening. The critical shortening of telomeres leads to cell cycle arrest and cellular senescence, also known as replicative senescence [10]. Assuming that cells have a limited potential for proliferation, telomere length can be used as a marker of a specific tissue's biological age [11]. Telomere shortening during aging has been demonstrated *in vivo* and has been associated with DNA damage. Oxidative stress throughout the lifetime of a cell can lead to DNA damage, promoting telomere shortening. Telomere length therefore reflects not only biological age, but also stress management capacity. Telomere shortening may be a major determinant of human aging not only at the cellular level, but

* Corresponding author. Geneva University, Geriatrics Department, 3, chemin du Pont-Bochet, 1226, Thônex, Switzerland. Tel.: +41 22 3056355; fax: +41 22 3056115.
E-mail address: dina.zekry@hcuge.ch (D. Zekry).

0022-510X/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2010.07.019

also at the organ and, perhaps, systemic levels [12]. The purpose of this study was to assess the diagnostic value of telomere length alone or combined with ApoE polymorphism, which is the best known genetic risk factor strongly associated with old age dementia, in four groups of patients: those with mild cognitive impairment (MCI), Alzheimer's disease (AD), vascular dementia (VaD) and mixed dementia (MD).

2. Methods

2.1. Patients and data collection

We carried out a prospective study in a 300 bed geriatric hospital (HOGER) of the University Hospitals of Geneva, Switzerland, for acute illness. Patients and data collection have been described elsewhere [13]. Briefly, patients were recruited by clinically trained staff. All patients over 75 years of age and consecutively admitted on selected days between January 2004 and December 2005 were included. We selected a random sample of patients for each day, using a computer-generated randomization table. The local ethics committee approved the protocol and patients or their families or legal representatives gave signed written informed consent. Medical history was recorded on a standardized form and the same geriatrician carried out physical examinations on all patients. The data recorded included age, sex, native language, marital status, living arrangement and educational level.

2.2. Cognitive diagnosis

The same neuropsychologist assessed all included subjects for possible clinical dementia, at least one week after inclusion, to reduce the possibility of concomitant delirium. The following neuropsychological screening battery was applied: the Mini mental state examination (MMSE) [14] and The Short Cognitive Evaluation Battery (SCEB) [15,16]. The short version of the Geriatric Scale was used to screen for depression [17]. Based on this screening, a comprehensive standardized battery of neuropsychological tests used in routine clinical practice was carried out by the same neuropsychologist, with formal clinical criteria used to determine the aetiology and severity of clinical dementia: The Mattis Dementia Rating Scale as a global scale [18], The Buschke Double Memory Test [19], which assesses episodic memory and provides cognitive support for both encoding and retrieval, discriminating effectively between normal elderly subjects and those with mild dementia; The Trail-Making Test [20], which measures mental flexibility, and The Verbal Fluency Test, which investigates verbal incitement, both of which assess executive function; The CERAD Figures [21], which measure visuospatial and construction abilities; The Lexis or Bachy test for language. Dementia severity was assessed with the Clinical Dementia Rating Scale [22]. Subsequently, the same geriatrician applied the formal clinical criteria for the aetiology of dementia: DSM IV-TR [23] for dementia, NINCDS-ADRDA [24] for AD and NINDS-AIREN [25] for VaD and MD. Cerebral imaging was also used to support the subgroup classification of dementia for all patients. Patients were assigned to five groups: i) cognitively normal, ii) patients with MCI [26] ii) AD, iii) VaD and iiii) MD. 11 patients with other types of dementia like fronto-temporal dementia were excluded from the analysis.

2.3. Telomere length measurements

Telomere length were determined as a function of fluorescence intensity, using an FITC-labeled peptide nucleic acid (PNA) probe (FITC-coupled) supplied with the telomere PNA/FITC for flow cytometry kit by DAKO. The method is ideal for estimating telomere length, as cell fluorescence intensity is directly correlated with telomere length.

2.3.1. In situ hybridization

Lymphocytes were prepared for hybridization in the presence of hybridization solution without probe or in hybridization solution containing fluorescein-conjugated PNA telomere probe, as described in Hultdin et al. [27].

2.3.2. Flow cytometry

Homogeneous lymphocyte subpopulations were identified. DNA was labeled with DAPI to identify cell populations with similar DNA content, with gating on the G1 population. FITC-labeled cells were counted in the gated population. As an internal control, telomere length was measured in a standard cell line (HL60), which allowed normalizing the flow cytometric measurements with respect to day to day variations. Image analysis was performed with the same flow cytometer (FACS, Fluorescence Activated Cell Sorting) in each case. Mean telomere fluorescence intensity was calculated as the difference between the fluorescence signal obtained with samples hybridized with the Telomere PNA Probe/FITC and the fluorescence signal obtained with a sample of the same cells incubated with the hybridization solution without probe. Results are expressed in telomere length index, which is the fluorescent signal obtained in the patient cells divided by the fluorescent signal of the control HL-60 cells. Thus, a telomere length index of 1 indicates a telomere length in the patient sample identical to the one observed in HL-60 cells. The intra-assay coefficient of variance of this measurement was less than 2%. In all cases, the cognitive status of individuals within pairs was unknown at the time of analysis. Genotype analyses: The ApoE genotype was analyzed by sequencing PCR fragments obtained from the ApoE coding region (2795 to 3276) using specific primers. The sequence signals at positions 2901(T/C) and 3041(C/T) were read manually.

2.4. Statistical methods

We checked the normality of the data distribution, by skewness and kurtosis tests, and carried out standard transformations to normalize non Gaussian variables. Data for continuous variables are presented as means $\pm$ 1 standard deviation (SD). Mann–Whitney u tests or Kruskal–Wallis ANOVA were used to compare data between cognitively normal, MCI and demented patients and between cognitively normal or patients affected with dementia of various aetiologies or different severities. Simple and multiple logistic and ordered logistic regression analysis were then carried out to check for associations between diagnosis or their severities and the independent variables: telomere length, ApoE polymorphism and age. The quality of the model was assessed with a variant from the coefficient of determination, called pseudo R^2 which can be interpreted as the proportion of the variance of diagnosis explained. Statistical analyses were performed with Stata software version 10.1.

3. Results

The 439 patients (mean age 85.1 $\pm$ 6.8; 76% women) enrolled were assigned to three groups: 204 cognitively normal, 48 with MCI and 187 demented (80 with AD, 86 with MD and 21 with VaD). Mean age and sex ratio were similar for all groups. Table 1 summarises the ApoE allele frequencies as a function of cognitive diagnosis. ApoEε4 was statistically associated with patients with dementia ($p<0.001$) compared to cognitively normal or MCI patients. On the contrary, the frequencies of the ApoE polymorphism did not differ significantly among the various aetiologies of dementia (AD, VaD and MD) ($p=0.385$).

No significant difference in telomere length was found between cognitively normal patients and those with dementia ($p=0.443$), or between cognitively normal patients and patients with MCI or dementia ($p=0.213$). Telomere length did not differ significantly

Table 1
A comparison of ApoE allele frequencies among cognitively normal subjects, patients diagnosed with MCI and demented patients, including the various dementia aetiologies.

	Number of cases (%)							
	Cognitively normal		MCI		Dementia		Total	
ApoEε2	36	(17.7)	16	(33.3)	24	(12.8)	76	(17.3)
ApoEε3	143	(70.1)	24	(50.0)	113	(60.4)	280	(63.8)
ApoEε4	25	(12.2)	8	(16.7)	50	(26.5)	83	(18.9)
Total	204	100%	48	100%	187	100%	439	100%

ApoEε4: at least one copy of ApoEε4; ApoEε2 or ApoEε3: no copies of ApoEε4. ApoEε4 is statistically associated with patients with dementia of various aetiologies ($p<0.001$).

the dementia aetiology ($p=0.769$) or severity ($p=0.195$). In ordered logistic regression analysis, age and ApoEε4 were predictive of dementia ($p=0.043$, and 0.016 respectively; pseudo $R^2=16.9\%$). Each supplementary year added 3% of additional risk of being demented (OR = 1.03, 95% CI = 1.00–1.06). Patients carrying at least one allele of ApoEε4 double their risk of dementia as compared to normal or MCI patients (OR = 2.12, 95% CI = 1.15–3.9) (Table 2) but telomere length did not reach statistical significance ($p=0.784$).

4. Discussion

The first study to investigate the association between telemore length and dementia was cross-sectional and had a strong selection bias for stroke and VaD inpatients. The authors compared patients with AD, VaD, stroke and/or other cardiovascular risk factors. The odds ratio for VaD was two times lower in individuals with long telomeres, increasing to more than three in patients with short telomeres [28]. Panoussian et al., using the MMSE as a marker of AD disease showed that telomere length and cognitive function were related [29]. These cross-sectional studies were carried out on small cohorts of younger elderly patients, using only the MMSE to assess cognitive function. In a larger study in an older population ($n=598$, mean age 90 years), telomere length was not predictive of dementia incidence, again based on MMSE alone [30]. A recent study by this group on 195 non demented stroke survivors with a mean age of 80 years showed that telomere length was predictive of post-stroke cognitive decline, dementia and death [31]. However, cognitive evaluation by MMSE alone is not sensitive or specific for detecting changes in thus an advanced age population (90 years for the first study), particularly after stroke (for the second study). All these studies, including ours, measured telomere length in white blood cells. This is logical with respect to the accessibility of the patient's material and previous studies, which suggest that telomere length in blood, can be used as a surrogate marker for telomere length in other tissues [32].

The principal strength of our cohort is that the same neuropsychologist carried out the same systematic neuropsychological assessment increasing the accuracy of cognitive diagnosis. This study is also the first of its type to consider a group of patients with MCI. In addition to telomere length, we have simultaneously analyzed the impact of ApoEε4 on the prevalence of dementia in very old subjects, which is the best known genetic risk factor strongly associated with old age dementia [33]. With respect to dementia aetiology, ApoEε4 is a risk factor for AD, but probably also for VaD [34]. This study in very old demented and non demented subjects shows that telomere length, alone or combined with the ApoE polymorphism cannot be used to distinguish between demented and non demented patients, regardless of the type of dementia considered or MCI.

Table 2
Multiple logistic and ordered logistic regressions predicting the risk of dementia from telomere length while adjusting for ApoE polymorphism and age.

Outcomes	Independent variables	Ordered logistic regression		
		Adjusted OR	95% CI	p
Dementia (compared to cognitively normal and MCI)				
	ApoEε2	1.00	–	–
	ApoEε3	1.04	0.64–1.69	0.877
	ApoEε4	**2.12**	1.15–3.9	**0.016**
	Telomere length	0.95	0.69–1.32	0.784
	Age	**1.03**	1.00–1.06	**0.043**
Dementia (compared to MCI)				
	ApoEε2	1.00	–	–
	ApoEε3	**3.19**	1.43–7.13	**0.005**
	ApoEε4	**3.48**	1.28–9.49	**0.015**
	Telomere length	0.55	0.30–1.01	0.055
	Age	1.02	1.00–1.06	0.974
Different types of dementia (Alzheimer's disease, vascular dementia or mixed dementia)				
	ApoEε2	1.00	–	–
	ApoEε3	0.92	0.37–2.29	0.858
	ApoEε4	0.93	0.42–2.54	0.891
	Telomere length	1.18	0.68–2.03	0.563
	Age	0.98	0.93–1.02	0.334

Bold entries = relevant results.

Acknowledgments

We would like to thank the teams of Mrs. O. Baumer, L Humblot and M Cos for technical assistance. This work was supported by grant 3200B0-102069 from the Swiss National Science Foundation.

References

[1] Papassotiropoulos A, Hock C. Biochemical markers of Alzheimer's disease: wish and reality. Neurobiol Aging 2002;23:513–4.
[2] Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, et al. Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci USA 1992;89:10114–8.
[3] Aviv A, Aviv H. Reflections on telomeres, growth, aging, and essential hypertension. Hypertension 1997;29:1067–72.
[4] Davis T, Kipling D. Telomeres and telomerase biology in vertebrates: progress towards a non-human model for replicative senescence and ageing. Biogerontology 2005;6:371–85.
[5] Jeanclos E, Krolewski A, Skurnick J, Kimura M, Aviv H, Warram JH, et al. Shortened telomere length in white blood cells of patients with IDDM. Diabetes 1998;47:482–6.
[6] Lindsey J, McGill NI, Lindsey LA, Green DK, Cooke HJ. In vivo loss of telomeric repeats with age in humans. Mutat Res 1991;256:45–8.
[7] Oexle K, Zwirner A. Advanced telomere shortening in respiratory chain disorders. Hum Mol Genet 1997;6:905–8.
[8] Nawrot TS, Staessen JA, Gardner JP, Aviv A. Telomere length and possible link to X chromosome. Lancet 2004;363:507–10.
[9] Vaziri H, Benchimol S. From telomere loss to p53 induction and activation of a DNA-damage pathway at senescence: the telomere loss/DNA damage model of cell aging. Exp Gerontol 1996;31:295–301.
[10] Blackburn EH. Switching and signaling at the telomere. Cell 2001;106:661–73.
[11] Friedrich U, Griese E, Schwab M, Fritz P, Thon K, Klotz U. Telomere length in different tissues of elderly patients. Mech Ageing Dev 2000;119:89–99.
[12] Harley CB, Vaziri H, Counter CM, Allsopp RC. The telomere hypothesis of cellular aging. Exp Gerontol 1992;27:375–82.
[13] Zekry D, Herrmann F, Grandjean R, Vitale-Tiar A-M, Gold G, Krause K-H. Does cognitive impairment influence hospitalization outcomes? A prospective study in aged inpatients. Int J Geriatr Psychiatry 2009;24:283–91.
[14] Folstein MF, Folstein SE, Mac Hugh PR. Mini Mental State: a practical method for grading the cognitive state of patients for the clinician. J Pychiatr Res 1975;12:189–98.
[15] Robert PH, Schuck S, Dubois B, Olie JP, Lepine JP, Gallarda T, et al. Screening for Alzheimer's Disease with the short cognitive evaluation battery. Dement Geriatr Cogn Disord 2003;15:92–8.
[16] Salomon PR, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux RD, et al. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998;55:349–55.
[17] van Marwijk HW, Wallace P, de Bock GH, Hermans J, Kaptein AA, Mulder JD. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. Br J Gen Pract 1995;45:195–9.

[18] Gardner R, Oliver-Munoz S, Fisher L, Empting L. Mattis Dementia Rating Scale: internal reliability study using a diffusely impaired population. J Clin Neuropsychol 1981;3:271–5.
[19] van der Linden M. Adaptation française de la procédure de Grober et Buschke. Marseille: Solal; 1999.
[20] Reitan RM. Validity of the Trail-Making Test as an indicator of organic brain damage. Percept Mot Skills 1958;8:271–6.
[21] Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Neurology 1994;44:609–14.
[22] Morris JC. The clinical dementia rating: current version and scoring rules. Neurology 1993;43:2412–4.
[23] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed Text Revision (DSM IV-TR). Washington, DC: American Psychiatric Association; 2000.
[24] McKahn G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group. Neurology 1984;34:939–44.
[25] Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–60.
[26] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.
[27] Hultdin M, Grönlund E, Norrback K, Eriksson-Lindström E, Just T, Roos G. Telomere analysis by fluorescence in situ hybridization and flow cytometry. Nucleic Acids Res 1998;26:3651–6.
[28] von Zglinicki T, Serra V, Lorenz M, Saretzki G, Lenzen-Grossimlighaus R, Gessner R, et al. Short telomeres in patients with vascular dementia: an indicator of low antioxidative capacity and a possible risk factor? Lab Invest 2000;80:1739–47.
[29] Panossian LA, Porter VR, Valenzuela HF, Zhu X, Reback E, Masterman D, et al. Telomere shortening in T cells correlates with Alzheimer's disease status. Neurobiol Aging 2003;24:77–84.
[30] Martin-Ruiz CM, Gussekloo J, van Heemst D, von Zglinicki T, Westendorp RG. Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: a population-based study. Aging Cell 2005;4:287–90.
[31] Martin-Ruiz C, Dickinson HO, Keys B, Rowan E, Kenny RA, Von Zglinicki T. Telomere length predicts poststroke mortality, dementia, and cognitive decline. Ann Neurol 2006;60:174–80.
[32] Friedrich U, Griese E, Schwab M, Fritz P, Thon K, Klotz U. Telomere length in different tissues of elderly patients. Mech Ageing Dev 2000;119:89–99.
[33] Coon KD, Myers AJ, Craig DW, Webster JA, Pearson JV, Lince DH, et al. A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. J Clin Psychiatry 2007;68:613–8.
[34] Davidson Y, Gibbons L, Purandare N, Byrne J, Hardicre J, Wren J, et al. Apolipoprotein E epsilon4 allele frequency in vascular dementia. Dement Geriatr Cogn Disord 2006;22:15–9.

DISCUSSION AND CONCLUSIONS

- **Discussion**

This series of elderly inpatients was found to be representative of the overall population hospitalized in the same geriatric hospital and highlights the quality of randomization in this study. No differences in demographic characteristics and functional status were found between the study sample and the entire population of patients admitted to the same hospital during the same inclusion period, or between the study sample and excluded patients or patients who refused to participate.

The principal strength of this large prospective clinico-biological study, performed in the same centre and by the same team, is it's clinically and biological rich prospective data collection from a large group of very ill hospitalized elderly patients. This study was carried out, firstly, to improve our understanding of the role of dementia of the very old, as a predictor of adverse outcomes when other risk factors are taken into account. Secondly, to better define the diagnostic and prediction performance of some biomarkers candidates. From the 449 patients (mean age 85.1 ± 6.8; 76 % women) enrolled 205 were cognitively normal, 49 had MCI and 195 were demented (77 with AD, 82 with mixed dementia and 21 with vascular dementia). The mean age and sex ratio were similar for all groups. The prevalence of dementia (44%) was very high. The reported prevalence of dementia in elderly inpatients (geriatric acute and sub acute wards) varies between 20 and 30%. A previous study in the same hospital 6 years ago reported a prevalence of 30%. This difference is statistically significant ($p = 0.000$) [Herrmann et al, 1999]. These findings probably reflect the systematic and complete assessment of cognitive impairment in the random sample used to determine dementia prevalence, done by the same neuropsychologist, increasing the accuracy of cognitive diagnosis. In addition, the neuropsychological assessment was done at least one week after inclusion, to reduce the possibility of concomitant delirium. The inclusion of a large number of patients with dementia in this study was useful, as it made it possible to measure the impact of dementia on the outcomes. Moreover, the age of the patients included in the study is consistent with the distribution of dementia in the population of industrialized countries (average 85 years). Our study was also unusual in its inclusion of a group of patients with MCI in addition to the demented and non demented groups.

In this study, the same geriatrician calculated all six comorbidity scores for each patient, by extensive review of the patient's medical records and administrative data for diagnoses established at or before enrolment in this study and through standardized interviews with patients and their representatives (surrogates). Contrary to previous clinical studies and in

according to clinico-pathological studies, our data showed that demented patients, non-demented patients and patients with MCI had similar levels of comorbidity. However, functional and nutritional status was poorer in the demented patients. Some illnesses are more likely to remain undiagnosed and thus untreated in demented patients.

A few series of autopsies have confirmed this hypothesis, showing that demented patients often have a number of comorbid conditions and that these conditions are frequently underestimated by clinicians. For example, in a study carried out in the same department in Geneva, 342 autopsies were studied, 120 of which concerned demented patients. The immediate cause of death was similar for demented and non-demented subjects. The leading causes of death were cardiovascular and infectious diseases [Kamoun et al, 2000].

We need to consider whether doctors are unwilling to investigate demented patients thoroughly and to diagnose diseases in these patients. Similar results were found in a cross-sectional population-based study in Finland where all inhabitants aged 64 years and more were included. The study showed that 66% of the 112 demented patients included had at least one undiagnosed disease, versus only 48% of the non-demented group. The demented subjects were more likely than the controls to have undiagnosed hypercholesterolaemia or hypothyroidism [Löppönen et al, 2004]. For the same cohort, almost 78% of patients suffering from mild dementia had at least one undiagnosed disease, versus 57% in the moderate dementia group and 55% in the severe dementia group. Note that there was no significant association between the number of undiagnosed diseases and the severity of dementia.

We carried out, for the first time, a prospective study comparing the use of six comorbidity scores the most widely used and validated in elderly subjects for the prediction of hospitalization, one-year and 5-years adverse outcomes in elderly patients with acute disease. Previous studies have used only one comorbidity score and have mostly been retrospective. Our data have shown that among the most used comorbidity scores, the CIRS and the GIC could improve hospital discharge planning in a geriatric hospital treating very old patients with acute disease, being useful for clinical decision-making purposes and for clinical research in older patients. They were the best predictors of intra-hospital, one-year and 5-years adverse outcomes. This is probably due to the fact that the CIRS as well as the GIC assumes that the impact of all diseases are additive. For these two scores, co-morbidity should take into account both the number of diseases and the occurrence of very severe diseases as determinants of health. Our data showed that the Charlson comorbidity index (CCI), the most extensively studied comorbidity index, failed to predict the studied adverse outcomes. In fact,

the CCI was designed and scaled to predict mortality based on the mortality of 607 patients admitted to a general internal medicine service in a single New England hospital during 1 month in 1984. This index does not take into account the severity of certain major diseases but only the presence of the disease. For example, in the case of congestive heart failure, patients with either a mild or a severe form of the disease will be assigned a score of one. This index may therefore fail to identify important diseases, or their severity, in the elderly, which may otherwise act as predictors of adverse outcomes. On the contrary, certain pathological conditions, such as acquired immunodeficiency syndrome, are heavily weighted in the index yet rarely encountered in the elderly, while other highly elderly prevalent conditions, such as chronic heart failure, are probably underestimated. The CCI has previously been found, in a retrospective manner, to be limited in determining the full range of diseases in elderly patients and our results confirmed, in a prospective way, that this score is not indicate to the aged population. In addition, our study confirmed that the Kaplan scale, a useful comorbidity index for clinical diabetes research distinguishing between vascular and nonvascular comorbidity is less useful for assessing comorbidity in the elderly. In the ICED, physical impairment is considered to be an additional dimension of comorbidity, in a consequence subjects with no disease but with problems with vision and hearing are directly scored ICED 3. Probably this was the reason why 80% of our patients were classified ICED class 4, confirming the low power of prediction of this score in a very old population Finally, the CDS performed the most poorly for predicting all the studied outcomes. The negative predictive value of the CDS, a medication-based score, was consistent with earlier findings and may be due to the use of preventive treatments or treatment for benign conditions in healthier patients.

Our data support that dementia does not predict adverse outcomes when other risk factors like comorbid conditions, functional and nutritional status are taken into account. Higher levels of comorbidity and poor functional status were more predictive than dementia for death in hospital, longer hospital stay or increase on formal care; dementia being a predictor only for institutionalization after discharge. Regarding one-year and 5-year mortality risk, the presence of dementia does not predict survival whereas the weight of multiple comorbidity conditions, functional impairment and nutritional status are significantly associated. In this study, there was only a trend for dementia to predict 5-year-mortality (with dementia tending to give higher mortality rates) in the univariate model. This trend disappeared completely when all the variables were integrated into the full model. Similarly, VaD and severe to

moderate dementia were associated with a higher risk of long-term mortality in the univariate model, but this association disappeared when all the factors studied were taken into account in the multivariate model. On the contrary, many studies have examined survival in relation to dementia and the majority has reported that dementia increases the risk of death compared to no dementia [Tschanz et al, 2004; Ganguli et al, 2005]. Recently, a Danish population-based cohort study (14 years of follow-up) involving 3,065 nondemented and 234 demented at baseline, showed that the hazard ratio of death (95% confidence interval) increased from 1.82 (1.55-2.14) for the very mildly demented to 9.52 (6.60-13.74) for the severely demented subjects [Andersen et al, 2010]. The majority of these studies are population based and have examined survival from the time of diagnosis of dementia, whereas our study, which was not designed for this purpose, was based on a selected group in a clinical setting and 42% of the cohort had dementia diagnosis at baseline.

In our population of very old patients, the 5-year mortality rate was almost 60% after discharge. This rate is similar to that reported in previous studies. Age itself is a well known negative prognostic risk factor for death and this factor accounted for almost 10% of the variance of the outcome in this study. Nonetheless, higher comorbidity and poor functional status both had a negative effect on survival. Previous studies have also shown that poorer functional status before and at the time of hospital admission is associated with higher short- and long-term mortality [Inouye et al, 1998; Epaulella et al, 2007] and higher comorbidity scores. Cognitive impairment is also often used as a predictor of poorer hospitalization outcomes, including mortality in particular, but only a few studies have also taken comorbid medical conditions and functional status into account [Epaulella et al, 2007; Drame et al, 2008; Tschanz et al, 2004; Ganguli et al, 2005]. We assessed long-term mortality in acutely ill very old patients with and without dementia. The groups with and without dementia were of similar age and had a similar level of comorbidity; and we took into account the various aetiologies of dementia and other important potential predictors of mortality, such as functional status. In some of these studies, cognition was assessed with the MMSE alone. The MMSE is neither sensitive nor specific for the detection of dementia in a very old population and, furthermore, does not distinguish between different types of dementia. One of the main strengths of this study was the standardized comprehensive assessment: the same neuropsychologist carried out the same systematic, complete neuropsychological assessment of all the included patients, increasing the accuracy of cognitive diagnosis. The same geriatrician scored the presence and extent of comorbidity for all patients and the same nurse

obtained the scores for functional tools. Our study was also unusual in its inclusion of a group of patients with MCI in addition to the demented and non demented groups. These patients behaved more like patients with normal cognition than demented patients.

In the univariate model, VaD and moderate to severe dementia were independent predictors of long-term mortality. Taking the other covariables into account had two interesting effects. Firstly, the effect of dementia severity and VaD completely disappeared. Secondly, comorbid medical conditions remained the most predictive indicator, regardless of cognitive status, with functional status the next most useful predictive factor, but only considering instrumental activities of daily living. No significant relationship with base activities was found in this model.

In addition, we evaluated the weight of a biological predictor (telomere length) alone and compared to the others studied health predictors. It was hypothesized and confirmed that poor health variables exceed biological factors like telomere length measure. Several studies have examined telomere length as determinant of mortality in the elderly. There is considerable inconsistency in the current literature. Some reports have shown associations of shorter telomere length with lower survival: Cawthon and colleagues [Cawthon et al, 2003] in their study of individuals 60 years old or older, demonstrated that the overall mortality rate of persons with short telomeres was nearly double that of individuals with long telomeres; Bakaysa et al. [Bakaysa et al, 2007] reported that twins with shorter telomere length have three times the risk of death compared with their co-twins with longer telomere length. In contrast other studies showed no association between leukocyte telomere length and survival in older individuals' aged more than 85 years [Bischoff et al, 2006; Martin-Ruiz et al, 2005]. More recently, Terry et al. had examined telomere length in centenarians in good health versus poor health. Healthy centenarians had significantly longer telomeres than did unhealthy centenarians ($p=0.0475$) [Terry et al, 2008]. They have demonstrated that investigations of the association between telomere length and exceptional longevity must take into account the health status of the individuals and have raised the possibility that perhaps it is not exceptional longevity but one's function and health that may be associated with telomere length. Our results confirmed this hypothesis.

Regarding this biomarker candidate, our data showed one strong negative result contrary to a previous study [Panossian et al, 2003]. In this first large collection in the very old with a yearly telomere length measure, provided no evidence to suggest that telomere length alone

could be used to distinguish between demented and non demented patients, regardless of the type of dementia, or to predict dementia or MCI conversion; nor combined with the ApoE polymorphism.

We would like to point out that thanks to the prospective design of this study, repeated measures of the presented assessments of function and of comorbidity and repeated telomere length analyses were done and would have probably added additional information to the research. This is of importance because of the dynamic of ageing. Five years are a long period in the life of an old person and only small events can dramatically change their course. For example an additional comorbidity at follow up year one could have a tremendous impact upon the "slope" of the functional decline curve in the subsequent years. We are entering to analyze repeated measurements of functionality and of comorbidity. In addition, the delta telomere (emerged from the repeated measures of telomere length), already analyzed as a predictor of dementia and MCI conversion (paper 9) is being analyzed as predictor of long-term mortality.

- **Conclusions**

The first important conclusion is that special efforts should be made to deal with existing comorbidities and to detect unreported problems in demented patients. Improving the detection and treatment of comorbid diseases represents a challenge for health professionals caring for patients with dementia. Greater attention to these complex issues on the part of families, carers and clinicians should improve outcomes for these patients.

The second important conclusion of our work is that it is unlikely that one particular index can be used to predict a variety of relevant outcomes. The choice will depend on the outcomes of interest. Based in our results, we can recommend more usefully the GIC in predicting vital outcomes probably because of its link to physiological aspects of diseases; and the CIRS in predicting care outcomes because of its link to functional aspects.

The third important conclusion is that comorbid medical conditions, functional and nutritional status should be considered, together with cognitive assessment, when predicting intra-hospital, short and long-term hospitalization adverse outcomes. In conclusion, understanding how to efficiently predict adverse outcomes in hospitalized elders is important for a variety of clinical and policy reasons. Evaluating these markers may increase the accuracy of short and long-term discharge planning in the very old.

Finally, telomere length alone can not be use as a predictor of dementia and MCI conversion. This is also true even combined with the ApoE polymorphism.

- **General conclusion**

In conclusion, in this cohort of oldest old, the presence of dementia is not a predictor of short or long-term survival after discharge, whereas higher levels of comorbidity and poor functional and nutritional status are. Comorbid medical conditions, functional and nutritional status should therefore be considered, together with cognitive assessment, when trying to predict long-term hospitalization outcomes in very old medically ill inpatients. Hospital discharge planning and prognosis can help physicians and family members plan for the care of patients who may be at increased risk of adverse outcomes in the coming years, especially regarding discussions of goals of care, treatment preferences, advance planning, and clinical therapeutic options. Hospitalization therefore may present a key trigger point to identify persons at greatest risk for mortality in the years following discharge. These findings have widespread implications for improved planning of the hospitalization period through the discharge of very ill elderly patients with acute disease.

REFERENCES

Aevarsson O, Svanborg A, Skoog I. (1998) Seven-year survival rate after age 85 years: relation to Alzheimer disease and vascular dementia. Arch Neurol 55:1226-32.

Aguero-Torres H, Fratiglioni L, Winblad B. (1998) Natural history of Alzheimer's disease and other dementias: review of the literature in the light of the findings from the Kungsholmen Project. Int J Geriatr Psychiatry 13:755-66.

Aguero-Torres H, Fratiglioni L, Guo Z, Viitanem M, von Strauss E, Winblad B. (1998). Dementia is the major cause of functional dependence in the elderly: 3-year follow-up data from a population-based study. Am J Public Health 88: 1452-6.

Allsopp RC, Vaziri H, Patterson C, et al. (1992) Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci USA 89:10114-8.

Andersen K, Lolk A, Martinussen T, Kragh-Sørensen P. (2010) Very mild to severe dementia and mortality: A 14-year follow-up - The Odense study. Dement Geriatr Cogn Disord 29:61-7.

Aviv A and Aviv H. (1997) Reflections on telomeres, growth, aging, and essential hypertension. Hypertension 29:1067-72.

Bakaysa SL , Mucci LA , Slagboom PE, et al. (2007) Telomere length predicts survival independent of genetic influences. Aging Cell 6:769-774.

Barclay LL, Zemcov A, Blass JP, Sansone J. (1985) Survival in Alzheimer's disease and vascular dementias. Neurology 35:834-40.

Bertozzi B, Barbisoni P, Franzoni S, Rozzini R, Frisoni GB, Trabucchi M. (1996) Factors related to length of stay in a geriatric evaluation and rehabilitation unit. Aging (Milano) 8:170-5.

Bischoff C, Graakjaer J, Petersen HC, et al. (2005) The heritability of telomere length among the elderly and oldest-old. Twin Res Hum Genet 8:433-9.

Bischoff C, Petersen HC, Graakjaer J, et al. (2006) No association between telomere length and survival among the elderly and oldest old. Epidemiology 17:190-4.

Blackburn EH. (2001) Switching and signaling at the telomere. Cell 106:661-73.

Bonsignore M, Heun R. (2003) Mortality in Alzheimer's disease. Dement Geriatr Cogn Didord 15:231-6.

Campisi J, Kim SH, Lim CS, Rubio M. (2001) Cellular senescence, cancer and aging: the telomere connection. Exp Gerontol 36:1619-37.

Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. (2003) Association between telomere length in blood and mortality in people aged 60 years or older. Lancet 361:393-395.

Chan SW and Blackburn EH. (2003) Telomerase and ATM/Tel1p protect telomeres from nonhomologous end joining. Mol Cell 11:1379-87.

Charlson ME, Pompei P, Ales KL, Mackenzie CR. (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373-83.

Davis T and Kipling D. (2005) Telomeres and telomerase biology in vertebrates: progress towards a non-human model for replicative senescence and ageing. Biogerontology 6:371-85.

DePinho RA. (2000) The age of cancer. Nature 408:248-54.

Di Iorio A, Longo A, Mitidieri Costanza A. (1999) Factors related to the length of in-hospital stay of geriatric patients. Aging (Milano) 11:150-4.

Drame M, Jovenin N, Novella JL, et al. (2008) Predicting early mortality among elderly patients hospitalised in medical wards via emergency department: the SAFES cohort study. J Nutr Health Aging 12:599-604.

Espaulella J, Arnau A, Cubí D, Amblàs J, Yánez A. (2007) Time-dependent prognostic factors of 6-month mortality in frail elderly patients admitted to post-acute care. Age Ageing 36:407-413.

Fogel JF, Hyman RB, Rock B, Wolf-Klein B. (2000) Predictors of hospital length of stay and nursing home placement in an elderly medical population. J Am Med Dir Assoc 1:202-10.

Folstein MF, Folstein SE, Mac Hugh PR. (1975) Mini Mental State: a practical method for grading the cognitive state of patients for the clinician. J Pychiatr Res 1975;12:189-98.

Ganguli M, Dodge HH, Shen C, Pandav RS, Dekosky ST. (2005) Alzheimer disease and mortality: a 15-year epidemiological study. Arch Neurol 62:779-84.

Gasser SM. (2000) A sense of the end. Science 288:1377-9.

Gijsen R, Hoeymans N, Schellevis FG, et al. (2001) Causes and consequences of comorbidity: a review. J Clin Epidemiol 54:661-74.

Greenfield S, Sullivan L, Dukes KA, et al. (1995) Development and testing of a new measure of case-mix for use in office practice. Med Care 33:AS47-55.

Guehne U, Angermeyer MC, Riedel-Heller S. (2006) Is mortality increased in mildly cognitively impaired individuals? A systematic literature review. Dement Geriatr Cogn Disord 21:403-10.

Guijarro R, San Román CM, Gómez-Huelgas R, et al. (2010) Impact of dementia on hospitalization. Neuroepidemiology 35:101-8.

Harley CB, Futcher AB, Greider CW. (1990) Telomeres shorten during ageing of human fibroblasts, Nature 1990;345:458-60.

Harley CB, Vaziri H, Counter CM, Allsopp RC. (1992) The telomere hypothesis of cellular aging. Exp Gerontol 27:375-82.

Herrmann F, Mermod J-J, Henderson S, Michel J. (1999) Epidemiology of dementia in Geneva. In: Michel J.-P. HPR, ed. Management of Aging. The University of Geneva Experience. Basel: Karger 94-100.

Inouye SK, Peduzzi PN, Robison JT. (1998) Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 279:1187-93.

Jeanclos E, Krolewski A, Skurnick J, et al. (1998) Shortened telomere length in white blood cells of patients with IDDM. Diabetes 47:482-6.

Kammoun S, Gold G, Bouras C, et al. (2000) Immediate causes of death of demented and non-demented elderly. Acta Neurol Scand 176:96-9.

Kaplan MH and Feinstein A. (1974) The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 27:387-404.

Katzman R, Hill LR, Yu ESH, et al. (1994) The malignancy of dementia: predictors of mortality in clinically diagnosed dementia in a population survey of Shanghai, China. Arch Neurol 51:1220-5.

Koedam EL, Pijnenburg YA, Deeg DJ, et al (2008). Early-onset dementia is associated with higher mortality. Dement Geriatr Cogn Disord 26:147-52.

Lang PO, Heitz D, Hedelin G, et al (2006). Early markers of prolonged hospital stay in older people: a prospective, multicenter study of 908 inpatients in French acute hospitals. J Am Geriatr Soc 54:1031-9.

Larson EB, Shadlen MF, Wang L, et al. (2004) Survival after initial diagnosis of Alzheimer disease. Ann Intern Med 140:501-9.

Lindsey J, McGill NI, Lindsey LA, Green DK, Cooke HJ. (1991) In vivo loss of telomeric repeats with age in humans. Mutat Res 256:45-8.

Löppönen MK, Isoaho RE, Raiha IJ et al. (2004) Undiagnosed diseases in patients with dementia-a potential target group for intervention. Dement Geriatr Cogn Disord 18:321-9.

Marengoni A, Agüero-Torres H, Cossi S, et al. (2004) Poor mental and physical health differentially contributes to disability in hospitalized geriatric patients of different ages. Int J Geriatr Psychiatry 19:27-34.

Martin-Ruiz CM, Gussekloo J, van Heemst D, von Zglinicki T, Westendorp RG. (2005) Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: A population-based study. Aging Cell 4:287-90.

McGonigal G, McQuade CA, Thomas BM, Whalley LJ. (1992) Survival in presenile Alzheimer's and multi-infarct dementias. Neuroepidemiology 11:121-6.

Mehta KM, Yaffe K, Covinsky KE. (2002) Cognitive impairment, depressive symptoms, and functional decline in older people. J Am Geriatr Soc 50:1045-50.

Nielsen H, Lolk A, Pedersen I, Autzen M, Sennef C, Kragh-Sørensen P. (1991) The accuracy of early diagnosis and predictors of death in Alzheimer's disease and vascular dementia: a follow-up study. Acta Psychiatr Scand 84:277-82.

Njajou OT, Cawthon RM, Damcott CM, et al. (2007) Telomere length is paternally inherited and is associated with parental lifespan. Proc Natl Acad Sci USA 104:12135-9.

Njajou OT, Hsueh WC, Blackburn EH, et al. (2009) Association between telomere length, specific causes of death, and years of healthy life in health, aging, and body composition, a population-based cohort study. J Gerontol A Biol Sci Med Sci 8:860-4.

Oexle K and Zwirner A. (1997) Advanced telomere shortening in respiratory chain disorders. Hum Mol Genet 6:905-8.

Papassotiropoulos A, Hock C, Nitsch RM. (2001) Genetics of interleukin 6: implications for Alzheimer's disease. Neurobiol Aging 22:863-71.

Panossian LA, Porter VR, Valenzuela HF, et al. (2003) Telomere shortening in T cells correlates with Alzheimer's disease status. Neurobiol Aging 24:77-84.

Parmelee PA, Thuras PD, Katz IR, Lawton MP. (1995) Validation of the cumulative illness rating scale in a geriatric residential population. J Am Geriatr Soc 43:130-7.

Rait G, Walters K, Bottomley C, Petersen I, Iliffe S, Nazareth I. (2010) Survival of people with clinical diagnosis of dementia in primary care: cohort study. BMJ 341:1-7.

Ramos LR, Simoes EJ, Albert MS. (2001) Dependence in activities of daily living and cognitive impairment strongly predicted mortality in older urban residents in Brazil: a 2-year follow-up. J Am Geriatr Soc 49:1168-75.

Rozzini R, Frisoni GB, Ferrucci L, et al. (2002) Geriatric Index of Comorbidity: validation and comparison with other measures of comorbidity. Age Ageing 31:277-85.

Soto ME, Andrieu S, Gillette-Guyonnet S, Cantet C, Nourhashemi F, Vellas B. (2006) Risk factors for functional decline and institutionalisation among community-dwelling older adults with mild to severe Alzheimer's disease: one year of follow-up. Age Ageing 35:308-10.

Stump TE, Callahan CM, Hendrie HC. (2001) Cognitive impairment and mortality in older primary care patients. J Am Geriatr Soc 49:934-40.

Tatemichi TK, Paik M, Bagiella E, Desmond DW, Pirro M, Hanzawa LK. (1994) Dementia after stroke is a predictor of long-term survival. Stroke 25:1915-19.

Terry DF, Nolan VG, Andersen SL, Perls TT, Cawthon R (2008). Association of longer telomeres with better health in centenarians. J Gerontol A Biol Sci Med Sci 63:809-812.

Tschanz JT, Corcoran C, Skoog I, et al.; Cache County Study Group. (2004) Dementia: the leading predictor of death in a defined elderly population: the Cache County Study. Neurology 62:1156-62.

Vaziri H and Benchimol S. (1996) From telomere loss to p53 induction and activation of a DNA-damage pathway at senescence: the telomere loss/DNA damage model of cell aging. Exp Gerontol 31:295-301.

von Korff M, Wagner EH, Saunders K. (1992) A Chronic Disease Score from Automated Pharmacy Data. Journal of Clinical Epidemiology 45:197-203.

von Zglinicki T, Serra V, Lorenz M, et al. (2000) Short telomeres in patients with vascular dementia: an indicator of low antioxidative capacity and a possible risk factor? Lab Invest 80:1739-47.

Zekry D, Duyckaerts C, Moulias R, Belmin J, Hauw J-J. (2002a) Alzheimer's disease and brain infarcts in the elderly: the agreement with neuropathology. J Neurol 249:1529-34.

Zekry D, Duyckaerts C, Moulias R, et al. (2002b) Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly. Acta Neuropathol 103:481-7.

Zekry D, Hauw J-J, Gold G. (2002c) Mixed dementia: epidemiology, diagnosis and treatment. J Am Geriatr Soc 50:1431-8.

Zekry D, Gold G, Hauw J-J. (2005) Les démences mixtes : Maladie d'Alzheimer, démence vasculaire, ou les deux? Repères en Gériatrie 50:131-48.

Zekry D, Herrmann FR, Grandjean R, et al. (2008) Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status. Age Ageing 37:83-9.

Zekry D, Herrmann F, Grandjean R, Vitale-Tiar A-M, Gold G, Krause K-H. (2009) Does cognitive impairment influence hospitalization outcomes? A prospective study in aged inpatients. Int J Geriatr Psychiatry 24:283-91.

Zekry D, Hermont Loures Valle B, Lardi C, et al. (2010a) Geriatrics index of comorbidity was the most accurate predictor of death in geriatric hospital among six comorbidity scores. J Clin Epid 63:1036-44.

Zekry D, Hermont Loures Valle B, Esposito F, et al. (2010b) Prospective comparison of six comorbidity indices as predictors of 5 years post hospital discharge survival in the elderly. Rejuvenation Res 13:675-82.

Zekry D, Herrmann F, Irminger-Finger I, et al. (2010c) Telomere length is not predictive of dementia or MCI conversion in the oldest old. Neurobiol Aging 31:719-21.

Zekry D, Herrmann F, Irminger I, et al. (2010d) Telomere length and ApoE polymorphism in mild cognitive impairment, degenerative and vascular dementia. J Neurol Sci 299:108-11.

Zekry D, Hermont Loures Valle B, Graf C, et al. (2011a) Prospective comparison of six comorbidity indices as predictors of 1 year-post hospital discharge institutionalization, readmission and mortality in the elderly. J Am Med Dir Assoc Jan 8. [Epub ahead of print]

Zekry D, Herrmann F, Graf C, et al. (2011b) Mild cognitive impairment, degenerative and vascular dementia as predictors of intra-hospital, short and long term mortality in the oldest old. Aging Clin Exp Res 23:60-66.

Zekry D, Irminger-Finger I, Genet C, et al. (2011c) Telomere length, comorbidity, functional, nutritional and cognitive status as predictors of 5 years post hospital discharge survival in the oldest old. J Nutr Health Aging, in press.

Zekry D, Herrmann FR, Graf C, et al. (2011d) High levels of comorbidity and disability cancel out the dementia effect in predictions of long-term mortality after discharge in the very old. Dem Ger Cog 32:103-10.