Mortality Risk and Its Association with Geriatric Domain Deficits in Older Outpatients: The Amsterdam Ageing Cohort

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Keywords

Comprehensive geriatric assessment · Geriatric domain deficits · Mortality · Outpatient · Older people

Abstract

Introduction: In older patients, life expectancy is determined by a complex interaction of multiple geriatric domains. A comprehensive geriatric assessment (CGA) captures different geriatric domains. Yet, if and how components of the CGA are related to mortality in an outpatient geriatric setting is unknown. In the Amsterdam Ageing Cohort, we therefore studied distribution and accumulation of geriatric domain deficits in relation to mortality. **Methods:** All patients received a CGA as part of standard care, independent of referral reason. We summarized deficits on the CGA, using predefined cutoffs, in 5 geriatric domains: somatic, mental, nutritional, physical, and social domain. Information on mortality was obtained from the Dutch municipal register. We used age- and sex-adjusted Cox proportional hazards analyses to relate the separate domains and accumulation of impaired domains to overall mortality. **Results:** From the 1,055 geriatric outpatients (53% female; age 79 ± 7 years), 172 patients (16%) had died after 1.7 ± 1.1

years. In 626 patients (59%), 3 or more domains were impaired. All domains were independently associated with mortality, with the highest hazard for the somatic domain (HR 3.7 [1.7–8.0]) and the lowest hazard for the mental domain (HR 1.5 [1.1–12.0]). In addition, accumulation of impaired domains showed a gradually increased mortality risk, ranging from HR 2.2 (0.8–6.1) for 2 domains to HR 9.6 (3.7–24.7) for all 5 domains impaired. **Conclusions:** This study provides evidence that impairment in multiple geriatric domains is highly prevalent and independently and cumulatively associated with mortality in an outpatient geriatric setting.

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Introduction

Over the next decades, the proportion of the world's population older than 60 years doubles, whereas the population older than 80 years triples [1]. As a result, the proportion of older patients needing health care will rapidly increase. Older patients are at increased risk of several adverse health outcomes and prognosis is closely associated with the presence of concomitant disease and the

degree of mental, nutritional, physical, and social impairment [2–4].

It is, therefore, important to assess older patients, particularly frail older patients, with a comprehensive geriatric assessment (CGA) [5]. The CGA is an important instrument within geriatric medicine, systematically assessing different geriatric domains [6, 7]. Guidelines recommend to include questionnaires and measurements of at least somatic, mental, cognitive, physical, and social functions to produce an inventory of health problems, which will serve to define individualized care goals and advance care planning [8, 9].

Previous research has shown the value of separate geriatric domains in predicting adverse health outcomes in hospitalized patients or in disease-specific populations, such as oncology or heart failure populations [10–15]. To the best of our knowledge and somewhat surprising, however, the relation between different geriatric domain deficits and mortality in older patients referred to an outpatient geriatric clinic has not been studied. We, therefore, investigated the distribution and accumulation of different geriatric domain deficits and their association with overall mortality in an ongoing longitudinal cohort of an outpatient geriatric clinic.

Materials and Methods

Patients

The Amsterdam Ageing Cohort is a novel ongoing longitudinal cohort study of the outpatient geriatric clinic at the Amsterdam University Medical Center, location VU University Medical Center. In this article, we present the first results of the cohort. All patients were referred to the outpatient day clinic for medical care with different reasons for referral, such as memory problems, falls, and decline in physical function. From this cohort, we included all patients who had a baseline visit between February 2016 and December 2019 and provided informed consent, resulting in 1,055 patients. We used no other exclusion criteria.

At baseline, all patients received a standardized and multidisciplinary GCA, administered by trained nurses and medical staff. All screening tools are widely used and, in our cohort, performed as part of routine medical care. In those who were referred with memory problems, additional neuropsychological examination and brain MRI was performed. Diagnoses were made in a multidisciplinary consensus meeting. The protocol of our cohort is approved by the local Medical Ethical Committee, all patients provided written informed consent.

Assessment of Geriatric Domains

We defined 5 geriatric domains: somatic, mental, nutritional, physical, and social domain. We scored the separate domains impaired as yes/no according to predefined cutoff values using individual components as described below and calculated the total sum of domains impaired (0–5).

Somatic Domain

We calculated the Charlson Comorbidity Index (CCI) based on medical history and medication used [16]. A score at or above 5 points was considered abnormal [17, 18]. As part of the CCI, we used renal function to score for the presence of moderate to CKD. To calculate renal function, we used the Modified Diet in Renal Disease (MDRD) study equation until first of April 2017, and afterward we used the Chronic Kidney Disease Epidemiology Collaboration method [19, 20]. Polypharmacy was defined as the (chronic) use of 5 or more drugs [21]. We scored the somatic domain impaired if the CCI was scored above cutoff and/or polypharmacy was present.

Mental Domain

Cognitive functions were assessed at baseline with the Mini Mental State Examination (MMSE) for global cognitive functioning; a score below 24 was considered abnormal [22]. The Geriatric Depression Scale (GDS-15) was used to detect depressive symptoms; a score at or above 6 points was considered abnormal, as it indicates a possible depression [23]. We scored the mental health domain impaired if the MMSE and/or GDS was abnormal.

Nutritional Domain

The Short-Form Mini Nutritional Assessment (MNA) was used to identify patients who were at risk for malnutrition; a score below 12 indicates risk of malnutrition [24]. BMI was calculated by measuring the weight and height of the patient; a score below 18.5 was considered abnormal [25]. We scored the nutritional domain impaired if the MNA and/or BMI was below cutoff.

Physical Domain

Maximal handgrip strength (HGS; 4 measures average; 2 measures per hand) was measured using a Jamar hand-held dynamometer [26]. Grip strength below 30 kg for men and below 20 kg for women is considered abnormal [27]. Gait speed was measured in m/s, calculated from time needed to complete a distance of 4 m at usual pace. Use of a walking cane or a walker was allowed when needed. When a patient was unable to walk, gait speed was recorded as 0. A gait speed below 0.8 is considered abnormal [28]. The ability to perform activities of daily living (ADL) independently was assessed using the Katz ADL questionnaire, where a score at or above 1 is abnormal [29]. We scored the functional domain impaired if at least 1 of the 3 measures (handgrip strength, gait speed and/or ADL) was abnormal.

Social Domain

We used information on living situation and needed care. We defined the social domain impaired if the patient was living in a nursing home or if professional care at home (for ADL support) was needed.

Mortality

For each patient, we obtained information on all-cause mortality (died yes/no with the date of death) from the Dutch municipal population register. This register was searched on January 22, 2020. Causes of death cannot be determined from this municipal registry. From these data, we derived our outcome measure: overall mortality. For the overall mortality, we included all patients and defined follow-up duration as time between date of baseline visit and date of death, or if alive, between date of baseline visit and January 22, 2020.

Table 1. Baseline characteristics for total group and stratified per amount of domains impaired

	<i>N</i>	Total	Amount of domains impaired					
		<i>n</i> = 1,055	0, <i>n</i> = 34	1, <i>n</i> = 142	2, <i>n</i> = 253	3, <i>n</i> = 278	4, <i>n</i> = 236	5, <i>n</i> = 112
<i>Demographics</i>								
Female, <i>n</i> (%)	1,055	561 (53)	11 (32)	59 (42)	119 (47)	143 (51)	161 (68)	69 (62)
Age	1,055	79±7	76±6	77±6	78±7	80±6	80±8	82±8
Education, in years	911	11±4	12±4	13±4	12±4	11±4	11±4	11±4
Follow-up, in years	1,055	1.7±1.1	1.6±1.0	1.8±1.2	1.8±1.1	1.7±1.2	1.6±1.1	1.4±1.0
Died, <i>n</i> (%)	1,055	172 (16)	1 (3)	6 (4)	28 (11)	53 (19)	53 (22)	31 (28)
<i>Referral data</i>								
Referred by GP, <i>n</i> (%)	1,048	665 (63)	19 (56)	90 (64)	170 (68)	179 (65)	137 (58)	70 (63)
Primary reason for referral	1,052							
Cognitive complaints, <i>n</i> (%)		687 (65)	26 (77)	100 (70)	163 (65)	184 (66)	146 (62)	68 (61)
Physical complaints, <i>n</i> (%)		365 (35)	8 (23)	42 (30)	89 (35)	93 (34)	89 (38)	44 (39)
<i>Somatic domain</i>								
Number of prescriptions	1,053	7±4	2±2	5±3	6±4	7±4	8±4	9±4
CCI	1,055	5±2	3±1	4±2	5±2	6±2	6±2	6±2
<i>Mental domain</i>								
MMSE	1,029	24±5	28±2	27±3	25±4	24±4	23±5	20±6
GDS	986	4±3	2±2	2±2	3±3	4±3	6±4	6±4
<i>Nutritional domain</i>								
MNA	975	11±3	13±1	13±2	12±3	11±3	10±3	9±2
BMI	991	26±5	26±4	26±4	26±5	26±5	25±5	25±6
<i>Physical domain</i>								
HGS, <i>female</i>	485	19±6	23±2	23±6	21±5	18±6	17±6	15±6
HGS, <i>male</i>	448	30±9	37±6	37±7	32±9	29±9	25±8	23±8
Gait speed	924	0.9±0.4	1.1±0.1	1.1±0.3	0.9±0.3	0.8±0.3	0.7±0.5	0.6±0.3
Katz ADL	972	0.8±1.4	0.0±0.0	0.0±0.2	0.3±0.6	0.6±1.0	1.3±1.7	2.3±1.8
<i>Social domain</i>								
Living at home, <i>n</i> (%)	1,050	1,002 (95)	34 (100)	140 (100)	247 (98)	272 (98)	218 (92)	91 (81)
Professional care at home, <i>n</i> (%)	1,030	267 (26)	0 (0)	0 (0)	12 (5)	47 (17)	102 (43)	106 (96)

Follow-up in years: from baseline visit to either date of death, or in case of alive, date of check Dutch municipal population register. Data are presented as mean ± SD, unless otherwise specified. The presence of an impaired domain is defined in Table 2. HGS, handgrip strength; GP, general practitioner; CCI, Charlson Comorbidity Index; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; MNA, Short-Form Mini Nutritional Assessment; ADL, activities of daily living.

Statistical Analyses

Statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY, USA). A *p* value <0.05 was considered statistically significant. Baseline characteristics were calculated for the total population and according to the sum of impaired geriatric domains. Next, the prevalence of impaired domains and its individual components were stratified for alive or dead. Continuous and dichotomized variables were compared using parametric and nonparametric tests where appropriate. To visualize the overlap and accumulation of domains impaired, a Venn diagram was created [30] and we assessed correlations using Cramer's V.

Next, we used pattern analyses to explore the amount and randomness of missing data. Since missing data were at random but not completely at random, we imputed the missing individual

components of the geriatric domains using multiple imputations with 15 imputation cycles. With the imputed individual components, we recreated the domains. Then, Cox proportional hazard models were used to assess associations between determinants and mortality risk, taking into account time to death using the pooled results of the 15 imputations. First, we analyzed the individual components used to create the geriatric domains (dichotomized according to Table 2). Second, we examined the association between the separate domains (somatic, mental, nutritional, physical, and social) and mortality risk. Third, we assessed the influence of the accumulation (i.e., sum) of domains impaired on mortality risk, using the presence of 0 or 1 domain impaired as the reference category. We performed all analyses adjusted for age and sex, and in addition for age². In addition, we repeated above Cox propor-

Table 2. Definition of domains and amount of impaired components/domains, stratified for mortality

Domain	Impaired if	Impaired in <i>n</i> (%)		<i>p</i> value
		alive <i>n</i> = 883	dead <i>n</i> = 172	
<i>Somatic</i>		720 (82)	165 (96)	<0.001
CCI [10]	>4 points	535 (61)	142 (83)	<0.001
Polypharmacy [15]	>5 number of prescriptions	575 (65)	133 (77)	0.002
<i>Mental</i>		487 (56)	108 (65)	0.032
MMSE [16]	<24 points	345 (40)	85 (52)	0.006
GDS [17]	>5 points	221 (26)	45 (30)	0.336
<i>Nutritional</i>		415 (48)	92 (58)	0.018
MNA [18]	<12 points	415 (50)	90 (63)	0.004
BMI [19]	<18.5 kg/m ²	16 (2)	10 (7)	0.001
<i>Physical</i>		580 (66)	140 (86)	<0.001
HGS [21]	<30 kg M, <20 kg F	352 (44)	97 (70)	<0.001
Gait speed [22]	<0.8 m/s	318 (39)	86 (63)	<0.001
Katz ADL [23]	≥1 points	279 (34)	84 (56)	<0.001
<i>Social</i>		196 (22)	83 (48)	<0.001
Living situation	In nursing home	30 (3)	18 (11)	<0.001
Needed care	Professional care present	186 (22)	81 (48)	<0.001

Group differences between alive or dead were calculated using χ^2 test. A *p* value <0.05 was considered statistically significant. HGS, handgrip strength; CCI, Charlson Comorbidity Index; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; MNA, Short-Form Mini Nutritional Assessment; ADL, activities of daily living.

tional hazard models using nonimputed data yielding comparable results (see online suppl. Table; for all online suppl. material, see www.karger.com/doi/10.1159/000512048). Finally, for illustrative purposes, we created Kaplan-Meier curves for the accumulation of domains impaired and report log rank tests, using the raw data without imputation. Data are represented as hazard ratios (HR) with accompanying 95% confidence intervals (CIs).

Results

Table 1 shows the baseline characteristics. After a mean follow-up duration of 1.7 ± 1.1 years, 172 (16%) patients had died. In 687 (65%) of the total group, the primary reason for referral was cognitive problems, whereas 365 (35%) were referred for somatic problems. The majority of patients had 3 or more domains impaired ($n = 626$ [59%]); this was similar for patients referred for cognitive problems as for somatic problems (58 and 61%). With increasing amount of impaired domains, patients were older and more often female. Further, with increasing amount of impaired domains, all individual components of the somatic, mental, nutritional, physical, and

social domain scores showed a tendency to deteriorate (Table 1).

To assess the impaired domains, their overlap, and accumulation, we created a Venn diagram. Figure 1 shows an even overlap and accumulation of the separate domains. The correlations between the impaired domains were low (Cramer's *V* ranging from 0.10 to 0.30).

Table 2 shows the amount of impaired components and domains, stratified for alive or dead. All domains, and the components used to construct them, were more often impaired in patients who had died. Only the proportion of patients with an abnormal GDS did not differ between patients alive and dead.

Next, we assessed the association between the CGA and mortality using Cox proportional hazard models (Table 3). First, we studied the association between the (dichotomized) individual components and mortality. We found all components, except a GDS >5, to be associated with mortality. Second, when we assessed the association between the separate domains and mortality, we found all domains to be associated with an increased mortality risk. The somatic domain showed the highest

Table 3. Cox proportional hazard models; influence of individual dichotomized components and separate domains on mortality

	Adjusted for age and sex	
	Individual component	Separate domain
<i>Somatic</i>		
Domain impaired		3.7 (1.7–8.0)*
>5 number of prescriptions	1.7 (1.2–2.4)*	
CCI >4	2.2 (1.4–3.3)*	
<i>Mental</i>		
Domain impaired		1.5 (1.1–2.0)*
MMSE <24	1.5 (1.1–2.0)*	
GDS >5	1.3 (0.9–1.8)	
<i>Nutritional</i>		
Domain impaired		1.9 (1.3–2.6)*
MNA <12	1.9 (1.3–2.6)*	
BMI <18.5	3.1 (1.6–6.2)*	
<i>Physical</i>		
Domain impaired		2.3 (1.4–3.9)*
HGS, female <20 kg	1.8 (1.1–3.0)*	
HGS, male <30 kg	1.7 (1.0–3.0)*	
Gait speed <0.8 m/s	1.9 (1.4–2.8)*	
Katz ADL ≥1	1.9 (1.4–2.6)*	
<i>Social</i>		
Domain impaired		2.5 (1.8–3.4)*
Living in nursing home	3.1 (1.9–5.1)*	
Professional care at home	2.5 (1.8–3.5)*	

Data are presented as HR (95% CI) for the presence of an impaired domain (as defined in Table 2) and the dichotomous variable, for mortality, using pooled data of 15 imputations. HGS, handgrip strength; HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; MNA, Short-Form Mini Nutritional Assessment; ADL, activities of daily living. * $p < 0.05$.

hazard (HR 3.7 [1.7–8.0]) and the mental domain the lowest hazard (HR 1.5 [1.1–2.0]).

Finally, we examined the effect of the accumulation of impaired domains on mortality. More domains impaired resulted in a higher hazard of mortality (p for trend <0.001). Figure 2 shows the corresponding Kaplan-Meier survival curve and HRs. Since age is an important and strong confounder, we repeated the analyses with age² in the models, after which the effect sizes in Table 3 and Figure 2 remained similar (results not shown).

Fig. 1. Venn diagram showing the domains impaired, their overlap, and accumulation. The diagram was created using [30]. The presence of an impaired domain is defined in Table 2.

Discussion/Conclusion

In this longitudinal cohort of an outpatient geriatric clinic, we not only show that impairment in multiple geriatric domains is highly prevalent but also demonstrate that geriatric domain deficits are independently and cumulatively associated with mortality. These findings illustrate the added value of the CGA in older patients referred to a geriatric outpatient clinic. Therefore, the CGA does not only function as an inventory of different health problems and related treatment options but could also be useful to determine the prognosis of older patients.

Our study adds to earlier studies by focusing on a broad range of geriatric domains and their accumulation in an outpatient geriatric population. To date, available literature focused mainly on the association of separate geriatric domains with mortality in specific patient categories, for example, oncology, renal or heart failure patients [12, 13, 15], hospitalized geriatric patients [10, 11, 14], or solely on individual components [2, 31–33], with inconsistent findings. As a result, knowledge on the relation between a CGA, its geriatric domains and mortality in an outpatient geriatric population has remained sparse. We show that a multi-domain approach is not only appropriate in disease-specific populations, with known

Fig. 2. Kaplan-Meier survival curve per total domains impaired, for total group (log rank <0.001). Observed survival is analyzed by Kaplan-Meier using nonimputed data, whereas the association of amount of domains and mortality is analyzed using Cox models, adjusted for age and sex, taking 0 and 1 domains impaired as reference, using pooled data of 15 imputations. * $p < 0.05$.

vulnerability to negative outcomes but also in a very heterogeneous population, referred for various reasons, of outpatient older subjects.

These results have important clinical implications. A multi-domain assessment helps to detect (modifiable) vulnerabilities, but also helps to detect a patient's vulnerability, irrespective of age and reason for referral. It informs physicians and patients about therapeutic priorities [34]. While patients with single domain deficits are in need of a problem-based disease-orientated approach, accumulation of domain deficits helps physicians to shift toward a more "goal-oriented, integrated approach" [35]. Identifying the most vulnerable patients (e.g., those with 3 or more impaired domains impaired) with a short life expectancy can subsequently lead to focus on, for example, advance care planning and an optimization of provided care, resulting in improvement of quality of life [3].

One can wonder if age did not drive the observed associations since age is an important and strong predictor of death. However, effect sizes remained comparable after correcting for age and even after correcting for age². Similarly, a specific domain, such as the physical domain containing measures of frailty, could have primarily caused the results [36], but again our results remained more or less similar when correcting for physical impairment. Finally, contrary to our expectations, presence of a GDS >5 was not associated with mortality. Yet, previous studies have shown an age-dependent association of GDS and mortality, with the strongest association at younger age [37, 38]. With increasing age, impairment in other do-

main related to mortality, seem to dilute this association [39]. These observations together with poor overlap of geriatric domain deficits as illustrated by our Venn diagram emphasize the clinical relevance of a multi-domain assessment approach in geriatric outpatients.

This study has several strengths. In contrast to previous literature, we were able to include a substantial, real-life, geriatric outpatient population and focused on a wide scope of domains and mortality. All patients underwent a standardized workup, including commonly used instruments, derived as part of medical routine care. This resulted in a well-defined phenotyping of the included patients, referred for cognitive as well as somatic problems. Furthermore, although unintentionally, we obtained our information on mortality from the municipal population register before COVID-19 caused excess mortality.

This study also has limitations. First of all, no guideline is available on how to define geriatric domains [5, 6]. Our construction of domains can thus be considered as somewhat arbitrary. This is especially true for the social domain. Since questionnaires (e.g., EDIZ, ZARIT, or CSI) providing more detailed information on the social domain, are missing, our approach should be considered as proxy for the social domain [40]. However, for the definition of the other geriatric domains, we used tests that are widely available and easily applicable, with acknowledged cutoff points, and commonly used in clinical practice [6]. Second, we lacked information on adverse health outcome measures other than death, such as functional decline, hospital admission, or institutionalization. Third,

our follow-up duration was on average 1.7 years. A different pattern of associated domains and mortality might have been found if our follow-up duration had been longer.

In conclusion, this study provides longitudinal evidence that impairment in multiple geriatric domains is highly prevalent and, irrespective of age, cumulatively associated with mortality in an outpatient geriatric setting. Depending on the number of impaired domains, this approach helps to make considerations on treatment decisions, care programs, or advanced care planning all aimed at improvement of quality of life and reducing unnecessary care consumption.

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Statement of Ethics

The protocol of our cohort is approved by the Medical Ethical Committee of the Amsterdam UMC, location VUmc under protocol number 2017.148, and all patients provided written informed consent.

Conflict of Interest Statement

Hanneke F.M. Rhodius-Meester performs contract research for Combinostics, all funding is paid to her institution. Sara A.J. van de Schraaf, Mike J.L. Peters, Emma E.F. Kleipool, Marijke C. Trappenburg, and Majon Muller report no disclosures.

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Author Contributions

Hanneke F.M. Rhodius-Meester drafted the manuscript and performed the analyses, Sara A.J. van de Schraaf acquired the data and performed the analyses, Mike J.L. Peters, Emma E.F. Kleipool, Marijke C. Trappenburg, and Majon Muller contributed to the concept and design of the study. All authors contributed to critical revision of the manuscript.

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