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Research Article

Defining Aging Phenotypes and Related Outcomes: Clues to Recognize Frailty in Hospitalized Older Patients

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Abstract

Background: Because frailty is a complex phenomenon associated with poor outcomes, the identification of patient profiles with different care needs might be of greater practical help than to look for a unifying definition. This study aimed at identifying aging phenotypes and their related outcomes in order to recognize frailty in hospitalized older patients.

Methods: Patients aged 65 or older enrolled in internal medicine and geriatric wards participating in the REPOSI registry. Relationships among variables associated to sociodemographic, physical, cognitive, functional, and medical status were explored using a multiple correspondence analysis. The hierarchical cluster analysis was then performed to identify possible patient profiles. Multivariable logistic regression was used to verify the association between clusters and outcomes (in-hospital mortality and 3-month postdischarge mortality and rehospitalization).

Results: 2,841 patients were included in the statistical analyses. Four clusters were identified: the healthiest (I); those with multimorbidity (II); the functionally independent women with osteoporosis and arthritis (III); and the functionally dependent oldest old patients with cognitive impairment (IV). There was a significantly higher in-hospital mortality in Cluster II (odds ratio [OR] = 2.27, 95% confidence interval [CI] = 1.15–4.46) and Cluster IV (OR = 5.15, 95% CI = 2.58–10.26) and a higher 3-month mortality in Cluster II (OR = 1.66, 95% CI = 1.13–2.44) and Cluster IV (OR = 1.86, 95% CI = 1.15–3.00) than in Cluster I.

Conclusions: Using alternative analytical techniques among hospitalized older patients, we could distinguish different frailty phenotypes, differently associated with adverse events. The identification of different patient profiles can help defining the best care strategy according to specific patient needs.

Keywords: Frailty—Aging phenotypes—Outcomes—Internal medicine and geriatric wards—Cluster analysis

Frailty has been conceptualized as a state of late-life decline and vulnerability due to a reduced ability to adapt to stressors (eg, acute illness) and is associated with an increased risk of adverse health outcomes and death (1–3). Different definitions of frailty have been proposed in the scientific literature to help clinicians, researchers, and other stakeholders. The most commonly used is the physical frailty phenotype by Fried and colleagues, which is based on criteria related to reduced physical reserves (weight loss, exhaustion, weakness, slowness, and reduced physical activity) (1). Other definitions, for example, the Frailty Index (4), the Clinical Frailty Scale (5), the Groningen or Tilburg Frailty Indicator (6,7), and the Edmonton Frail Scale (8) include additional deficits concerning different domains, such as cognition and mood, organ diseases, pharmacotherapy, functional autonomy, and social conditions. Most of the existing frailty tools have been developed and validated in the frame of community-dwelling older adults; only few studies were specifically oriented to predict the outcomes of hospitalized older people (9,10). When applied to the same population, the different existing definitions overlapped only partially in the identification of frail people, although all the definitions helped to predict adverse

outcomes (10–14). Because frailty does not identify a specific disease but is a complex phenomenon with a multifactorial etiology, it is likely that a diagnostic gold standard does not exist. Thus the identification of different frailty profiles with the associated different care needs might be of greater practical help than to look for a unifying definition, in order to better manage frail people. With this background, we analyzed data from the REPOSI registry on hospitalized older patients with the aims (i) to identify patient profiles providing features that describe homogeneous subsets of patients on the basis of clinically relevant variables available in the registry (ie, lifestyle, physical and cognitive status, functional performance, comorbidities, and medications) and (ii) to study the association of the identified phenotypes with clinical outcomes (in-hospital mortality, 3-month postdischarge mortality, and rehospitalization).

Methods

Setting and Participants

The present study is based on data prospectively collected in the frame of the REPOSI project. REPOSI (REgistro POliterapie SIMI) is an ongoing collaboration between the Italian Society of Internal medicine (SIMI), the IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri," and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, launched in 2008 with the aim to investigate various aspects related to multimorbidity and polypharmacy in an older acutely hospitalized population. REPOSI is a multicenter prospective registry designed to collect information on patients aged 65 or older, consecutively admitted to internal medicine or geriatric wards of Italian hospitals during 4 index weeks (one for each season). Since 2014, Spanish hospitals also participated in the data collection. A standardized web-based case report form, with detailed instructions for the compilation, was provided to the attending physicians. Specifically, a detailed explanation on how to fill geriatric scales has been also introduced in order to improve the standardization of the compilation at different times and among several centers (internal medicine and geriatric wards). Moreover, a clinical monitor dedicated to the project was always available to support physicians during the compilation of case report form. The principal data collected include sociodemographic factors, clinical and laboratory data, and pharmacological therapies. After discharge, additional follow-up data were collected via telephone calls at 3 months. Participation was voluntary, and all participants signed an informed consent. More detailed description of the data set is available in reference (15). For the purpose of this study, data collected in 2010, 2012, and 2014 were analyzed because postdischarge follow-up data were added to the REPOSI data set only since 2010.

The REPOSI project was approved by the local ethical committees of the participating centers.

Variables

The authors prespecified a list of variables that are usually included in the assessment of frailty (4) and looked for those available in the REPOSI registry. In addition, they considered those variables that they considered to be related to an unhealthy condition and available in the frame of hospitalized patients. The retrieved variables considered for the analyses were grouped as follows:

- Sociodemographic, anthropometric, and lifestyle data: sex, age, body mass index, living condition, smoke, and alcohol consumption.
- Medical history data (at admission) collected according to the Cumulative Illness Rating Scale (CIRS) (16); in particular, presence of hypertension, diabetes, ischemic heart diseases, chronic obstructive pulmonary disease, chronic kidney disease, heart failure, arthropathies and dorsopathies (here named arthritis), neoplasm, osteoporosis (including also fractures and prosthesis), liver diseases, thyroid disorders, depression (excluding bipolar disorders), dementia, sensorial deficits (including hearing and visual impairment); hospitalization during the 6 months preceding the index admission; number of diagnoses and drugs.
- Functional status: performance in activities of daily living measured by the Barthel Index (17).
- Cognition and mood: the Short Blessed Test (SBT) (18) and the 4-item Geriatric Depression Scale (GDS-4) (19).
- Clinical and laboratory parameters (at admission): systolic blood pressure, heart rate, mean corpuscular volume, total cholesterol, hemoglobin, and estimated creatinine clearance according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (20).

Statistical Analysis

Exploring the relationships between variables

Multiple correspondence analysis (MCA) (21) was performed in order to study the relationships between categorical variables. MCA is an explorative multivariate statistical technique that allows to summarize the information contained in a large amount of originally related variables into a small set of unrelated variables, named factorial axes. Results of MCA can be graphically represented on the plane identified by the factorial axes. Original categories are represented on the plane as points with specific coordinates on each axis to form clouds of categories, with the distance between points providing an approximate description of the association/relationship among categories. Also, a cloud of individuals can be represented using coordinates on the newly identified factorial axes, so that patients with similar coordinates share similar profiles.

More details are provided in Supplementary Material.

Identification of possible frailty profiles

In order to identify patient profiles potentially related to a frailty condition, an agglomerative hierarchical cluster analysis (HCA) was performed. Clustering techniques allow to classify patients within homogeneous subsets (clusters) through the definition of a distance between individuals on the basis of their characteristics. The score (coordinates) obtained on the first three factorial axes identified through the MCA was used to calculate distances (22). The stability of the clusters identified through the HCA (ie, internal validation) was investigated by means of resampling methods (bootstrap). The similarity between each clustering procedure on the resample data and that on the original data was assessed via the Jaccard's coefficient (23). To this aim 1,000 bootstrap resamples with replacement were randomly generated from the original data. Each participant was then assigned to the cluster in which it was most frequently classified. MCA and HCA were performed on a complete case basis.

Association of clusters with adverse outcomes

Multivariable logistic regression analysis was used to evaluate the association among the identified clusters and outcomes (in-hospital and 3-month mortality and rehospitalizations), adjusting by the country (Spain vs Italy) and type of ward (geriatric vs internal medicine). Statistical analysis was carried out using software SAS software

Version 9.4 (SAS Institute, Cary, NC) and R (R Development Core Team, 2006), with FactoMineR and ca packages added.

Results

Study Population

Globally 3,915 patients, hospitalized in 116 internal medicine and geriatric wards (15 from Spain), were enrolled in the REPOSI registry in years 2010 (*N* = 1,380), 2012 (*N* = 1,323), and 2014 (*N* = 1,212). Less than 5% of patients were enrolled in Spanish hospital wards. The flow diagram of patients included in the study is reported in Supplementary Figure 1. Patient characteristics at hospital admission are given in Table 1.

Of the patients enrolled, 50% were women; their mean age was 78.7 years (*SD* = 7.4). According to body mass index cutoffs, 978 (27.7%) patients were underweight and 1,278 (36.2%) were overweight or obese. Most of the patients presented a good degree of independence according to the Barthel Index (47.1%). The most frequent morbidities were hypertension (76.5%), diabetes (28.6%), and heart diseases (24.7%). According to the SBT, almost half of the patients (44.5%) had a moderate-to-severe cognitive impairment. Overall 2,348 patients (60.0%) were on polypharmacy (≥5 drugs).

The complete case sample was represented by 2,841 patients who were finally included in the MCA and HCA analyses.

Multiple Correspondence Analysis

In a preliminary analysis, the following variables carrying a negligible contribution in the explanation of the factorial axes were discarded: systolic blood pressure, heart rate, mean corpuscular volume, neoplasm, depression, sensorial deficits, total cholesterol, liver,

Table 1. Sociodemographic, Clinical, and Laboratory Characteristics at Hospital Admission of 3,915 Patients Enrolled in REPOSI Registry

Variables	No. (%)	Missing (No.)
Year		
2010	1,380 (35.2)	
2012	1,323 (33.8)	
2014	1,212 (31.0)	
Country		
Italy	3,746 (95.7)	
Spain	169 (4.3)	
Sex		
Male	1,956 (50.0)	
Female	1,959 (50.0)	
Age, mean (*SD*)	78.7 (7.4)	
Young old (65–75 years)	1,380 (35.2)	
Middle old (76–84 years)	1,603 (41.0)	
Oldest old (≥85 years)	932 (23.8)	
Body mass index, mean (*SD*)	25.9 (5.1)	385
Underweight (<23 kg/m^2)	978 (27.7)	
Normal weight (≥23 kg/m^2)	1,274 (36.1)	
Overweight (≥27 kg/m^2)	661 (18.7)	
Obese (≥30 kg/m^2)	617(17.5)	
Living arrangement		137
Alone	831 (22.0)	
With relatives	2,508 (66.4)	
Others (caregiver)	206 (5.4)	
Nursing home	233 (6.2)	
Alcohol intake		102
Never	1,829 (48.0)	
Former drinker	288 (7.5)	
Drinker	737 (19.3)	
Occasional drinker	959 (25.2)	
Smoke		94
No	2,068 (54.1)	
Former smoker	1,422 (37.2)	
Yes	331 (8.7)	
Barthel Index[a]		64
No or negligible dependence (91–100)	1,815 (47.1)	
Mild dependence (75–90)	675 (17.6)	
Moderate dependence (50–74)	494 (12.8)	
Severe dependence (25–49)	352 (9.1)	
Total dependence (0–24)	515 (13.4)	
Short Blessed Test		355
Normal (0–4)	1,348 (37.9)	
Possible cognitive impairment (5–9)	628 (17.6)	
Moderate cognitive impairment (10–19)	1,135 (31.9)	
Severe cognitive impairment (20–28)	449 (12.6)	

Table 1. *Continued*

Variables	No. (%)	Missing (No.)
Geriatric Depression Scale		585
Normal (0–1)	1,923 (57.7)	
Probable depression (2–4)	1,407 (42.3)	
Hemoglobin[b]		17
No anemia	1,704 (43.7)	
Mild anemia	922 (23.6)	
Moderate anemia	1,055(27.1)	
Severe anemia	217 (5.6)	
Creatinine clearance		40
Stage I (>90)	399 (10.3)	
Stage II (≤90)	1,587 (41.0)	
Stage III (≤60)	1,384 (35.7)	
Stage IV (≤30)	373 (9.6)	
Stage V (≤15)	132 (3.4)	
Number of drugs		
0	123 (3.1)	
1	206 (5.3)	
2–4	1,238 (31.6)	
5–9	1,931 (49.3)	
≥10	417 (10.7)	
Previous hospital admissions	1,271 (32.5)	
Number of diagnoses		
0–4	1,432 (36.6)	
≥5	2,483 (63.4)	
CIRS—Severity Index, median (IQR)	1.6 (1.4–1.8)	45
<1.4	1,006 (26.0)	
≥1.4	717 (18.5)	
≥1.6	999 (25.8)	
≥1.8	1,148 (29.7)	
CIRS—Comorbidity Index, median (IQR)	3 (2–4)	45
0	282 (7.3)	
1–3	2,152 (55.6)	
>3	1,436 (37.1)	
Diagnosis		
Hypertension	2,984 (76.5)	
Diabetes mellitus	1,107 (28.6)	
Ischemic heart diseases	957 (24.7)	
Chronic obstructive pulmonary disease	702 (18.1)	
Chronic kidney disease	698 (18.0)	
Heart failure	696 (18.0)	
Arthritis	647 (16.7)	
Osteoporosis	531 (13.7)	
Dementia	397 (10.2)	

Notes: CIRS = Cumulative Illness Rating Scale; IQR = interquartile range; SD = standard deviation.

[a]Evaluated during hospital stay.

[b]No anemia (male: ≥13 g/dL; female: ≥12 g/dL); mild anemia (male: ≥11 g/dL and <13 g/dL; female: ≥11 g/dL and <12 g/dL); moderate anemia (male and female: ≥8 g/dL and <11g/dL); severe anemia (male and female: <8 g/dL). Hypertension (ICD-9: 401–405); chronic kidney disease (ICD-9: 585); diabetes mellitus (ICD-9: 250); chronic obstructive pulmonary disease (ICD-9: 4912); heart failure (ICD-9: 428); dementia (ICD-9: 290 / 294 / 310 / 331); osteoporosis (ICD-9: 733) included also fractures and prosthesis (ICD-9: 800–829; V436); cardiac diseases (ICD-9: 410–414); arthritis (ICD-9: 710–724).

and thyroid disorders. Thus, values concerning 23 variables were used. The CIRS-CI and CIRS-SI were not used to assess MCA solution; however, they were plotted on the cloud of categories (supplementary variables—see Supplementary Material). The first three factorial axes in the MCA explained almost 71% of the overall variability in the data and were used to calculate the distances in the subsequent HCA.

Supplementary Figure 2 shows the resulting cloud of categories projected on the plane defined by the first and second factorial axes and Supplementary Figure 3 the cloud of categories projected on the plane defined by the second and third axes with detailed description. Briefly, according to the configuration of the cloud of categories, the first axis could be interpreted as the expression of the burden of disease, the second axis as the expression of musculoskeletal and cognitive morbidity, and the third axis as the expression of cognitive deterioration and functional dependence.

Hierarchical Cluster Analysis

HCA, performed on the scores of the first three components, identified four main clusters of patients. The Bootstrap showed a quite good stability of results (the four means of all Jaccard's coefficients were about 0.87). Figure 1 represents the cloud of individuals,

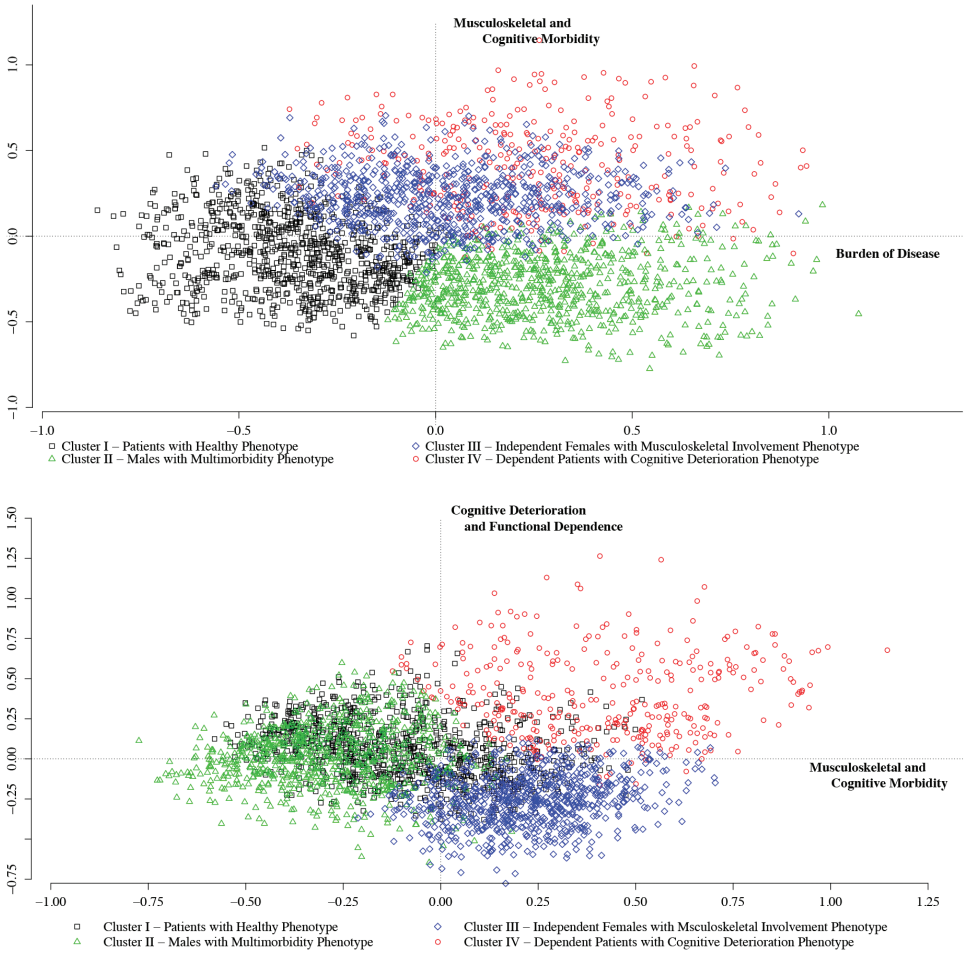

Figure 1. Results from hierarchical cluster analysis: the cloud of individuals according to clusters. (Upper panel) The cloud is plotted on the plane determined by the first and the second factorial axes. (Lower panel) The cloud is plotted on the plane identified by the second and the third factorial axes.

according to cluster distribution, projected on the plane defined by the first and the second factorial axes (upper panel) and that identified by the second and the third factorial axes (lower panel). The distribution of patients' characteristics within each cluster is reported in Supplementary Table 1.

As Supplementary Table 1 shows, Cluster I (924 patients), mainly associated with negative scores of the first axis, included the healthiest individuals, mainly young old men with low prevalence of severe diseases and less frequently on polypharmacy (patients with healthy phenotype). Cluster II (791), mostly associated with negative scores of the second axis, included patients, mostly men (87.5%), with a severe multimorbidity profile (ie, severe cardiovascular, pulmonary, and renal diseases) and on polypharmacy (90.3%) (men with multimorbidity phenotype). Cluster III (785), associated with negative scores of the third axis, was largely represented by middle old women (94.5%) functionally independent in their daily activities (near 42% of them lived alone and 47% had a BI > 91) and characterized by a healthy lifestyle (74% never drank and 88% never smoked). Almost half of patients with a diagnosis of osteoporosis and arthritis (data not shown) are included in this cluster (independent women with musculoskeletal involvement phenotype). Overweight and obese individuals were mostly included in Clusters II and III (68.9%). Cluster IV (341), associated with positive scores of the second and third axes, was composed of the oldest patients, mostly women (65%), with increasing cognitive impairment and severe-to-total dependence. The underweight condition was highly prevalent in this cluster (42.8%). The majority of patients with a diagnosis of dementia (78.6%—data not shown) were included in this cluster (dependent patients with cognitive deterioration phenotype).

Association With Outcomes

Among the 2,841 patients included in the analyses, for 15 it was not known whether they were discharged alive, so that 2,826 were assessable. Table 2 shows the prevalence of adverse outcomes (in-hospital mortality, 3-month mortality, and rehospitalization) and the length of hospital stay within each cluster. Globally 71 (2.5%) patients died during the hospital stay (Supplementary Figure 1). Among 2,008 patients with available follow-up, 181 (9.0%) died within 3 months from discharge. During the 3 months after discharge, overall 552 patients (27.5%) were rehospitalized at least once. Table 3 reports the results of multivariable logistic regression models. There were a significantly higher in-hospital and 3-month mortality in Cluster II and Cluster IV with respect to Cluster I. A higher 3-month mortality was found in Spanish patients. No statistically significant association was found between cluster classification and rehospitalization, but patients in Cluster II had a slightly higher risk of being rehospitalized than those in Cluster I (odds ratio 1.33, 95% confidence interval 1.00–1.76). The type of ward was not associated with adverse outcomes.

Table 2. Prevalence of Adverse Outcomes and Length of Hospital Stay Within Each Cluster

	Cluster I *N* = 924	Cluster II *N* = 791	Cluster III *N* = 785	Cluster IV *N* = 341
In-hospital mortality, *n* (%)	13 (1.4)	25 (3.2)	9 (1.2)	24 (7.1)
3-Month mortality, *n* (%)	49 (7.8)	71 (12.4)	29 (5.0)	32 (14.2)
3-Month rehospitalization, *n* (%)	121 (19.4)	137 (24.3)	122 (21.1)	465 (20.7)
Length of hospital stay, median (IQR)	9 (6–13)	9 (6–14)	9 (6–14)	10 (6–15)

Note: IQR = interquartile range.

Table 3. Results of Multivariable Logistic Regression Models for In-hospital and 3-Month Mortality

	In-hospital Mortality		3-Month Mortality	
	OR	(95% CI)	OR	(95% CI)
Cluster I	Reference		Reference	
Cluster II	2.27	(1.15–4.46)	1.66	(1.13–2.44)
Cluster III	0.79	(0.34–1.87)	0.60	(0.37–0.96)
Cluster IV	5.15	(2.58–10.26)	1.86	(1.15–3.00)
Country (Spain vs Italy)	1.79	(0.63–5.14)	3.39	(1.71–6.70)

Note: CI = confidence interval; OR = odd ratio.

Discussion

Main Study Findings

Using alternative analytical techniques, we explored the relationships between commonly and easily assessable variables potentially related to the frailty syndrome in older hospitalized people, and we were able to identify four distinct clusters of patients. Two of these clusters were likely related to a frailty condition, but with different characteristics: The first was mainly composed of middle old men affected by multiple chronic diseases (men with multimorbidity phenotype) and the second one by the oldest patients, mostly women, with severe cognitive decline and loss of independence (dependent patients with cognitive deterioration phenotype). On the other end, we identified a cluster of healthier individuals with a low prevalence of multimorbidity and polypharmacy (patients with healthy phenotype). Finally, we identified a fourth cluster composed of middle old women, with the highest prevalence of osteoporosis, arthritis, and related complications (eg, fractures and replacement interventions) but with no significant functional impairment (independent women with musculoskeletal involvement phenotype), often affected by cardiovascular and metabolic morbidities. Our results confirmed an association of the former two clusters with adverse outcomes (in-hospital or 3-month mortality), being the patients with cognitive deterioration phenotype those with the highest in-hospital mortality. The patients with the multimorbidity phenotype had a slightly higher risk of rehospitalization, although not statistically significant.

Interpretation and Practical Implications

Although the physical frailty phenotype has received a wider consensus by the scientific community (24), some studies demonstrated that a definition of frailty encompassing a broader spectrum of deficits (such as comorbidities and cognitive and mood decline) could predict the susceptibility to adverse outcomes with higher discrimination than a definition limited only to physical dysfunction (25,26).

A previous study showed that measuring frailty in older people admitted to emergency departments for minor injuries helps to screen those at risk of functional decline (27). Thus the characterization of the clinical phenotype among older adults acutely admitted to the hospital (internal medicine and geriatric wards) and their stratification according to their risk profile that we propose here could have important implications. It provides clinicians with a useful tool for the stratification of patients on the basis of their specific needs and/or the screening of patients at risk of frailty with implication on their diagnostic and therapeutic management. Indeed, besides the two phenotypes related to frailty conditions and characterized by a higher risk of adverse outcomes, we identified one cluster of middle old women that, although not associated with a higher incidence of adverse outcomes, could be seen as prefrail, as suggested by the musculoskeletal involvement and the higher prevalence of cardiovascular (87.5% of hypertension and 19.7% of ischemic heart disease) and metabolic diseases (29.9% of diabetes). Previous findings established that declines in executive functioning are associated with risk of frailty onset (28,29) In our study population, the rehospitalization rates within 3 months from discharge were on average high (about 20%) in all four clusters. From a public health perspective, the high prevalence of early rehospitalization even in the healthiest individuals from Cluster I points out, on one side, the frequent inadequacy of hospital referrals and of the corresponding response from a care setting such as the hospital. Hospitals indeed are traditionally organized as services for the provision of acute cares to organ diseases and not for the management of needs involving the cognitive domain and function. Thus our findings point out the need of a better implementation and integration of social and health care assistance of these patients outside the hospital, in order to improve the postacute phase after hospital discharge, prevent rehospitalization, and delay the progression of frailty.

Limitations and Strengths

The large number of participating centers and their allocation through all Italy and Spain make the study representative of the overall Italian and Spanish settings of internal medicine and geriatric wards, even if the latter were less in number. Being the REPOSI a multicenter registry based on voluntary work, missing data are one of the main limitations of the analyses. The assessment of anthropometric and laboratory parameters (eg, body mass index and cholesterol) and geriatric scales (eg, SBT, GDS, and BI) was

not mandatory at hospital admission, especially during short-term hospitalization. This could partially explain the large amount of missing data for those variables. Comparing the overall population and that included in the analyses, only small differences are noted and none that could be considered clinically significant. Thus missing data have limited impact on the selection of patients included in the analyses. Any difference among Spanish and Italian patients were reflected in the different composition of patient nationality included within each cluster (see Supplementary Table 1). Some possibly relevant variables were either not included (eg, data on the economic status and physical performance) or expected to be underreported (eg, data on hearing and visual impairment and on diagnosis of depression, osteoporosis, dementia, falls, and bedsores). This represents certainly a limitation in the attempt to characterize such a complex phenomenon, as the frailty syndrome, and precludes the possibility to make a comparison with other indicators. On the other hand, most of considered variables were commonly available and easily assessable in daily clinical practice by physicians and other stakeholders. Second, we could not explore the association between phenotypes and the risk of adverse events over a longer time. However, the well-known high rate of short-term adverse event occurring after the hospital admission of an old person (30) makes them a priority of the management plan. Finally, our results were obtained from a hospitalized older cohort so that, although they showed a good degree of stability—internal validation—as proven by the Bootstrap, their generalizability to other settings (ie, community-dwelling people and nursing home residents) should be investigated.

Conclusions

Assessing for frailty at hospital admission has been compared with "predicting speed at traffic lights," and its clinical utility has been debated if the information on how and how much the patient status had changed over a certain time before the admission is lacking (31). However, it is well known that hospitalization per se represents an accelerating event, a critical turning point at which the slope, whatever the trajectory is, becomes sharper (30,32). Therefore, it is especially in the setting of older inpatients, among whom the chance of adverse events is high, that the identification of different patient profiles, rather than the distinction between those at risk and those not at risk, can help to define the best management according to specific patient needs. This could be helpful both for the clinician and for those involved in the organization of care provision.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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