European Journal of Internal Medicine 56 (2018) 11–18

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Original Article

Implementation of the Frailty Index in hospitalized older patients: Results from the REPOSI register

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ARTICLE INFO

Keywords:
Frailty
Internal medicine and geriatric wards
Physical and cognitive impairment
Multimorbidity

ABSTRACT

Background: Frailty is a state of increased vulnerability to stressors, associated to poor health outcomes. The aim of this study was to design and introduce a Frailty Index (FI; according to the age-related accumulation of deficit model) in a large cohort of hospitalized older persons, in order to benefit from its capacity to comprehensively weight the risk profile of the individual.

Methods: Patients aged 65 and older enrolled in the REPOSI register from 2010 to 2016 were considered in the present analyses. Variables recorded at the hospital admission (including socio-demographic, physical, cognitive, functional and clinical factors) were used to compute the FI. The prognostic impact of the FI on in-hospital and 12-month mortality was assessed.

Results: Among the 4488 patients of the REPOSI register, 3847 were considered eligible for a 34-item FI computation. The median FI in the sample was 0.27 (interquartile range 0.21–0.37). The FI was significantly predictive of both in-hospital (OR 1.61, 95%CI 1.38–1.87) and overall (HR 1.46, 95%CI 1.32–1.62) mortality, also after adjustment for age and sex.

Conclusions: The FI confirms its strong predictive value for negative outcomes. Its implementation in cohort studies (including those conducted in the hospital setting) may provide useful information for better weighting the complexity of the older person and accordingly design personalized interventions.

1. Introduction

The increasing number of hospitalized older persons is severely burdening the traditional organization of healthcare systems. In particular, the complexity of the older patients requires a comprehensive assessment to prioritize necessities and adapt/personalize interventions. In this context, the frailty concept has been center of a growing interest because potentially capable of levering the reshaping of our systems around a more biologically driven parameter. In fact, frailty is an age-related condition defined by the homeostatic reduction of the organism. It describes a state of increased vulnerability to stressors and increased risk to adverse health outcomes [1]. In other words, frailty may represent an opportunity for replacing the concept of chronological age with a novel concept focused on the biology of the system, thus a more accurate background on which clinical decisions can be taken.

The Frailty Index (FI) proposed by Rockwood and Mitnitski [2, 3] is one of the most promising tools for measuring frailty, in particular for its easiness of implementation in the routine clinical practice. It is defined following a arithmetical model aimed at capturing the age-related accumulation of health deficits. To date, the FI has been largely proposed and validated in community-dwelling older people [4], and only recently its potential utility has been suggested in hospitalized older people [5]. The design and implementation of the FI in the hospital setting will give access to an innovative way of comprehensively capturing the complexity of the older individual in a crucial healthcare component. In fact, the FI may potentially serve both as outcome of interest as well as possible confounder/independent variable for statistical models in which the complexity of the older patient is not adequately captured by the traditional variables (e.g., age, diseases, monodimensional scales/questionnaires). Therefore, the present study

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https://doi.org/10.1016/j.ejim.2018.06.001
Received 23 January 2018; Received in revised form 8 May 2018; Accepted 4 June 2018
Available online 12 June 2018

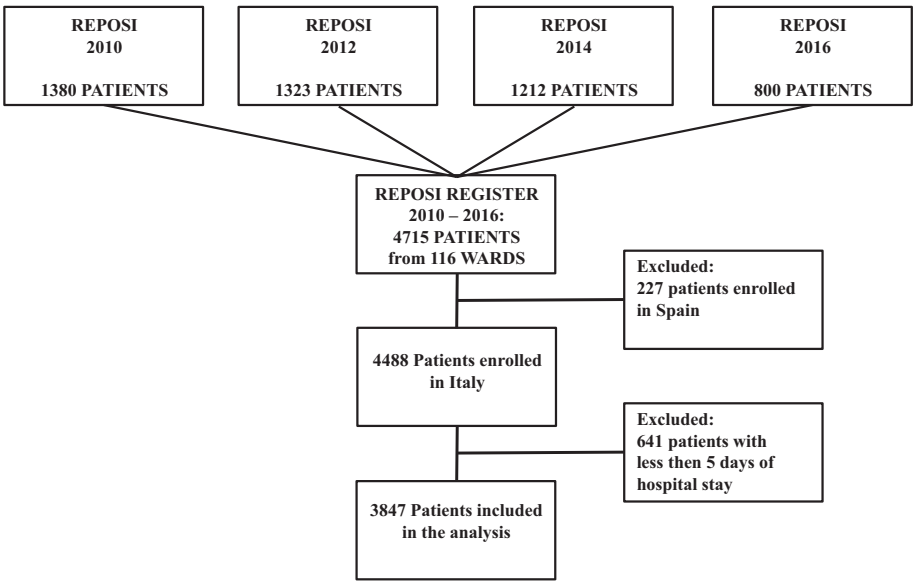

Fig. 1. Flow-chart of the study.

is aimed at designing and implementing the FI in the REgistro POliterapie SIMI (REPOSI Register), a large database of hospitalized older persons admitted to several internal medicine and geriatric wards across Italy. The FI is here designed according to the data available in the register (implicitly showing the possibility of replicating it taking advantage of data collected for different purposes) and tested/validated for its internal consistency and capacity to predict negative outcomes (i.e., in-hospital and overall mortality).

2. Methods

2.1. Setting and participants

The REPOSI is a multicentre prospective register, launched in the 2008 with the main purpose to investigate the patterns of multimorbidity and polypharmacy in hospitalized older patients. The REPOSI register collected information on patients aged 65 years and older consecutively admitted to internal medicine and geriatric wards of an Italian network of hospitals during four index weeks (one for each season). Since 2014, some Spanish hospitals joined the group in data collection. The data routinely collected during the surveys included socio-demographic factors, laboratory data, capacity to perform activities of daily living (i.e., Barthel Index, BI) [6]), cognitive function and mood (via the Short Blessed Test (SBT) [7] and the Geriatric Depression scale,GDS) [8], respectively), clinical conditions and multimordity (i.e., Cumulative Illness Rating Scales (CIRS) [9]), and medications. After 3 and 12 months from the hospital discharge, follow-up data have been collected via phone calls since the 2012 survey. Participation in the study is voluntary and informed consent is signed by all participants. A detailed description of REPOSI was published elsewhere [10, 11].

For the purpose of the present study, patients enrolled from 2010 to 2016 were considered. A minimum length of hospital stay of 5 days was used as inclusion criteria in order to exclude too healthy and too critically ill patients, thus rendering our sample more homogeneous. The rationale for this choice resides in the potentially different medical priorities that patients with an extremely low length of stay may have compared to the vast majority of hospitalized individuals.

2.2. The Frailty Index (FI)

The FI was computed following the criteria described by Searle et al. [12], and taking into account a wide range of signs, symptoms, disabilities and diseases available in the REPOSI database. These variables were all associated to the individual's health status and encompassed a wide range of physiological systems. The prevalence of the variables composing the FI (i.e., deficits) had to increase with age. These variables must not show signs of too easy or difficult saturation. A minimum of 30 deficits is recommended in order to obtain a robust estimate of the frailty status of the individual [12].

2.3. Statistical analysis

Each variable included in the FI (i.e., deficit) was generally assigned a score equal to '0' (absence of the deficit) or '1' (presence of the deficit). The FI was calculated as the ratio between the number of deficits that the patient presented divided by the total number of the deficits considered for its computation. Ordinal variables (such as the Barthel Index and the Short Blessed Test) were ranked and graded scores between '0' and '1' (mild = '0.3', moderate = '0.5', severe = '0.7') were accordingly assigned. When a continuous variable was used to assess a deficit (e.g., body mass index or laboratory data), a coding was required. To choose the most appropriate cut-points, nonlinear relationships among each variable and the hazard of overall mortality were investigated using Cox regression models [13], with restricted cubic spline with at least 3 knots [14] and adjusting for age and sex. Survival times were calculated as the time elapsed since hospital admission to death, or alternatively to the discharge date, or to the last available follow-up. When the cut-points usually adopted in the literature were associated with an increased hazard, those were preferred. Otherwise, the cut-points were defined upon a graphical inspection of the resulting shape of the hazard ratios.

In order to control for missing values in some of the REPOSI variables, a multiple imputation procedure was adopted [15]. Multiple imputation procedures imply missing values to be filled with plausible values in order to create several complete datasets, to reproduce the uncertainty of missing values predictions. Mainly two different approaches are available for multiple imputation. Because both continuous and ordinal variables were included and had to be filled in the FI, the chained equation approach was preferred [16]. Herein, each variable was separately imputed according to a pre-specified sequence and conditioning on the basis of selected predictors, using linear regression or logistic models. Each dataset was then separately analyzed using standard statistical analysis. Results were pooled for making inference.

Table 1
Socio demographic and clinical characteristics of 3847 patients in the REPOSI Register at hospital admission.

Variables	N	%	Mean (St Dev)	Median (IQR)	Missing
Study Year					
2010	1144	29.7			
2012	1140	29.6			
2014	905	23.5			
2016	658	17.1			
Sex					
Males	1865	48.5			
Females	1982	51.5			
Age (years)			79.0 (7.4)		
Body Mass Index (BMI)			25.8 (5.1)		409
Barthel Index				91 (65–100)	40
Negligible dependence (91–100)	1919	50.4			
Mild dependence (75–90)	744	19.5			
Moderate dependence (50–74)	490	12.9			
Severe dependence (25–49)	275	7.2			
Total dependence (0–24)	379	10.0			
Hemoglobin (gr/dl)			11.7 (2.3)		14
Platelets (10^3/μl)			235.3 (102.8)		27
Leucocytes (10^3/μl)			9.2 (6.2)		20
Creatinine (mg/dl)			1.2 (0.8)		26
Creatinine Clearance			59.6 (24.2)		26
Short Blessed Test (SBT)				8 (2–14)	272
Normal (0–4)	1353	37.9			
Possible cognitive impairment (5–9)	619	17.3			
Moderate cognitive impairment (10–19)	1138	31.8			
Severe cognitive impairment (20–28)	465	13.0			
CIRS Severity Index (IS)			1.7 (0.3)	1.6 (1.5–1.8)	
CIRS Comorbidity Index (IC)				3 (2–4)	
Diagnosis at Admission					
Hypertension	2943	76.5			
Dyslipidemias	1978	51.4			
Respiratory diseases	1526	39.7			
Upper GastroIntestinal disorders	1200	31.2			
Diabetes	1153	30.0			
Kidney diseases	1067	27.7			
Muskoloskeletal diseases/ Prosthesis/Fractures	1062	27.6			
Ischaemic heart disease	954	24.8			
Neurologic disorders/Parkinson	875	22.7			
Lower GastroIntestinal disorders	757	19.7			
Stroke/TIA/cerebrovascular diseases	709	18.4			
Psychiatriac disease	693	18.0			
Heart failure	666	17.3			
Tumors	635	16.5			
Depression	589	15.3			
Liver diseases	585	15.2			
Tyroid disorders	510	13.3			
Anxiety	469	12.2			

Legend: St dev = standard deviation, IQR = interquartile range.

2.4. Association of the FI with mortality

A multivariable logistic regression analysis was used to evaluate the association between the FI and in-hospital mortality, with adjustment for sex and age [14]. Analyses were conducted both on the complete and imputed datasets. The association with overall mortality was also investigated. Kaplan-Meier survival curves were drawn according to the 33rd and 67th percentiles of the FI after multiple imputation was performed [17]. Statistical analyses were carried out using software SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA) [18] and R (R Development Core Team, 2006) [19], with mice library added [20].

Table 2
. List of variables and cut points included in the REPOSI frailty index.

Variable/Deficit	Cut Point	Score
BMI	< 21 Kg/m^2	1
	≥21Kg/m^2	0
BI - Hygiene (Grooming)	0–1	1
	3–4	0.5
	5	0
BI - Bathing	0–1	1
	3–4	0.5
	5	0
BI - Eating	0–2	1
	5–8	0.5
	10	0
BI - Using Toilet	0–2	1
	5–8	0.5
	10	0
BI - Climbing (up and down) stairs	0–2	1
	5–8	0.5
	10	0
BI - Dressing	0–2	1
	5–8	0.5
	10	0
BI - Fecal ~~In~~continence	0–2	1
	5–8	0.5
	10	0
BI - Urinary ~~In~~continence	0–2	1
	5–8	0.5
	10	0
BI - Mobility Impairment	0–3/0–1–3 [WheelChair]	1
	8–12/4–5 [WheelChair]	0.5
	15	0
BI - Transferring (bed/chair)	0–3	1
	8–12	0.5
	15	0
Short Blessed Test (SBT)	20–28	1
	10–19	0.7
	5–9	0.3
	0–4	0*
Hemoglobin	< 11 g/dL	1
	≥11 g/dL	0
Platelet Count	< 100 or ≥ 320 [F] < 150 or ≥ 250 10^3/μl [M]	1
	≥100 & < 320 [F] ≥150 & < 250 10^3/μl [M]	0
White Blood Cells	< 4000 or > 10,000 10^3/μl	1
	≥4000 & ≤10,000 10^3/μl	0
Creatinine Clearance	< 30 g/dL	1
	≥30 g/dL	0
Severity of hypertension	Yes (≥ 3)	1
	Yes (2)	0.5
	No hypertension	0
Diabetes	Yes	1
	No	0
Kidney diseases	Yes	1
	No	0
Respiratory disease	Yes	1
	No	0
Heart failure	Yes	1
	No	0
Ischaemic heart disease	Yes	1
	No	0
Tumors	Yes	1
	No	0
Tyroid disorders	Yes	1
	No	0
Stroke/TIA/cerebrovascular disease diseases	Yes	1
	No	0
Upper gastrointestinal disorders	Yes	1
	No	0
Lower gastrointestinal disorders	Yes	1
	No	0
Liver diseases	Yes	1
	No	0
Skeletal muscle diseases	Yes	1
	No	0

(*continued on next page*)

Table 2 (*continued*)

Variable/Deficit	Cut Point	Score
Psychiatric disease	Yes	1
	No	0
Neurologic disorders edddisorders/ Parkinson	Yes	1
	No	0
Dyslipidemias	Yes	1
	No	0
Depression	Yes	1
	No	0
Anxiety	Yes	1
	No	0

Legend: BI = Barthel index, TIA = transient ischemic attack, F = female, M = male.

* As the SBT generally requires a cooperative patient to be assessed, patients not able to complete the test due to severe dementia were assigned the highest score.

3. Results

3.1. Study population

Among 4715 patients enrolled in the REPOSI database between 2010 and 2016 across a total of 116 hospital wards, 4488 were enrolled in Italy. The 3847 patients (101 wards) hospitalized for at least 5 days were included in the present analysis (Fig. 1). Table 1 describes the patients' characteristics at their hospital admission. The prevalence of men and women was quite similar, with a slight predominance of the latter. Median age was 79 years, and almost a quarter of the patients was aged 85 years or older.

The complete list of deficits for the calculation of the FI included 34 variables (Table 2), including:

- o body mass index (as a proxy of nutritional status);
- o ten individual items of the Barthel Index [6];
- o the Short Blessed Test (SBT) [7]. Since this scale requires a cooperative patient to be assessed, those participants unable to complete the test due to severe dementia were considered as presenting the deficits;
- o hemoglobin, estimated creatinine clearance (according to the Chronic Kidney Disease Epidemiology Collaboration formula), white blood cells and platelets count;
- o eighteen diagnoses or clinical conditions as consideredin the CIRS [9]. In some cases (i.e. neurologic disorders, dyslipidemias, depression, anxiety, thyroid disorders and respiratory disease), specific therapeutic prescriptions were used to better assess the diagnoses.

The complete case sample accounted for a total of 3200 patients (83.2% of the original REPOSI population). The distribution of the FI is displayed in Fig. 2. It shows a positively skewed distribution with the median equal to 0.27 (interquartile range 0.21–0.37). No patient presented a FI value equal to or higher than 0.8. The FI showed a nearly linear relationship with age, with an increment of 0.044 points (95%CI 0.033–0.050) for age increasing from 73 to 84 years. Women presented a slightly higher FI then men (difference 0.015; 95%CI 0.024–0.006), although the difference lost its statistical significance after adjustment for age. Overall, 142 patients died during the hospital stay, and 362 within 12 months from the discharge. The FI was associated with in-hospital mortality (Odds Ratio [OR] 1.668; 95%CI 1.438–1.934 for each 0.1 FI increment), even after taking into account for age and sex (OR 1.605; 95%CI 1.375–1.873). The FI was also associated with overall mortality (HR 1.417, 95%CI 1.316–1.525; adjusted HR 1.372, 95%CI 1.270–1.482). Fig. 3 shows the Kaplan-Meier curves for mortality according to FI tertiles.

For the purpose of the present study, 15 complete datasets were generated by the means of multiple imputation. Sensitivity analyses from the multiple imputed datasets yielded results that were substantially identical to those obtained from the primary analyses (Fig. S1).

4. Discussion

The FI based on the age-related accumulation model proposed by Rockwood and Mitnitski is here operationalized in a large sample of hospitalized older patients, the REPOSI register. Our analyses confirm the predictive value of the FI for mortality, even when, as in our case, this parameter is applied to hospitalized patients. Through our analyses, we make available in the REPOSI database a variable of extreme interest for adequately capturing the clinical complexity of the older persons. Our FI, generated in agreement with the established recommendations [12], presents all the required features of a robust FI. In fact, our FI 1) is composed by a high number of variables (i.e., 34) stemming from a comprehensive geriatric assessment, 2) presents a skewed distribution (consistent with existing literature), and 3) is rarely higher than the 0.7 threshold (usually indicated as a sort of biological limit rendering the burden of accumulated deficits incompatible with

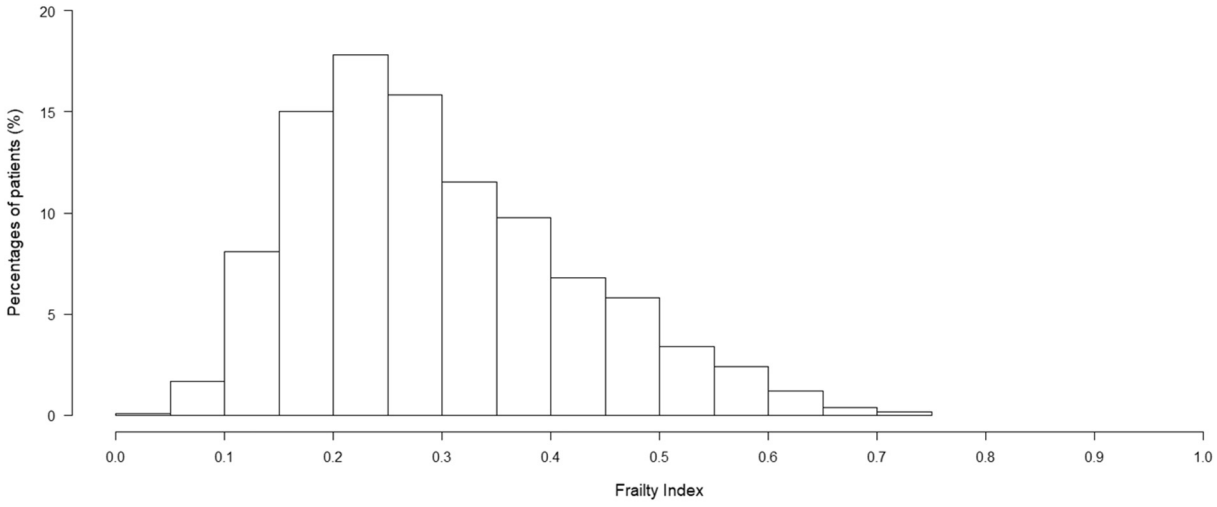

Fig. 2. Distribution of the FI in the 3200 patients of the complete case.

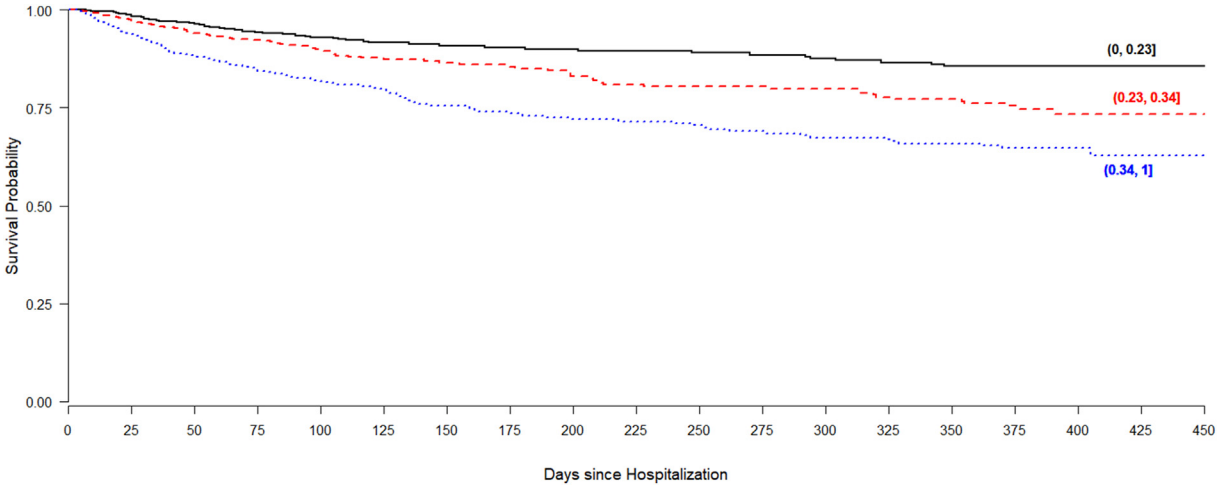

Fig. 3. Kaplan-Meier survival curves according to 33rd and 67th percentiles of the FI.

life). By including a FI in the REPOSI, we will make possible to better refine future analyses in this large database of a major Italian network of internal medicine and geriatric wards. The availability of the FI will specifically provide:

1) the possibility of adopting a single variable representative of the clinical/biological complexity of the individual for adjusting future analyses. This might be particular important for those studies hampered by a limited statistical power;
2) a measure for comparing the clinical status of the REPOSI population with other databases (also generated in different settings and for different purposes). It is noteworthy the FI is increasingly used across healthcare settings (e.g., community, nursing homes [21], primary care [22]), and specialties other than geriatrics – as neurology [23] or infectious disease medicine [24]). The FI may thus serve as a standard for sharing the same language and evaluate in a standardized way the biological age of the individual independently of his/her chronological age;
3) a global and sensitive marker for measuring the effectiveness of interventions put in place during the hospital stay. Differently from what happens when testing modifications of categorical variables, the continuous design of the FI makes it particularly sensitive to changes. Moreover, since it reflects the overall status of the organism, it provides a more reliable feedback about the modifications that the organism may exert as a whole.

Interestingly, the FI can be retrospectively generated taking advantage of already existing databases, originally developed for different purposes (as in the present case). Although perceived as potentially burdening given the number of information the Frailty Index FI requires to be generated, its computation is relatively easy, because it summarizes information routinely collected during a clinical visit. Its simplicity becomes evident if considering that the FI has recently been included in the frame of primary care routine in the United Kingdom [22].

The quantitative (and not qualitative) nature of this tool does not affect its internal structure, as soon as the predefined operational criteria are met [12]. Our results are in line with those reported in previous studies, for example by Hubbard and colleagues [25]. If considered under this perspective, the present findings are largely confirmatory of the prognostic capacity of the FI. Nevertheless, the capacity to replicate this model in a different cohort (as demonstrated by the consistent characteristics of the variable) and the similar association with negative outcomes shows the external validity of this arithmetic model. The specific implementation of the FI in the REPOSI database by the means of this "methodological" paper also paves the way for future analyses to be conducted in this cohort that, to date, might be limited by inadequate tools for capturing the complexity of the frail older patient.

However, some limitations are worth to be mentioned. We could not reassess the FI at the hospital discharge and the follow-up visits. Thus, we cannot speculate about its trajectories over time and their predictive capacity for other adverse outcomes. Furthermore, our analyses were perhaps affected by a certain number of missing values present in the REPOSI register database. However, the results of the multiple imputation procedures confirmed the robustness of the Frailty Index showing almost the same results as on the complete case series.

In conclusion, older people are a very heterogeneous population presenting different unmet clinical needs. In order to provide person-tailored interventions, it is important to bypass some traditional paradigms (for example, those based on the obsolete concept of disease), and promote the use of comprehensive evaluations and global markers of biological age. In this context, the FI designed by Rockwood and Mitnitski is an extremely interesting model. Its implementation in the REPOSI register will allow to better benefit from this huge clinical database, opening it to a novel concept of frailty.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.06.001.

Appendix A. Collaborators of the REPOSI (REgistro POliterapie SIMI, Società Italiana di

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