European Journal of Internal Medicine xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Original article

Development of a new predictive model for polypathological patients. The PROFUND index

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ARTICLE INFO

Article history:
Received 29 September 2010
Received in revised form 31 October 2010
Accepted 25 November 2010
Available online xxxx

Keywords:
Polypathology
Multimorbidity
Frailty
Mortality
Prognostic index

ABSTRACT

Background: There is a concern about the accuracy of the available prognostic indexes when applying them to the emergent population of polypathological patients (PP).
Methods: To develop a 1-year mortality predictive index on PP, we developed a multicenter prospective cohort-study recruiting 1.632 PP after hospital discharge, outpatient clinics, or home hospitalization, from 33 hospitals. Potential risk factors were obtained in the 1.525 PP who completed follow-up. Each factor independently associated with mortality in the derivation cohort (757 PP from western hospitals) was assigned a weight, and risk scores were calculated by adding the points of each factor. Accuracy was assessed in the validation cohort (768 PP from eastern hospitals) by risk quartiles calibration, and discrimination power, by ROC curves. Finally, accuracy of the index was compared with that of the Charlson index.
Results: Mortality in the derivation/validation cohorts was 35%/39.5%, respectively. Nine independent mortality predictors were identified to create the index (age ≥85 years, 3points; No caregiver or caregiver other than spouse, 2points; active neoplasia, 6points; dementia, 3points; III–IV functional class on NYHA and/or MRC, 3points; delirium during last hospital admission, 3points; hemoglobinemia <10 g/dl, 3points; Barthel index <60 points, 4points; ≥4 hospital admissions in last 12 months, 3points). Mortality in the derivation/validation cohorts was 12.1%/14.6% for patients with 0–2points; 21.5%/31.5% for those with 3–6 points; 45%/50% for those with 7–10 points; and 68%/61.3% for those with ≥11points, respectively. Calibration was good in derivation/validation cohorts, and discrimination power by area under the curve was 0.77/0.7. Calibration of the Charlson index was good, but discrimination power was suboptimal (area under the curve, 0.59).
Conclusions: This prognostic index provides an accurate and transportable method of stratifying 1-year death risk in PP.

1. Introduction

Polypathological patients (PP) have become an emerging population in most clinical arenas [1–3]. Their prevalence in Primary Care, as well as in different medical and surgical hospital areas, is notably high and will most likely increase in the forthcoming years [1,4,5]. The term PP is patient-centered and applies those patients suffering from chronic diseases from 2 or more of eight predefined categories; these categories were established by a panel of experts using criteria of end-effect on function of key organs (independent of the primary disease), frequent chronic conditions with high mortality/potential of becoming unstable, or frequent comorbidities when mental/functional impairment thresholds were definitively reached (Table 1) [1–3]. Their complexity, disease and symptom burden, clinical vulnerability, poor health-related quality of life, tendency towards functional deterioration, and the impact on relatives and caregivers have been well described [1,6,7]. Because of all these factors, their mortality during hospitalization and in Primary Care follow-up is outstandingly high [1–3,6].

Survival prognostication is a cornerstone for clinicians in patient management and for health-care providers in designing health policies. It is not only a professional but also an ethical concern to clear possible areas of uncertainty in this issue that could avoid baseless nihilist attitudes or, on the contrary, diagnostic–therapeutic fury-futility. This is especially important in high-risk populations in order to reassess care

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0953-6205/$ – see front matter
doi:10.1016/j.ejim.2010.11.012

Please cite this article as: Bernabeu-Wittel M, et al, Development of a new predictive model for polypathological patients. The PROFUND index, Eur J Intern Med (2010), doi:10.1016/j.ejim.2010.11.012

Table 1
Functional definition of polypathological patient: the patient who suffers chronic diseases included in two or more of the following clinical categories.

Category A
A.1 Chronic heart failure with past/present stage II dyspnea of NYHA[a].
A.2 Coronary heart disease
Category B
B.1 Vasculitides and/or systemic autoimmune diseases
B.2 Chronic renal disease (creatininaemia >1.4/1.3 mg/dL in men/women or proteinuria[b], during ≥3 months
Category C
Chronic lung disease with past/present stage 2 dyspnea of MRC[c], or FEV1<65%, or basal $SatO_2 \leq 90\%$
Category D
D.1 Chronic inflammatory bowel disease
D.2 Chronic liver disease with evidence of portal hypertension[d]
Category E
E.1 Stroke
E.2 Neurological disease with permanent motor deficit, leading to severe impairment of basic activities of daily living (Barthel index <60).
E.3 Neurological disease with permanent moderate–severe cognitive impairment (Pfeiffer's test with ≥5 errors).
Category F
F.1 Symptomatic peripheral artery disease
F.2 Diabetes mellitus with proliferate retinopathy or symptomatic neuropathy
Category G
G.1 Chronic anemia (Hb<10 g/dL during ≥3 months) due to digestive-tract losses or acquired hemopathy not tributary of treatment with curative intention.
G.2 Solid-organ or hematological active neoplasia not tributary of treatment with curative intention.
Category H:
Chronic osteoarticular disease, leading to severe impairment of basic activities of daily living (Barthel index <60)

[a] Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
[b] Albumin/Creatinine index >300 mg/g, microalbuminuria >3 mg/dL in urine, albumin >300 mg/day in 24-h urine, or albuminuria/min >200 μg/min.
[c] Short of breath when hurrying or walking up a slight hill.
[d] Presence of clinical, analytical, echographic, or endoscopic data of portal hypertension.

goals; redefine medically necessary therapies; focus on symptom control; assess other physical, psychosocial, and spiritual problems' and consider earlier palliative care. With the knowledge of a reasonable precise prognosis, clinicians can feel more comfortable raising important issues like care goals, treatment preferences, advanced planning, and clinical therapeutic options with patients and their families [8,9].

When assessing prognosis in PP populations, we are faced with many difficulties. Organ- or disease-specific indexes are not suitable due to the usual co-protagonism and similar weight of two or more chronic disabling diseases in PP. More generic and recent instruments require subjective assessments of risk by clinicians, include disused functional scales, use difficult algorithms, or are based on administrative data [9–12]. Hence, they are not often used in routine practice, and most clinicians and investigators continue to use the Charlson–Deyo index as the gold-standard tool when referring to prognosis in patients with comorbidity [13–15]. Nevertheless, the Charlson–Deyo index has been around for over 20 years; during this time, new diagnostic–therapeutic options have drastically changed the course of many of the included conditions (like peptic ulcer, cardiovascular diseases, AIDS, or some neoplasias), so there is a generalized concern among clinicians that it may have lost some of its accuracy [15].

For all of the abovementioned reasons, we developed this multicenter project with the aim of obtaining an accurate prognostic tool specially designed for this vulnerable population, and then compare its fitness to the Charlson–Deyo index.

2. Patients and methods

This was an observational prospective, multi-institutional study carried out by researchers from the Polypathological Patient and Advanced Age Study Group of the Spanish Internal Medicine Society. The study inclusion period ranged from February 2007 to June 2008 (17 months).

2.1. Reference population

All PP treated in the Internal Medicine and Geriatric areas (in-hospital, as well as in outpatient clinics, and at-home hospitalization patients) from the 33 Spanish hospitals (17 tertiary teaching centers and 16 secondary/basic general hospitals) participated in the study (all participant centers are listed on the PROFUND Researchers list).

2.2. Inclusion criteria

Patients ≥18 years old who met criteria of PP (see Table 1) were consecutively included, after providing their written informed consent [16]. In-hospital patients were included at discharge, and those identified at outpatient clinics (internal medicine outpatient clinics, Day Hospital, and/or at-home hospitalization patients) were included during any one of their visits. Patients who died during their hospital stay and those who did not concede to participate in the study were excluded.

2.3. Development of the study, data collection, and follow-up

After receiving informed consent, a complete set of demographical, clinical, functional, analytical, pharmacological, as well as socio-familial data were collected from all included patients.

Demographic data included age, gender, residence, employment data, and the main caregiver's profile; clinical data included the different diseases, the fulfillment of polypathology criteria, stage of different diseases (NYHA and MRC dyspnea rates [17,18], and Child–Pugh stage [19]), assessment of Charlson's comorbidity index [13,14], different symptoms and signs, body mass index (BMI), assessment of basal as well as inclusion ability in performing daily-living (ADL) and instrumental activities (IA) by means of Barthel (BI), and Lawton–Brody indexes (L–B) [20,21], assessment of basal cognitive impairment using the Spanish validated version of Pfeiffer's questionnaire (PQ) [22], and number of hospital admissions in the last 12 and 3 months, respectively; laboratory data included plasma creatinine (CR (mg/dL)), hemoglobin (HB (g/dL)), albumin (ALB (g/dL), glycated hemoglobin (HbA1c (%)), and ultrasensitive C reactive protein (us-CRP (mg/L); pharmacological data included number and type of chronically prescribed drugs at basal status; and socio-familial data included socio-familial risk determined using the Gijón scale (GS) [23]. The GS is a validated scale that assesses the overall socio-familial situation exploring 5 specific dimensions (family, economics, housing, social relations, and social network support) on a 1–5 Likert scale (score rank 5–25 points); a score <10 confers low social risk, 10–16 confers risk of social claudicating, and >16 points defines an established social problem.

All included patients were followed-up during a 12-month period. After this period, time survival was assessed, and, in the case of death, chronology of the demise was incorporated. Therefore, we looked at mortality as both a dichotomous and as time-dependent outcome. For the dichotomous outcome, subjects were categorized depending on whether or not they survived 12 months from their initial interview date. For the continuous outcome, survival time was defined as the number of days between the baseline interview and the date of death.

2.4. Definitions

Nutritional status was categorized by means of WHO criteria for BMI values (overweight–obesity (BMI>24.9), normal weight (BMI between 18.5 and 24.9), underweight (BMI<18.5)) [24]; hypoalbuminemia was defined as albumin levels <3.5 g/dL (severe hypoalbuminemia when values were <1.8 g/dL, moderate when values were between 1.8–2.69 g/dL, and slight hypoalbuminemia when values were between 2.7 and 3.5 g/dL); Polypharmacy was defined as the chronic prescription

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of ≥5 drugs. Dependence in functional status for ADL and IA was defined by a BI<60 points and by a LB<8 for females/<5 for males, respectively; cognitive impairment was defined by 3 or more errors on the PQ (4 or more if the patient had not completed elementary school and 2 or more if the patient had a college education); this was categorized as mild–moderate impairment (between 3 and 7 errors), and severe (8 or more errors); and finally socio-familial risk/problem was defined as a GS score ≥10. The need for a caregiver was defined when the patient was functionally dependent (BI<60) and/or cognitively impaired (PQ≥3 errors).

2.5. Derivation and validation of PROFUND SCALE. Statistical analysis

The included population was divided into a derivation cohort (containing approximately one half of the participating hospitals (from the west of Spain) and patients) and a validation cohort (containing approximately half of the remaining participating hospitals (from the east of Spain and the islands) and patients).

The PROFUND scale was derived and validated as follows: unadjusted relationships between potential risk factors and mortality were assessed in the derivation cohort using logistic regression models. Significant variables ($p<0.05$) were entered into a multiple backward logistic regression model. Risk factors that remained significant after adjustment ($p<0.05$) were used to create the predictive model. Analysis of risk factors associated to death as a time-dependent variable was performed by Cox regression models, in which the outcome was time to death.

The 1-year mortality risk scoring system was created by assigning points to each risk factor by dividing each beta coefficient in the model by the lowest beta coefficient and rounding to the nearest integer. Subjects in the derivation and validation cohorts were divided into quartiles based on their risk scores.

To test the stability of our final model, we tried alternate methods (forward and bidirectional selection techniques) to determine whether the resultant model would differ from our original model.

To validate the index, we determined the calibration of the index by comparing in the validation cohort the predicted mortality (divided into probability risk quartiles) to the observed mortality by means of Kaplan–Meier curves (and log-rank test) and also by calculating the Hosmer–Lemeshow goodness-of-fit test. Then we evaluated the discrimination of the index by applying the point scoring system created in the development cohort to the validation cohort, thereby determining risk scores for each participant, and calculating the area under the receiver operating characteristic (ROC), for the final model in both the derivation and validation cohorts. We chose to validate our predictive index in a different region of the country from where it was developed in order to test geographic transportability as well as diagnostic accuracy.

Finally we compared the discrimination power of the PROFUND index in the whole cohort with those of the Charlson–Deyo index (CDI), the CDI adjusted by age, the Barthel, and the Lawton–Brody index by calculating the AUC of their ROC curves.

The dichotomous variables were described as whole numbers and percentages and the continuous variables as mean and standard deviation (or median and rank in those with no criteria of normal distribution). The distribution of all variables was analyzed with the Kolmorogov–Smirnov test. All statistics were performed using the SPSS 16.0 computer pack.

Table 2
Comparative main basal clinical features of the derivation and validation cohorts of polypathological patients included in the PROFUND project.

Clinical features (mean ± SD/median [IQR]/*N* [%])	Derivation cohort ($n=757$)	Validation cohort ($n=768$)
Age	79 ± 9	78.8 ± 9.8
Sex (males)	408 (54.3%)	417 (54.7%)
Requiring caregiver/having caregiver	391(51.7%)/530(70%)	407(53.8%)/590(78%)
Illiteracy rate (men/women)	37.5% (34.3%/41.4%)	41.6% (38.1%/45%)
Patients included in tertiary teaching/basic-secondary hospitals	394 (52%)/363 (48%)	422 (55%)/346 (45%)
Number of defining categories/patient	2.7 ± 0.83	2.7 ± 0.84
Patients with ≥3 categories	384 (50.7%)	389 (49.3%)
Prevalence of defining categories in recruited PP		
Category A (heart diseases)	598 (79%)	590 (77)
Category C (lung diseases)	355 (47%)	345 (45)
Category E (neurological diseases)	271 (36%)	306 (40)
Category B (kidney/autoimmune diseases)	243 (32.2%)	247 (32.7%)
Category G (chronic neoplasia/anemia)	197 (26%)	197 (25.7%)
Category F (peripheral arterial disease/diabetes with neuropathy)	202 (27%),	188 (24.5%),
Category H (degenerative osteoarticular disease)	125 (16.5%)	135 (17.5%)
Category D (liver disease)	51 (6.7)	58 (7.6)
Number of other comorbidities/patient	3.1 ± 1.6	3.2 ± 1.7
Patients with ≥4 other comorbidities	246 (33 %)	287 (37%) ($p=0.047$)
Most frequent other comorbidities		
Hypertension	559 (73%)	536 (70%)
Arrhythmias	268 (35.9%)	291 (37%)
Atrial fibrillation	255 (34.2%)	279 (35.4%)
Other arrhythmias	13 (1.7%)	12 (1.6%)
Diabetes without visceral involvement	213 (28%)	239 (31%)
Dyslipidemia	218 (29%)	226 (29.4%)
Anxiety and depressive disorders	98 (13%)	102 (13.3%)
Benign prostate hyperplasia	73 (10%)	88 (11.5%)
Osteoporosis	45 (6%)	56 (7.3%)
Mean plasmatic creatinine (mg/dl)/hemoglobin (g/dl)	1.28 ± 0.8/11.8 ± 2.2	1.23 ± 0.8/11.5 ± 2
Albumin (g/dl)/body mass index	3.3[0.8]/28.5 ± 6	3.3[0.9]/28.4 ± 6
Mean HbA1c (%)/us-CRP (mg/dl)	7.1% ± 1.6/6.3[20]	7.1% ± 1.6/7.1[17]
Charlson index/Charlson index adjusted by age	4 [2]/8.5 [2.4]	4 [3]/8.1 [2]
Patients with basal III–IV class of NYHA/III–IV class of MRC	226(47.4%)/178 (51.6%)	245(49%)/186 (54.5%)
Patients with active neoplasia at inclusion/metastatic disease	85 (11.2%)/39 (44%)	77 (10%)/30 (33%)
Hospitalizations in last 12 months	1.85 ± 1.6	1.95 ± 1.7
Patients with delirium in last hospital admission	72 (10%)	115 (15%) ($p=0.01$)
Basal Barthel index/basal Lawton–Brody index	69.4 ± 31/F = 2 [4]; M = 3[4]	69.6 ± 31/F = 2 [4]; M = 3[5]
Inclusion Pfeiffer scale/Gijon's socio-familial risk scale	2 [4]/10.4 ± 3.5	2 [5]/10.2 ± 3.2
Number of prescribed drugs at inclusion/patients with polypharmacy	7.9 ± 3/598 (83%)	8.1 ± 3.3/640 (87%)

IQR: interquartile range; HbA1c: glycated hemoglobin; us-CRP: ultrasensitive C-reactive protein; NYHA: New York Heart Association; MRC: Medical Research Council; F=female; M=male.

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3. Results

A total of 1632 PP (75% hospitalized, 17.5% outpatient, and 7.5% at-home patients) were included in the study, and 93.44% of them ($N=1525$) completed the 12-month follow-up. The main demographical, clinical, and care features of the whole inclusion cohort have already been described [24]. Division of the cohort was performed with the patients who completed the follow-up. The compared main basal features of patients in the derivation ($n=757$) and validation cohort ($n=768$ patients) are detailed in Table 2. We found no significant differences in clinical features of PP included after discharge, at outpatient clinics, or hospital-at-home, but in inclusion BI, which was higher in outpatients (69 ± 31) with respect to those included after discharge in the derivation cohort (60 ± 33; $p=0.01$); and in the validation cohort (71 ± 33 with respect to 56 ± 34, $p=0.001$).

3.1. Derivation of PROFUND index

The global mortality rate in the derivation cohort was 35%. All risk factors associated to 12-month mortality in the unadjusted analysis of the derivation cohort are detailed in Table 3. Additionally, all 10/8 dimensions of the BI/LB were also associated to the primary end-point, respectively. Other possible risk factors (gender, profession, caregiver's age and gender), inclusion criteria (hospital discharge, outpatient, or hospital-at-home), hospital type (tertiary teaching, or basic-general/secondary), all inclusion categories, other comorbidities, number of other comorbidities per patient, need of chronic home oxygen therapy, number of prescribed drugs, polypharmacy, glycated hemoglobin, and creatininemia >1.5 and >2 mg/dL) were not associated to mortality.

Only nine of these factors (one demographical, four clinical, one analytical, one functional, one socio-familial, and one care feature) were independently associated to the primary end-point and, for this reason, were used to develop the index, dividing their beta coefficient in the model by the lowest beta coefficient (which was dyslipidemia) (Table 4). With respect to basal daily living activities, we developed different models including the global basal BI, its ten dimensions, and both. When incorporating the ten dimensions of daily activities, global BI was excluded in the final stepwise model, whereas dependence for eating and for dressing was incorporated as independent predictors; the remaining independent variables remained identical in both analysis. Nevertheless, this latest model obtained poorer results in the validation cohort when compared with the model, which included the basal global BI. For this reason, and because the Barthel index is a universally extended and easy-to-perform tool in clinical practice, we finally chose the model with this factor. Global as well as the eight dimensions of instrumental activities by means of the Lawton–Brody scale, Pfeiffer's scale, socio-familial assessment, and the remaining factors of the unadjusted analysis were not independent factors in the backward stepwise model. The alternative strategies (forward and bidirectional selection techniques) resulted in no differences in the resulting prognostic variables of the modelling. Cox regression models, in which the outcome was time to death, also resulted in the same selection of variables.

After being divided into death-risk quartiles, mortality ranged from 12.8% in the lowest, to 67.9% in the highest risk quartile. A detailed stratification of the four risk quartiles according to predicted probabilities is detailed in Table 5.

All patients were assigned their respective PROFUND scores (score range 0–20) and divided into four different score groups. One year mortality rates were as follows: 0–2 points: 12.1%; 3–6 points: 21.5%; 7–10 points: 45%; and 11 or more points: 68%. A detailed description of the time-dependent primary end-point according to the four score strata is stated in Fig. 1a; mean survival rate was 348 ± 5 days in the first group, 320 ± 6 in the second group, 278 ± 10 in the third group, and 216 ± 11 in the fourth group ($p<0.0021$ in all-risk-group comparisons).

Table 3
Unadjusted analysis of risk factors associated to 12-month mortality in the derivation cohort of polypathological patients of Spain.

Characteristics	Mean/Percentages (OR (CI))	p
Demographics		
Age (years)	78 vs. 81	<0.0001
<70	24%	
70–74	30% (1.37 (0.7–2.7))	0.37
75–79	25% (1.06 (0.6–0.9))	0.8
80–84	34.6% (1.7 (0.97–2.9))	0.06
≥85	49.5% (3.1 (1.8–5.2))	<0.0001
Requiring caregiver	48% (1.96 (1.6–2.4))	<0.0001
Clinical features		
Number of inclusion categories	2.6 vs. 2.8	0.001
≥4 inclusion categories	47.4% (1.86 (1.24–2.8))	0.002
Category E (neurological diseases)	40.2% (1.44 (1.05–1.96))	0.021
Category G (neoplasias)	47.2% (2 (1.46–2.8))	<0.0001
Heart failure (≥II of NYHA)	37.8% (1.35 (0.993–1.8))	0.055
Neurological disease with motor impairment	55.1% (2.5 (1.5–4.1))	<0.0001
Dementia	60.8% (3.48 (2.3–5.35))	<0.0001
Recurrent urinary tract infections	52.4% (2.1 (0.8–5))	0.08
III–IV functional class on NYHA	44.7% (1.86 (1.3–2.7))	0.001
III–IV functional class on MRC	42.7% (1.8 (1.15–2.7))	0.01
III–IV functional class on NYHA and/or MRC	44.3% (2 (1.5–2.7))	<0.0001
Child–Pugh's B–C stage liver disease	41.5% (5.6 (1.4–22))	0.014
Delirium in last hospital admission	62.5% (3.55 (2.1–5.9))	<0.0001
One or more falls in last 12 months	47.9% (1.9 (1.3–2.8))	0.001
Body mass index (kg/m^2)	27.6 vs. 29	0.01
<25 kg/m^2	41.5% (1.5 (1.07–2.1))	0.017
Analytical parameters (blood–plasma)		
Hemoglobin <10 g/dl	49.1% (2.1 (1.5–3))	<0.0001
Albumin <3.5 g/dl	40.4% (1.85 (1.35–2.5))	<0.0001
Albumin <3 g/dL	50% (2.27 (1.6–3.2))	<0.0001
us-CRP >5 mg/dl	43.6% (1.86 (1.2–2.84))	0.004
Psychological–functional–socio-familial features		
Barthel index <60[a]	55% (3.5 (2.6–4.9))	<0.0001
Lawton–Brody index <8(F)/<5(M)[b]	55% (1.7 (1.3–2.4))	0.001
Cognitive impairment (≥3 errors in PS)	45.7% (2.13 (1.6–2.9))	
≥5 Errors in PS	51.4% (2.5 (1.8–3.5))	<0.0001
Social risk/established problem	41% (1.85 (1.3–2.5))	<0.0001
No caregiver or caregiver other than spouse	46% (1.5 (1.3–1.7))	<0.0001
Healthcare features		
Inclusion after discharge/outpatient/at-home	37%/27%/34%	0.07
≥4 Hospital admissions in last 12 months	53.2% (2.3 (1.46–3.7))	<0.0001

OR: odds ratio; CI: confidence interval; NYHA: New York Heart Association; MRC: Medical Research Council; us-CRP: ultrasensitive C-reactive protein; F: female/M: male; PS: Pfeiffer's scale.

[a] All ten dimensions of Barthel index were also associated to mortality.

[b] All eight dimensions of Lawton–Brody index were also associated to mortality.

Table 4
Multivariate analysis of risk factors associated to 12-month mortality in the derivation cohort of polypathological patients of Spain.

Characteristics	Odds ratio (CI)/p	PROFUND index
Demographics		
≥85 years	1.71 (1.15–2.5)/0.008	3
Clinical features		
Active neoplasia	3.36 (1.9–5.8)/<0.0001	6
Dementia	1.89 (1.1–3.1)/0.019	3
III–IV functional class on NYHA and/or MRC	2.04 (1.4–2.9)/<0.0001	3
Delirium in last hospital admission	2.1 (1.5–4.9)/0.001	3
Analytical parameters (blood–plasma)		
Hemoglobin <10 g/dl	1.8 (1.2–2.7)/0.005	3
Psychological–functional–socio-familial features		
Barthel index <60	2.6 (1.38–3.4)/<0.0001	4
No caregiver or caregiver other than spouse	1.51 (1.02–2.2)/0.038	2
Healthcare features		
≥4 Hospital admissions in last 12 months	1.9 (1.07–3.29)/0.028	3
Total score items = 9		0–30 points

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Table 5
Calibration of PROFUND index in the derivation and validation cohort by death-risk quartiles according to predicted probability of death, and performance of goodness-of-fit Hosmer–Lemeshow test.

Risk quartile	Derivation cohort	Validation cohort
First quartile	12.8%	14.6%
Second quartile	24.1%	24.4%
Third quartile	44.8%	46.6%
Fourth quartile	67.9%	61.3%
Hosmer–Lemeshow test	$p=0.432$	$p=0.063$

The calibration obtained in the derivation cohort was good ($p=0.432$ in the Hosmer–Lemeshow goodness-of-fit test); besides, discrimination power of the PROFUND index obtained in the derivation cohort was also good (AUC = 0.77 [0.731–0.805] in ROC curve).

3.2. Validation of PROFUND index

Global mortality in the validation cohort was 39.5%. Mortality according to risk quartiles of predicted probability ranged from 14.6% in the lowest to 61.3% in the highest risk quartile.

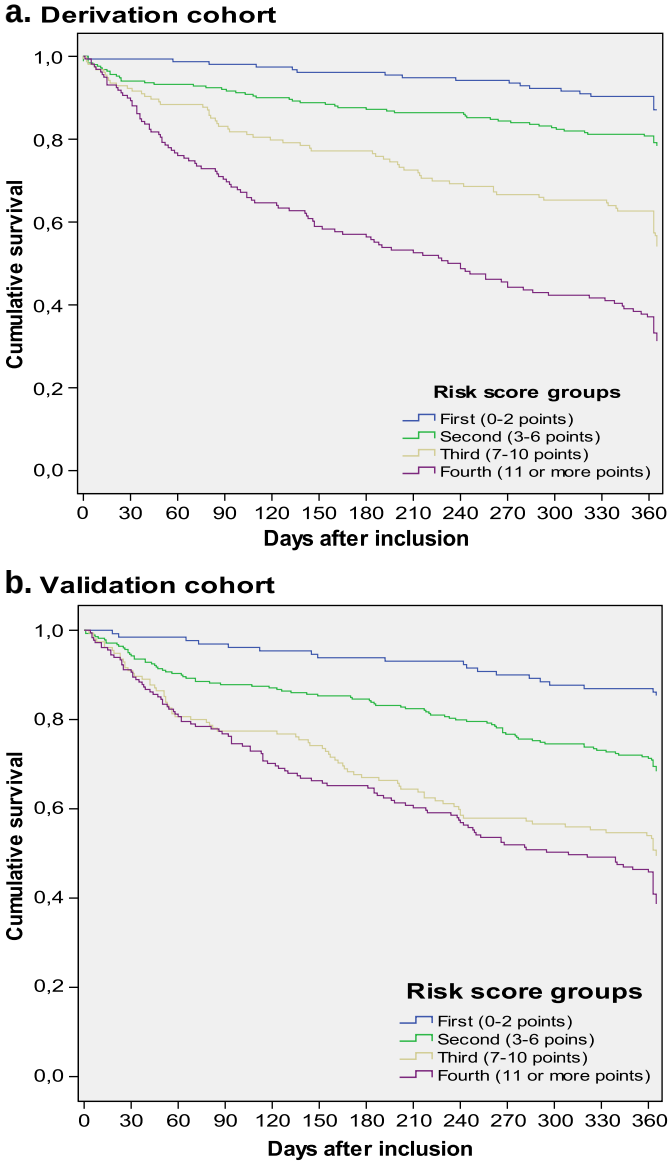

Fig. 1. Kaplan–Meier 12-month survival curves of polypathological patients from Spain, by their PROFUND index death-risk scores in the derivation (a) and validation cohorts (b).

When assessing individual patient scores, mortality was 14.6% in the first group, 31.5% in the second, 50% in the third, and 61.3% in the fourth group. A detailed description of the time-dependent primary end point according to death-risk scores is stated in Fig. 1b; the mean survival rate was 340 ± 6 days in the first group, 304 ± 7 in the second group, 254 ± 11 in the third group, and 239 ± 10 in the fourth group ($p<0.0001$ in all risk quartile comparisons, but $p<0.08$ in comparison between the third/fourth groups). Accuracy testing of the PROFUND index showed good calibration ($p=0.063$) in the Hosmer–Lemeshow goodness-of-fit test (Table 5) and also a good discrimination power (AUC = 0.7 [0.67–0.74] in ROC curve).

3.3. Comparison of the PROFUND index with the Charlson–Deyo index

When assessing accuracy of the Charlson–Deyo Index (CDI) in the whole cohort (derivation+calibration cohorts) by its risk grouping, we obtained a global mortality of 0% in the first risk group for both CDI and CDI adjusted by age (predicted mortality 12%), 29%/23.4% in CDI and CDI adjusted by age, in the second risk group (predicted mortality 26%), 35.7%/25.6% in CDI and CDI adjusted by age, in the third risk group (predicted mortality 52%), and 46%/38.8% in CDI and CDI adjusted by age, in the fourth risk group (predicted mortality 85%); we obtained good calibration with the Hosmer–Lemeshow goodness-of-fit test ($p=0.87$ for CDI and $p=0.95$ for CDI adjusted by age, respectively). However, discrimination power for both CDI and CDI adjusted by age obtained suboptimal results (AUC = 0.59 [0.56–0.62] for CDI and 0.62 [0.59–0.64] for CDI adjusted by age). Comparative 12-month mortality discrimination power of the PROFUND index, CDI, CDI adjusted by age, the Lawton–Brody index, and the Barthel index in the whole cohort (derivation + validation) is detailed in Fig. 2.

4. Discussion

We have developed and validated a new accurate and easy-to-perform prognostic index specifically designed for polypathological patient populations. The PROFUND index includes demographical (age), clinical (presence of neoplasia, dementia, disabling dyspnea, and delirium in last hospital admission), laboratory (hemoglobin), functional (BI), socio-

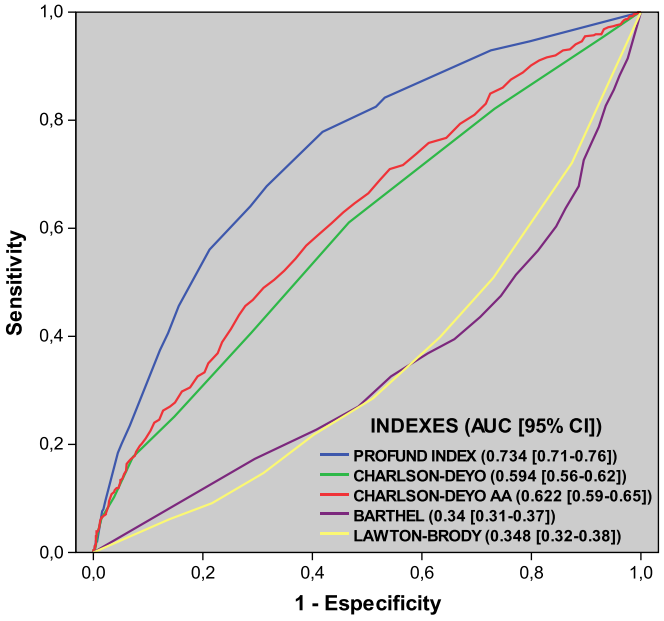

Fig. 2. Comparative 12-month mortality discrimination power of PROFUND index, Charlson–Deyo index, Charlson–Deyo index adjusted by age, Barthel index, and Lawton–Brody index, in a multiinstitutional population of polypathological patients from Spain, by means of ROC curves and determination of area under the curve. AUC: area under the curve; CI: confidence interval; AA: adjusted by age; Barthel: Barthel index; Lawton–Brody: Lawton–Brody index.

Please cite this article as: Bernabeu-Wittel M, et al, Development of a new predictive model for polypathological patients. The PROFUND index, Eur J Intern Med (2010), doi:10.1016/j.ejim.2010.11.012

familial (No caregiver or caregiver other than spouse), and care (number of hospitalizations in last 12 months) variables. The cut-off point of 85 years is consistent with present clinical perception (nowadays ages between 75 and 85 are routinely not excluded from "intense management" in clinicians' minds in most cases) but also with future trends in life expectancy increase [4,5]. As a matter of fact, people are living longer and are reaching older ages with better health status. However, these people progressively accumulate chronic conditions, so the intersection of older ages and polypathology is and will be of notable interest. All clinical–laboratory items of the index are demonstrated risk factors of poor health outcomes in different conditions [9,11,25–27]; with respect to III–IV functional class of NYHA and/or MRC, we think it is a practical approach to assess severity of heart failure and chronic lung diseases because of its easy determination, the frequent coexistence of both conditions in many PP, and their good correlation with more technical, and also more difficult approaches like left ventricular function and spirometry [28–31]. Furthermore, hemoglobinemia is a relatively easy laboratory measure, probably easier than other measures proposed in other prognostic indexes [11]. The Barthel index is nowadays the most universally used tool to assess daily living activities, and its administration can be performed by any healthcare professional in 2–3 min [20,25]; in our modelling, the inclusion of the global index added significantly more calibration and discrimination power than the two individual dimensions independently associated to mortality (dependence in eating and dressing), for all these reasons, we considered its inclusion in our index appropriate. Finally the prognostic weight of socio-familial and care factors underscores the importance of integrally evaluating frail populations not only for clinical management but also in order to accurately establish prognosis.

Our index showed also good geographical transportability through its validation in a cohort of PP from different regions than those included in the derivation cohort. Generalizability of any prognostic index is an important but often forgotten issue; in this sense spectrum transportability is now ongoing in a cohort of PP recruited at the Primary Care level (non-published data); nevertheless, underfitting of the PROFUND index is difficult to exclude at the stage of development, but we think that all important prognostic variables with respect to this population have been included. With respect to reproducibility, we think that the index is not overfitted; on the contrary, it probably fits well to real patterns rather than to random noise, because the ratio of the number of variables to the number of patients experiencing events was not at all small [32]. Nevertheless, only future studies assessing its performance in terms of reproducibility and different aspects of transportability are needed to exactly define its external validity.

Polypathological patients are a remarkably homogeneous, emergent population in all hospitals, with a prevalence range of 20–45% depending on the evaluated areas [1,2,24]. They are characterized by their high complexity, symptom load, clinical vulnerability, high prevalence of functional impairment, dependence on their caregivers, and social frailty [1–3,24]. Furthermore, PP are included in the so-called patients with "multiple complex chronic diseases", who are consuming around 40–55% of all hospital stays, so they are nowadays considered a priority by many healthcare organizations, which have proposed innovative care pathways in order to improve their overall attention [33,34]. For all of these reasons, different specific health interventions could be desirable in order to optimize their healthcare delivery, as well as to improve their health outcomes. Being able to count on a simple clinical tool that accurately stratifies these high-risk patients into four mortality risk groups (ranging from around 10–15% to around 60–65%) is of extreme value in clinical, policy making, and epidemiological scenarios. In clinical settings, our index may be useful in identifying both high- and low-risk patients so that specific interventions can be targeted to each group. Better identification of low–moderate risk PP may speed up and intensify health interventions thereby avoiding poor outcomes; on the other hand, better identification of patients at high risk of death may lead to an earlier onset of palliative care, redefining the usefulness of medical therapies, and enhanced provision of comfort measures. Our index may also be useful when risk adjustment is needed to compare patient outcomes among different health care organizations in order to improve future medical care. Finally, the PROFUND index may be also useful in epidemiological as well as interventional studies in order to avoid bias, and in order to make it easier to include PP in different clinical trials.

With respect to CDI and CDI adjusted by age, our index showed higher discrimination power, and better calibration. The reasons are probably due to the nature of the index and the included variables. CDI is sustained only by clinical diseases and age, while our index is sustained by a spectrum of multi-level variables, as the result of a global–integral approach to patients; taking into account other areas, that have already been demonstrated as independent prognostic factors like functional, socio-familial, and care issues. The loss of accuracy of CDI probably lies in the notable improvements of different therapies, which have deeply changed the outcome of many of the diseases, that conform the index (like cardiovascular diseases, different neoplasias, AIDS, and gastroduodenal diseases), and in the improvement in global life expectancy. An additional explanation could be the fact that prognostic factors used in the CDI (presence of some diseases) are someway overlapped to the inclusion criteria for PP definition. Other authors have already pointed towards this loss of CDI accuracy in predicting health-related quality of life [35].

Finally our mortality index has some limitations. Since our index focused on hospital-based PP, it is possible that it may not be applicable to primary-care PP, since many diseases of these PP populations are not in such advanced stages as those of hospital-based populations. Reproducibility in other cohorts of hospital-based PP, as well as future assessment of historical transportability, is also necessary in order to assure generalizability of the PROFUND index.

In conclusion, we developed and validated a prognostic index specifically focused on polypathological patients using nine simple measures of different clinical areas that can be easily determined with a routine patient overall evaluation. The index has good calibration and discrimination power and was successfully validated in a geographically different cohort. It effectively stratifies polypathological patients into groups at varying risks of death, and it can be used in a variety of different policy making, epidemiological, clinical, and research settings. Our findings provide further evidence of the importance of integrally evaluating frail populations not only for clinical management but also in order to accurately establish prognosis.

5. Learning points

- Polypathological patients conform a homogeneous population in our hospitals. They are characterized by their high 1-year death risk.
- Nine risk factors were independently associated to mortality and used to develop the PROFUND prognostic index. These were age ≥85 years, 3 points; No caregiver or caregiver other than spouse, 2 points; active neoplasia, 6 points; dementia, 3 points; III–IV functional class on NYHA and/or MRC, 3 points; delirium during last hospital admission, 3 points; hemoglobinemia <10 g/dL, 3 points; Barthel index <60 points, 4 points; ≥4 hospital admissions in last 12 months, 3 points.
- Mortality of PP in the derivation/validation cohorts was 12.1%/14.6% for patients with 0–2 points; 21.5%/31.5% for those with 3–6 points; 45%/50% for those with 7–10 points; and 68%/61.3% for those with ≥11points, respectively.
- Accuracy of PROFUND index in terms calibration and discrimination, as well as geographical transportability, was good.

Conflict of interest

The authors have no conflicts of interest to report.

Author's contribution

All authors have contributed substantially to the work.

Please cite this article as: Bernabeu-Wittel M, et al, Development of a new predictive model for polypathological patients. The PROFUND index, Eur J Intern Med (2010), doi:10.1016/j.ejim.2010.11.012

Ethics committee approval

The present study has been approved by the ethics committee of Hospitales Universitarios Virgen del Rocío.

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Acknowledgment

The study was supported by *Instituto de Salud Carlos III* (ISCIII, FIS 07/0047), Ministerio de Sanidad y Consumo, Spain.

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