Original Article

Development of a Six-Month Prognostic Index in Patients With Advanced Chronic Medical Conditions: The PALIAR Score

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Abstract

Context. Efforts in developing useful tools to properly identify the end-of-life trajectory of patients with advanced medical diseases have been made, but the calibration and/or discriminative power of these tools has not been optimal.

Objectives. Our objective was to develop a new, reliable prognostic tool to identify the probability of death within six months in patients with chronic medical diseases.

Methods. This was a multicenter, prospective, observational study in 41 Spanish hospitals, which included 1778 patients with one or more of the following: advanced conditions such as heart failure, respiratory failure, chronic renal failure, chronic liver disease, and/or chronic neurological disease. All patients were followed over six months. Each factor independently associated with death in the derivation cohort (884 patients from eastern areas of Spain) was assigned a prognostic weight, and the score was calculated by summing up the factors. The score's accuracy in the validation cohort (894 patients from western areas of Spain) was assessed by analyzing its calibration and discriminative power; we also calculated sensitivity, specificity, and positive and negative predictive values.

Results. Mortality in the derivation/validation cohorts was 37.6%/37.7%, respectively. We identified six independent predictors of mortality (≥85 years, three points; New York Heart Association Class IV/Stage 4 dyspnea on the modified Medical Research Council, 3.5 points; anorexia, 3.5 points; presence of pressure ulcer(s), three points; Eastern Cooperative Oncology Group Performance Status of three or more, four points; and albuminemia ≤2.5 g/dL,

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four points). Mortality in the derivation/validation cohorts according to risk group was 20%/21.5% for patients with zero points; 33%/30.5% for those with 3–3.5 points; 46.3%/43% for those with four to seven points; and 67%/61% for those who reached 7.5 or more points, respectively. The calibration was good (Hosmer-Lemeshow test, $P = 0.39$), as was the discriminative power (area under the receiver operating characteristic curve of 0.69 [0.66–0.72]). The sensitivity (85%), specificity (86%), positive and negative predictive values (64% and 80%, respectively) at 180 days were high.

Conclusion. The PALIAR score is a precise and reliable tool for identifying the end-of-life trajectory in patients with advanced medical diseases. J Pain Symptom Manage 2014;47:551–565.

Key Words

Complex chronic diseases, palliative medicine, end-of-life trajectory, mortality, prognostic score

Introduction

Patients with chronic medical diseases have become an emerging population in the past several years.[1,2] Socioeconomic advances, together with technical innovations and improvements in health care systems, have led to higher life expectancy, and subsequently higher rates of chronic conditions. People live longer and survive numerous diseases that become chronic and progressive.[3] This results in the accumulation of conditions leading to severe organ failure (heart, lung, liver, kidney, and neurological) in the last years of life;[3,4] more and more often we see how, in the last stages of our lives, we accumulate serious diseases that significantly affect well-being and cause disabilities. This emergent epidemiological paradigm, characterized by the co-occurrence of organ failure(s), advanced age, and frailty in the same patient can change the already-established trajectories of functional and vital decline in the forthcoming years,[3–5] challenging our approach to optimize medical and supportive care.

It is well known that patients with advanced noncancerous diseases can benefit from early commencement of palliative care services, supportive care, and hospice.[6,7] However, assessing the palliative care needs of these patients is dependent on identifying the terminal phase, which can be problematic. It is not easy for clinicians and managers to identify the beginning of the terminal phase of a chronic illness to plan important issues with patients and families such as hospice eligibility or risks and benefits of tests and treatments; in many scenarios, the borders among good practice, nihilism, and therapeutic fervor still remain obscure.[8] This is especially important in high-risk populations to reassess care 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 reasonably accurate prognosis, clinicians can feel more comfortable raising important issues such as care goals, treatment preferences, advanced planning, and therapeutic options with patients and their families.

Because of the importance of this issue, various clinicians and groups have made tremendous efforts in developing useful tools to properly identify the end-of-life trajectory of patients with advanced medical diseases.[9–12] However, despite different modifications to some of the developed tools (such as the National Hospice Organization [NCO; now the National Hospice and Palliative Care Organization] criteria), their calibration and/or discriminative power has not been optimal (mainly because of the moderate positive predictive value), so clinicians usually use them as screening tools rather than as prognostic procedures.[13–16] Also, the usefulness of other generic prognostic tools (without specific oncological dimensions), developed and validated for patients with cancer (such as the

Table 1
Inclusion Criteria for Patients With Advanced Chronic Medical Conditions[a]

Chronic Medical Conditions
Chronic heart failure with basal NYHA functional Class III–IV
Chronic lung failure with basal dyspnea stage ≥3 of mMRC and/or $satO_2$ <90% at room air and/or chronic home oxygen treatment
Chronic renal failure in stage ≥4 of the NKF (glomerular filtration rate <30 mL/min), and/or basal creatininemia ≥3 mg/dL
Chronic liver disease with clinical, biological, endoscopical, or echographic data of portal hypertension and/or hepatocellular failure (Child-Pugh score higher than seven points)
Chronic neurological disease with established cognitive impairment (seven or more errors in Pfeiffer's questionnaire and/or ≤18 points in Mini-Mental State Examination), and/or established functional impairment for activities of daily living (Barthel Index <60 points)

NYHA = New York Heart Association; mMRC = modified Medical Research Council; NKF = National Kidney Foundation.
[a]Patients were eligible for the study if suffering from one or more of the above non-reversible conditions, regardless of their primary cause.

Eastern Cooperative Oncology Group Performance Status scale [ECOG-PS] or the Palliative Prognostic Index [PPI]),[17–20] has not been appropriately tested in patients with advanced medical conditions.

For all these reasons, we performed a multicenter prospective study to develop a clinical tool for identifying the six-month mortality risk for patients with advanced medical diseases, and to compare it with the National Hospice Organization (NHO) criteria, the ECOG-PS, and the PPI.

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 Society of Internal Medicine. The study was approved by the ethical committees of all participating centers. The study inclusion period ranged from February 2009 to September 2010 (18 months). The methodology issues have already been extensively described.[21]

Reference Population

All patients treated in the Internal Medicine and Geriatric areas (in hospital, as well as in outpatient clinics, and those receiving care at home) from the 41 Spanish hospitals (17 tertiary teaching centers and 16 secondary/basic general hospitals) participating in the study (Appendix) were considered potential participants.

Inclusion Criteria

Patients aged 18 years or older, who met the criteria from Table 1, were consecutively included, after providing written informed consent or the proxy consent of their relatives (in the case of cognitive impairment and/or delirium). Patients with any active neoplasm (with the exception of basal cell and/or squamous carcinoma, and those with local prostate cancer in active treatment), those on lung/kidney/liver/heart transplantation waiting lists, those in clinical agony, and those who did not concede to participate in the study were excluded.

Development of the Study, Data Collection, and Follow-Up

After receiving informed consent, a complete set of demographic, sociofamilial, clinical, functional, analytical, pharmacological, and prognostic data were collected from all included patients.[21]

Demographic and sociofamilial data included age, gender, residence, employment, the need for a caregiver, and the main caregiver's profile. Clinical data included the different diseases and all possible comorbidities, the fulfillment of polypathology criteria,[22] stage of each disease (New York Heart Association class,[23] Modified Medical Research Council Dyspnea Scale score,[24] and Child-Pugh stage[25]), Charlson-Deyo Index assessment,[26,27] different symptoms and signs, body mass index (BMI), assessment of baseline (previously to admission, in patients recruited in hospital wards) as well as inclusion (in all patients) ability in performing activities of daily living (ADLs) by means of the Barthel Index (BI)[28] ECOG-PS,[17] Palliative Performance Scale version 2 (PPSv2),[29,30] and number of hospital admissions in the last 12 and three months, respectively.

Laboratory data included plasma creatinine (Cr [mg/dL]), sodium (Na [mEq/L]),

bilirubin (Bb [mg/dL]), albumin (ALB [g/dL]), hemoglobin (HB [g/dL]), leukocytes ($n/\mu L$), lymphocytes ($n/\mu L$), and prothrombin time (by means of international normalized ratio). Pharmacological data included number and type of chronically prescribed drugs at baseline. Finally, we included the PPI and the NHO criteria as prognostic data.

All patients were followed-up during a six-month period. Survival time was assessed and, in the case of death, the number of days to death were recorded. Therefore, we looked at mortality as both a dichotomous and a time-dependent outcome. For the dichotomous outcome, subjects were categorized depending on whether or not they survived six 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.

Definitions

Obesity was defined as BMI higher than 30 and cachexia as BMI lower than 20;[24] hypoalbuminemia was defined as albumin levels lower than 3.5 g/dL (severe when <1.8 g/dL, moderate when 1.8−2.69 g/dL, and slight when 2.7−3.5 g/dL); polypharmacy was defined as the chronic prescription of five or more drugs. Dependence in functional status for ADLs was defined by a BI lower than 60 points. The need for a caregiver was defined as when the patient was functionally dependent (BI < 60) and/or cognitively impaired (Pfeiffer questionnaire with three or more errors). Anorexia was defined as the presence of appetite loss and/or food refusal leading to weight loss in the last three months.

Derivation and Validation of PALIAR: Statistical Analysis

We divided the included population into two cohorts containing approximately one-half of the participating hospitals. The derivation cohort included patients from the eastern part of Spain, and the validation cohort patients from the western part of Spain and the Islands.

Unadjusted relationships between potential risk factors and mortality were assessed in the derivation cohort using logistic regression models. Those variables that obtained a *P*-value lower than 0.25, as well as others that were clinically relevant, were entered into a multiple backward logistic regression model (the total number of independent variables included was 51). Risk factors that remained significant after the multivariable analysis ($P < 0.05$) were used to create the predictive model. To test the stability of our final model, we tried alternative methods (forward and bidirectional selection techniques) to determine whether the resultant model would differ from our original model.

The six-month 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 or half-integer. Subjects in the derivation and validation cohorts were divided into quartiles based on their predicted probabilities of dying, obtained in the model. We also performed Kaplan-Meier curves (and log-rank test), considering death as a time-dependent variable, to assess differences in survival trajectories of the four risk strata.

To validate the score, we determined the calibration of the score by comparing the predicted mortality (divided into probability risk-quartiles and deciles) to the observed mortality in the validation cohort, and calculating the Hosmer-Lemeshow goodness-of-fit test (H-L test) of the full range of scores. Then, we evaluated the discrimination power of the score by applying the point scoring system created in the derivation cohort to the validation cohort, thereby determining risk scores for each participant, and calculating the area under the receiver operating characteristic (ROC) curve. We chose to validate our predictive score in a different region of the country from where it was developed to test geographic transportability and diagnostic accuracy.

To compare the PALIAR score with the NHO criteria, we determined the sensitivity, specificity, and the positive and negative predictive values (PPV and NPV, respectively) of the four risk groups differentiated by the PALIAR score, with the presence/absence of NHO criteria. For this purpose, we assumed the development of the main event (death) as an absolute truth criterion, 30, 60, 90, 120, 150, and 180 days after inclusion.

We also compared the precision of the PALIAR score with the PPI. To compare the

Table 2
Comparative Main Baseline Clinical Features of the Patients in the Derivation and Validation Cohorts

Clinical Features[a]	Derivation Cohort ($N=884$)	Validation Cohort ($N=894$)[b]
Age, yrs	78.2 ± 9	79.2 ± 10
Sex (male)	450 (50.3)	431 (49.7)
Requiring caregiver/having caregiver	680 (76.1)/748 (87.5)	705 (79)/744 (86)
Prevalence of inclusion criteria in recruited patients		
Chronic neurological disease	404 (45.2)	374 (42.3)
Chronic heart failure	340 (38)	351 (39.7)
Chronic lung failure	295 (33)	308 (34.8)
Chronic renal failure	111 (12.4)	98 (11.1)
Chronic liver disease	50 (5.6)	60 (6.8)
Number of defining categories/patient	1.34 ± 0.6	1.35 ± 0.6
Patients with ≥2 inclusion criteria/≥3 inclusion criteria	268 (30)/40 (4.5)	258 (29)/44 (5)
Health care venue at inclusion		
In hospital	766 (87)	830 (92)
Hospital at home/palliative care at home	35 (4)	14 (2)
Outpatient clinic	83 (9)	50 (6)
Number of other comorbidities/patient	5 ± 2.5	4.6 ± 2.6 ($P<0.001$)
Patients with ≥4 other comorbidities	670 (75)	570 (65; $P<0.001$)
Other frequent comorbidities		
Hypertension	643 (72)	601 (68)
Arrhythmias	348 (39)	363 (41.5)
Atrial fibrillation/other arrhythmias	313 (35)/35 (4)	332 (38)/31 (3.5)
Diabetes	391 (44.3)	403 (45)
Without visceral involvement/with visceral involvement	256 (29)/135 (15)	260 (29)/143 (16)
	306 (34)	268 (30)
Dyslipidemia	213 (23)	174 (20)
Coronary heart disease	197 (22)	198 (22.4)
Chronic anemia	182 (20)/65 (7)/27.2	179 (20)/73 (8)/26.9
Obesity (BMI >30)/cachexia (BMI <20)/mean BMI	167 (19)	156 (18)
Chronic degenerative osteoarticular disease	93 (10)	63 (7)
Peripheral arterial disease	161 (18)/100 (11)	133 (15)/140 (15.8)
Venous thromboembolic disease/pulmonary hypertension	108 (12) and 140 (16)	95 (11) and 139 (16)
	177 (20)	119 (13.5; $P<0.001$)
Anxiety and depressive disorders	80 (9)	64 (7.5; $P=0.02$)
Benign prostate hyperplasia	132 (15)	83 (9.5; $P<0.001$)
Thyroid disease (hypo-/hyperthyroidism)	64 (7)/65 (7)	51 (6)/54 (6.1)
Osteoporosis	39 (4.4)	33 (4)
Peptic gastroduodenal disease/Biliary lithiasis		
Autoimmune diseases, vasculitides		
Most prevalent symptoms		
Asthenia	220 (24)	186 (21)
Anorexia	194 (22)	156 (18; $P=0.03$)
Pain	180 (20)	151 (17)
Patients with basal class IV of NYHA/class IV of mMRC	130 (14)	100 (11.2)
	123 (14)	122 (14)
Pressure ulcers	29 (2)	45 (3; $P=0.02$)
Nausea/vomiting		
Charlson Index/Charlson Index adjusted by age	3 [3]/7 [3]	3 [2]/7 [2]

BMI = body mass index; NYHA = New York Heart Association; mMRC = modified Medical Research Council.
[a]Quantitative data are described by their mean values ± standard deviation or their median values and interquartile ranges (in brackets); qualitative data are described by the total number and its respective percentage in parenthesis.
[b]*P*-values are detailed in parenthesis when significant differences were detected.

calibration, we used the H-L test; and to compare the discrimination power, we calculated the area under the ROC curve. We also compared the sensitivity, specificity, PPV, and NPV of the four risk groups differentiated by the PALIAR score, with the cutoff points of the PPI index higher than two, four, and six points, assuming the same absolute truth criterion, as previously described.

Finally, we compared the PALIAR score with the Charlson-Deyo Index (CDI), and with the age-adjusted CDI, by means of the H-L test, and the area under the ROC curve.

The dichotomous variables were described as whole numbers and percentages, and the continuous variables as mean and standard deviation (or median and interquartile rank in those with no criteria of normal

Table 3
Comparative Main Baseline Laboratory Functional, and Health Care Features of the Derivation and Validation Cohorts

Features[a]	Derivation Cohort ($N=884$)	Validation Cohort ($N=894$)[b]
Leukocytes	8998 [4900]	8995 [4700]
Lymphocytes (/μL)	1235 [900]	1200 [838]
Hemoglobin (g/dL)/prothrombin time (INR)	$11.8 \pm 6/1.1 \pm 0.41$	$11.7 \pm 5.3/1.11 \pm 0.5$
Albumin (g/dL)/plasmatic creatinine (mg/dL)	3.1 [0.6]/1.04 [0.8]	3.02 [0.7]/1.1 [0.7]
Cholesterol (mg/dL)/sodium (mEq/L)/bilirubin (mg/dL)	152 [48]/138 ± 6/0.6 [0.5]	150 [53]/138 ± 7/0.7 [0.6]
Basal Barthel Index	40 [70]	40 [65]
Patients with <60 points	611 (68)	582 (66)
Patients with <40 points	446 (50)	444 (50)
Patients with <20 points	319 (36.1)	314 (35)
Basal ECOG-PS	20 [20]	20 [20]
Patients with Grade 0–I (fully ambulatory)	231 (25.9)	226 (25.5)
Patients with Grade ≥II	663 (74.1)	658 (74.4)
Patients with Grade ≥III	380 (42.5)	397 (44.9)
Patients with Grade IV (bedridden)	185 (20.7)	181 (20.5)
Basal palliative performance score	50 [30]	50 [30]
Patients with ≤70 points (reduced)	837 (93.7)	817 (92.5)
Patients with ≤50 points (mainly)	621 (69.5)	582 (66)
Patients with ≤30 points	272 (30.5)	278 (31.5)
Number of prescribed drugs/patients with 10 or more drugs	8.5 ± 3.5/309 (35)	7.8 ± 3.5/247 (28; $P<0.003$)
Hospitalizations in last 12/3 mo	$2.1 \pm 0.5/1.4 \pm 0.9$	$2.1 \pm 0.5/1.4 \pm 0.9$
Included in palliative care programs	81 (9.1)	64 (7.2)
Psychological/spiritual support	22 (2.5)/69 (7.7)	28 (3.2)/121 (13; $P<0.01$)
Financial/social support by means of dependence laws	252 (28)	148 (17; $P<0.001$)

INR = international normalized rank; ECOG-PS = Eastern Cooperative Oncology Group Performance Status.
[a]Quantitative data are described by their mean values ± standard deviation or their median values and interquartile ranges (in brackets); qualitative data are described by the total number and its respective percentage in parenthesis.
[b]*P*-values are detailed in parenthesis when significant differences were detected.

distribution). The distribution of all variables was analyzed with the Kolmorogov-Smirnov test. Statistics were performed using the SPSS 19.0 (SPSS, Inc., Chicago, IL) and Epidat 3.1 (Dirección Xeral de Innovación e Xestión da Saúde Pública, Santiago de Compostela, Spain) computer packs.

Results

A total of 1847 patients were included, with a mean age of 78.74 ± 10 years. A total of 51% was male. The most frequent inclusion criteria were chronic neurological disease (814 patients, 44.1%) followed by chronic heart failure (718, 38.9%), chronic lung failure (615, 33.3%), chronic renal failure (225, 12.2%), and chronic liver disease (115, 6.2%). The mean number of inclusion criteria was 1.35 ± 0.6, and the mean number of comorbidities was 4.85 ± 2.6. The six-month follow-up was completed in 1778 patients (96.8%); there was no difference between these patients and those lost during follow-up. The baseline features of patients in the derivation and validation cohorts are detailed in Tables 2 and 3.

Derivation of the PALIAR Score

In the derivation cohort ($n=884$), 332 patients died during the follow-up period (37.6%). The factors associated with mortality in the unadjusted analysis are detailed in Table 4. All other possible risk factors (gender, profession, residence, caregiver's age and gender, and hospital type [tertiary teaching or basic general/secondary]), all inclusion categories, other comorbidities, number of other comorbidities per patient, other symptoms, number of prescribed drugs, polypharmacy, drugs other than those detailed in Table 4, and the remaining analytical parameters (HB, lymphocyte count, Bb, Na, prothromobin time, and cholesterol levels), were not associated with mortality.

Only six of these factors (one demographic, three clinical, one analytical, and one functional) were independently associated with the primary endpoint, and for this reason were used to develop the score, dividing their beta coefficient in the model by the lowest beta coefficient, which was biliary lithiasis (odds ratio [OR] = 0.54, 95% confidence interval [CI] = 0.26–1.1; $P=0.08$]; Table 5).

Table 4

Unadjusted Analysis of Risk Factors Associated With Six-Month Mortality in the Derivation Cohort ($N = 884$)

Characteristics	RR (95% CI)	*P*-value
Demographics-sociofamilial features		
≥85 yrs	2 (1.5–2.7)	<0.0001
Needing a caregiver	2.5 (1.8–3.7)	<0.0001
No caregiver/caregiver other than first-degree relative	1.5 (1.14–2)	0.002
Clinical and pharmacological features		
Neurological diseases with motor impairment	1.5 (1.1–2)	0.005
Dementia	1.9 (1.5–2.5)	<0.0001
Delirium (actual and/or in last hospital admission)	2.9 (2–4)	<0.0001
Pressure skin ulcers	3 (2–4.5)	<0.0001
IV functional class on NYHA and/or MRC	1.9 (1.3–2.9)	0.01
Anorexia	2.3 (1.7–3)	<0.0001
Asthenia (%)	46 vs. 35 (1.6 [1.2–2.1])	0.004
Nausea-vomiting (%)	55 vs. 37 (2.1 [0.99–4.4])	0.053
No use of calcium and/or vitamin D (%)	38 vs. 26 (1.5 [1.02–2])	0.037
No use of oral anticoagulants (%)	26 vs. 18 (1.4 [1.03–1.8])	0.005
Use of opioids (%)	57.8 vs. 35 (2.5 [1.5–4.3])	<0.0001
Use of neuroleptics (%)	49 vs. 32 (2 [1.5–2.8])	<0.0001
Lower body mass index (kg/m^2)	25 vs. 28	<0.0001
Higher Charlson index/adjusted by age	4 vs. 3/7 vs. 6	<0.0001
Laboratory parameters (blood-plasma)	148 vs. 160	<0.0001
Lower cholesterol (mg/dL, %)	60 vs. 36 (2.6 [1.5–4.5])	<0.0001
Cholesterol <100 mg/dL	3.3 vs. 3.9	0.08
Lower albumin (mg/dL, %)	54 vs. 36 (2.1 [1.4–3.3])	0.001
Albumin <2.5 g/dL	1448 vs. 1475	0.13
Lower lymphocyte count (/μ, %)	49 vs. 37 (1.7 [1.02–2.7])	0.034
Lymphocyte count <500/μL	1.5 vs. 1.3	0.011
Higher creatininemia (mg/dL, %)	51 vs. 37 (1.8 [1.06–3])	0.028
Creatininemia≥3 mg/dL		
Psychological-functional features		
Barthel Index[a]	27 vs. 47	<0.0001
Barthel Index <60 (%)	44 vs. 24 (2.5 [1.8–3.4])	<0.0001
Barthel Index <40 (%)	50 vs. 26 (2.8 [2.1–3.7])	<0.0001
Barthel Index <20 (%)	54 vs. 29 (2.8 [2.1–3.8])	<0.0001
Palliative Performance Scale (PPS)	37 vs. 50	<0.0001
PPS ≤70 (%)	40 vs. 7 (8.6 [3–24])	<0.0001
PPS ≤50 (%)	46 vs. 19 (3.7 [2.6–5.2])	<0.0001
PPS ≤30 (%)	57 vs. 29.5 (3.1 [2.3–4.2])	<0.0001
ECOG-PS ≥III (%)	55 vs. 26 (3.5 [2.6–4.6])	<0.0001
ECOG-PS-IV (%)	61 vs. 32 (3.4 [2.4–4.7])	<0.0001
Health care features		
Inclusion in-hospital/outpatient/hospital-at-home (%)	39/11/61.5	<0.0001
≥4 Hospital admissions in last 12 mo (%)	45 vs.37 (1.4 [0.95–2.4])	0.08
≥3 Hospital admissions in last 3 mo (%)	47 vs. 37 (1.5 [0.97–2.7])	0.06

RR = relative risk; 95% CI = 95% confidence interval; NYHA = New York Heart Association; MRC = Medical Research Council; PPS = Palliative Performance Status; ECOG-PS = Eastern Cooperative Oncology Group Performance Status.

[a]All 10 dimensions of the Barthel Index also were associated with mortality.

All the remaining sociofamilial, clinical, analytical, functional, and health care 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 modeling.

After this, all patients were assigned their respective PALIAR scores (score range 0–21). Patients were then grouped into death-risk quartiles according to the probability awarded to every patient by the model, mortality ranging from 20.1% in the lowest to 67% in the highest risk quartile. The six-month mortality rates in the four different score groups were: zero points: 20.1%; 3–3.5 points: 33.1%; four to seven points: 46.3%; and 7.5 or more points: 67%. A detailed stratification of the four risk quartiles according to predicted probabilities appears in Table 6.

A detailed description of the time-dependent primary endpoint according to the four score strata by means of Kaplan-Meier survival estimates is shown in Fig. 1a. The calibration obtained in the derivation

Table 5
Multivariate Analysis of Risk Factors Associated With Six-Month Mortality in the Derivation Cohort ($N = 884$)

Characteristics	Odds Ratio (95% CI)	*P*-value	PALIAR Score
Demographics			
≥85 yrs	1.68 (1.18–2.39)	0.004	3
Clinical features			
Anorexia	1.84 (1.19–2.86)	0.006	3.5
Functional class IV on NYHA and/or MRC	1.90 (1.16–3.11)	0.01	3.5
Presence of skin pressure ulcer(s)	1.75 (1.06–2.88)	0.029	3
Laboratory parameters (blood-plasma)			
Albumin <2.5 g/dL	2.04 (1.33–3.12)	0.001	4
Functional features			
ECOG-PS ≥3	2.07 (1.47–2.90)	<0.0001	4
Total score items = 6			0–21 points

CI = confidence interval; NYHA = New York Heart Association; MRC = Medical Research Council; ECOG-PS = Eastern Cooperative Oncology Group Performance Status.

cohort was good ($P = 0.926$ in the H-L test, and P ranging from 0.03 to <0.0001 in all risk-group comparisons by log-rank test). When assessing discrimination power, the PALIAR score obtained an area under the ROC curve of 0.71 (95% CI = 0.69–0.75) in the derivation cohort.

Validation of the PALIAR Score

Global mortality in the validation cohort ($n = 894$ patients) was 37.7%. Mortality according to risk quartiles of the predicted probability ranged from 21.5% in the lowest to 61% in the highest risk quartile (30.5% in the second group and 43% in the third; Table 6). The mortality assessment as a time-dependent primary endpoint according to death-risk scores, by means of Kaplan–Meier curves, is detailed in Fig. 1b. Accuracy testing of the PALIAR score showed a good calibration ($P = 0.39$ in the H-L test), and also a good discriminative power (area under the ROC curve = 0.7, 95% CI = 0.67–0.72) in the validation cohort.

Table 6
Calibration of the PALIAR Score in the Validation Cohort ($N = 894$) by Death-Risk Quartiles and Deciles, According to Predicted Probability of Death, Compared With the Observed Death Rate; and Performance of the Goodness-of-Fit Hosmer-Lemeshow Test

	Validation Cohort	
Risk Deciles and Quartiles	Predicted (%)	Observed (%)
First, second, and third deciles (0 points)	21	21.5
Fourth decile (3 points)	31	23
Fifth decile (3.5)	33	37.1
Sixth decile (4 points)	34.5	39.5
Seventh decile (6–6.5 points)	44.5 (41.2–46.8)	43.2
Eighth decile (7–7.5 points)	47.6 (47–50.4)	47.3
Ninth decile (8–10.5 points)	59 (50.5–62.9)	65
Tenth decile (11–21 points)	71 (63–90)	67
First quartile (0 points)	21	21.5
Second quartile (3–3.5 points)	32 (31–33)	30.5
Third quartile (4–7 points)	46 (43–47)	43
Fourth quartile (7.5–21 points)	62 (50–90)	61
Hosmer-Lemeshow test (*P*-value)	0.387	

Comparison of the PALIAR Score With the NHO Criteria

The comparison of the PALIAR score (categorizing patients by those with zero points [lowest risk group], three to 21 points [low-intermediate to high-risk groups], four to 21 points [high-intermediate to highest risk groups], and 7.5–21 points [highest risk group]) with respect to NHO criteria is detailed in Table 7. Succinctly, the new scale showed higher sensitivity and NPV than the NHO criteria in the lowest risk group (zero points); and higher specificity and PPV in the high-intermediate risk (four or more points) and the highest risk group (7.5 or more points) than the NHO criteria.

Comparison of the PALIAR Score With the PPI

When assessing accuracy of the PPI in the whole cohort, we obtained a good calibration (H-L test, $P = 0.2$), but a slightly poorer discrimination power than the PALIAR score, as detailed in Fig. 2. The comparison of

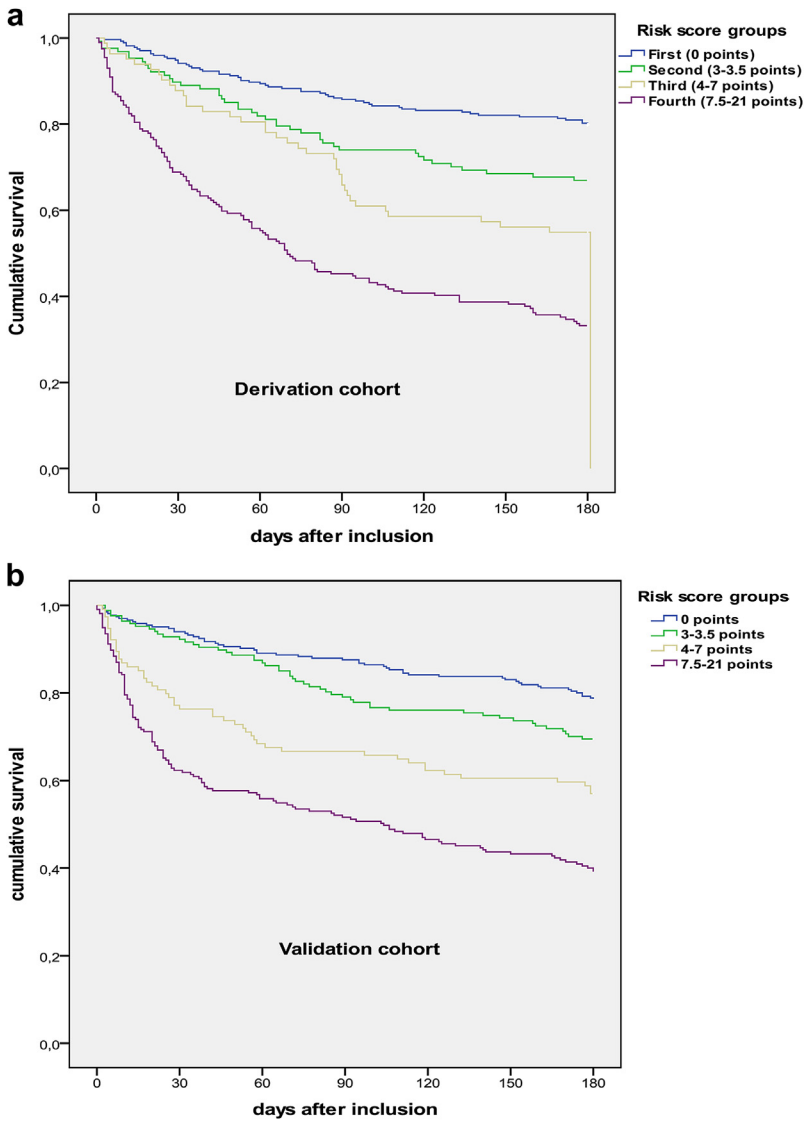

Fig. 1. Kaplan-Meier six-month survival curves of Spanish patients with advanced chronic medical conditions, by their PALIAR score death-risk groups in the a) derivation cohort ($n = 884$) and b) validation cohort ($n = 894$).

sensitivity, specificity, PPV, and NPV of the PALIAR score with respect to the PPI by means of the ascending cutoff points of higher than zero, two, four, and six points also is shown in Table 7. Altogether, at the lower cutoff points, the PALIAR score obtained a higher NPV, and in the higher cutoff points, the PALIAR score also obtained a higher PPV.

Comparison of the PALIAR Score With the CDI

Calibration of the CDI and the age-adjusted CDI in the validation cohort by the H-L test was good for the CDI ($P = 0.09$) and poor for the CDI adjusted by age ($P < 0.001$). Discrimination power for both the CDI and the CDI adjusted by age obtained suboptimal results (area under the ROC curve = 0.52, 95% CI = 0.5–0.55) for the CDI, and 0.58 (95% CI = 0.55–0.6) for the CDI adjusted by age (Fig. 2).

Discussion

In the present study, we report on the development and validation of a comprehensive, easy-to-use, new prognostic score, which reasonably assesses six-month mortality in patients

Table 7
Comparison of Sensitivity, Specificity, PPV, and NPV, Detecting End-of-Life Trajectory, Among the PALIAR Score, NHO Criteria, and the PPI Index, in the Validation Cohort ($n = 894$)[a]

Index	Sensitivity (180–30 d), %	Specificity (30–180 d), %	PPV (30–180 d), %	NPV (180–30 d), %
PALIAR (>0 points)	85–90	34–38	20–45	80–94
PALIAR (≥3 points)	66–73	53–58	23–49	71–94
PALIAR (≥4 points)	52–64	71–76	30–57	70–91
PALIAR (≥7.5 points)	39–51	82–86	35–64	70–90
NHO criteria	69–75	55–69	24–61	77–92
PPI (>2 points)	90–94	22–25	18–42	70–94
PPI (>4 points)	70–78	49–54	22–47	75–92
PPI (>6 points)	54–66	67–71	27–53	72–91

PPV = positive predictive value; NPV = negative predictive value; NHO = National Hospice Organization; PPI = Palliative Performance Index.
[a]For each dimension and scale, the lowest-highest values among the two extreme time points of follow-up (30 and 180 days) are detailed.

with advanced medical diseases. The PALIAR score is based on six dimensions (age, three clinical dimensions, one biological parameter, and one functional measure).

Age is an obvious cornerstone in all prognostic tools, and its cutoff point has increased progressively in the past years, according to the longer life expectancy in our societies; in this sense, the cutoff age of 85 years is concordant with life-expectancy data, clinical data, and social perceptions.[31,32] This result is also concordant with the fact that nowadays, chronological age alone is a relative parameter, acquiring progressive prognostic importance in older patients. In other studies, sociofamilial- and caregiver-related parameters were independent determinants of survival.[8,33] However, these parameters did not reach enough weight in the multivariate analysis of the present study, probably because in these advanced stages of chronic diseases, the most important parameters of short-term survival are the clinical and biological ones.

The three clinical dimensions of the score (anorexia, severe dyspnea, and pressure ulcers), as well as the plasma albumin level, are well-established independent factors of a bad prognosis in many medical conditions, and their assessment is easy to perform.[8,34–39] All three clinical dimensions are common in patients with severe chronic conditions, are disabling for patients and their families, and represent an important challenge to health care professionals. Anorexia is present in up to a third of the elderly, and is a key factor in the development of a cachexia syndrome in patients with severe chronic conditions, leading to sarcopenia, loss of function, and progressive dependence.[36,37] Dyspnea at rest is one of the most disabling symptoms in patients with advanced heart and lung diseases, and it is a major cause of inability to perform ADLs, which in the most severe cases is also hindered by last-choice medical treatments (continuous oxygen and opioids). Pressure ulcers are one of the major causes of morbidity in frail and elderly patients (prevalence of 3–11% in hospitalized patients with acute diseases and 33% in chronic care facilities), and dramatically increase the global costs of care.[38] Finally, hypoalbuminemia is a potent predictor of poor outcomes in many acute and chronic diseases, and health care scenarios.[37] In our study, the optimal cutoff point was 2.5 g/dL, probably because of the low levels of albuminemia in both cohorts (3.1/3.02 g/dL, in derivation/validation cohorts, respectively).

The most powerful functional predictor in the present study was the ECOG-PS. In the unadjusted analysis, all three functional instruments (BI, PPS, and ECOG-PS), which were tested in the study, showed significant predictive power. However, in the different multivariant models and techniques (including forward, backward stepwise, and Cox regression models, all possible combinations of the three scales, and interaction rules), the only scale that maintained significant independent predictive power was the ECOG-PS (Stages ≥3, capable of only limited self-care, confined to bed or chair for more than 50% of the waking hours). The ECOG-PS is one of the most comprehensive functional assessment methods in cancer medicine; it is the cornerstone in the decision-making process for many oncologists

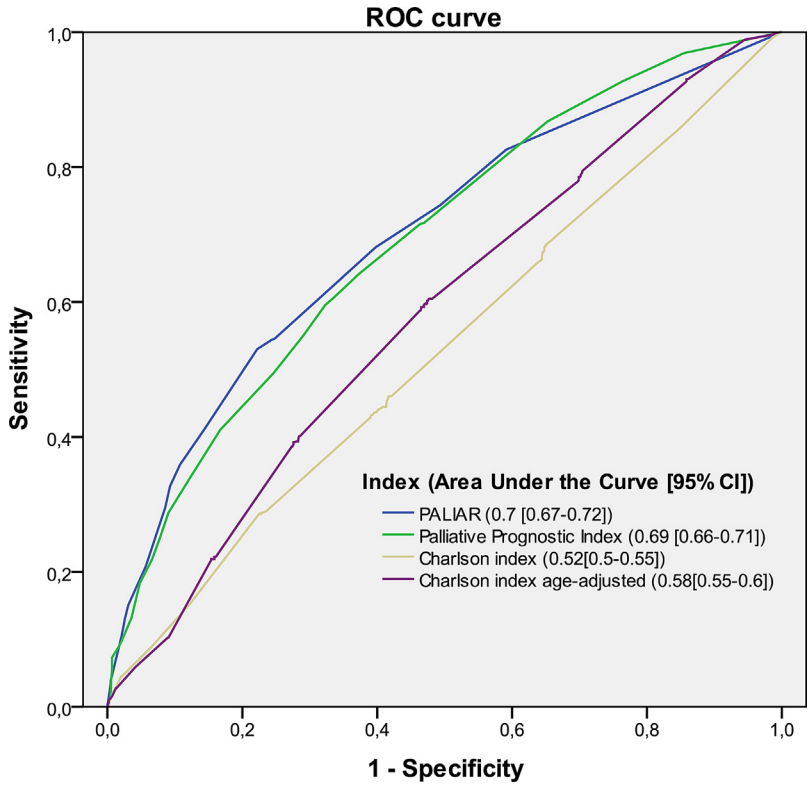

Fig. 2. Comparative six-month mortality discrimination power of the PALIAR score, the Palliative Prognostic Index, the Charlson-Deyo Index, and the Charlson-Deyo Index adjusted by age in the validation cohort ($n = 894$ patients) of a multi-institutional population of Spanish patients with advanced chronic medical conditions, by means of area under the ROC curves (using the full range of scores). ROC = receiver operating characteristic; CI = confidence interval; AA = adjusted by age.

with respect to cancer treatment options.[40–42] Nevertheless, its usefulness in patients with advanced medical diseases has neither been established nor explored. We think that our results with respect to the ECOG-PS are consistent with those obtained for populations of patients with cancer because functional status is determined mainly by disease progression, independent of origin. In this sense, an approach with a powerful and easy-to-use tool such as the ECOG-PS makes sense.[40] Our results do not mean that the BI and PPS are not useful in the management of these patients; but analyzing the present results, a reasonable approach could be to use the ECOG-PS when attempting to establish prognosis, and to use the BI and/or the PPS when specifically planning the strategies for and needs of medical, nurse, and sociofamilial care delivery.

The PALIAR score obtained a good calibration and a powerful discrimination in both derivation and validation cohorts, improving on those obtained by the NHO criteria, the CDI, and the CDI adjusted by age, and slightly on those obtained by the PPI. In addition, the validity indexes (sensitivity, specificity, PPV, and NPV) of the PALIAR score were much better than those of the NHO criteria, and were slightly better than those obtained by the PPI. One of the most difficult aims in the survival prediction of patients with advanced medical diseases has always been the PPV, which is poor or discrete in all tools already in use;[13–16] this is also the case in this study. In this sense, even moderate improvements in PPV with the development of new scores, such as those obtained with the PALIAR score with respect to the NHO criteria, are desirable.

The second important issue that our data have shown is the poor precision and poor validity indexes of the CDI a fact already detected in recent studies.[33] This contrasts with the good overall fitness obtained by the PPI,

the behavior of which was only slightly lower than values obtained with the PALIAR score. Future studies aimed toward a recalibration of the PPI's risk strata in this specific population of patients will probably equip this tool with additional and complementary usefulness.

Finally, the PALIAR score is not exempt from some limitations. Most patients were recruited in hospital, so it is possible that it may not be applicable to other clinical scenarios such as hospices or primary care settings. Additionally, the scarce representation of patients with advanced liver diseases (5.6–6.1% of the derivation-validation cohorts, respectively), could subtract some fitness in this specific population. Future studies including other similar populations and other health care scenarios are necessary to assess the generalizability of the PALIAR score.

In conclusion, the PALIAR score emerges as a well-calibrated and reasonably discriminative tool in assessing the advent of the end-of-life trajectory in patients with advanced chronic medical diseases. This new score has proven higher validity indexes than the classic NHO criteria, and reliably stratifies patients into groups at varying risks of death over a six-month period; this could be a valuable aid for clinicians, together with clinical judgment, in establishing objectives and planning the care of these vulnerable patients.

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