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TITLE PAGE

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ABSTRACT

Objectives: Two concepts have recently been rediscovered to improve the care of patients with advanced chronic conditions: early identification of palliative care needs and the concept of end-of-life trajectories in chronic illnesses. The objective of this study was to evaluate this conceptual intersection, identifying what indicators work best for this early identification and if there are distinguishing features in other indicators that support the conceptual model of end-of-life trajectories, beyond the functional variables that describe such trajectories.

Setting: Three primary care services, an acute care hospital, an intermediate care centre and four nursing homes in a mixed urban-rural district in Barcelona, Spain.

Participants: 782 women (61.5%) and men with a NECPAL CCOMS-ICO© test positive were recruited.

Outcome measures: The characteristics and distribution of the variables of the NECPAL CCOMS-ICO© tool are analysed with respect to the three trajectories described. These indicators have been arranged by domain (functional, nutritional and cognitive status, emotional problems, geriatric syndromes, social vulnerability and others) and according to their static (severity) and dynamic (progression) behaviour.

Results: The indicators globally associated with this early end-of-life identification are: functional (44.3%) and nutritional progression (30.7%), emotional distress (21.9%) and some geriatric syndromes (15.7% delirium, 11.2% falls). The rest of the indicators (functional and cognitive severity criteria, others geriatric syndromes - such as decubitus ulcers or dysphagia-, a repetition infections, comorbidity, use of resources or need of palliative care criteria) showed differences in the associations per illness trajectories ($p< 0.005$).

Conclusions: Dynamic indicators best identify patients with advanced chronic conditions who have palliative care needs. The evaluation of the other variables allows defining clusters of patients with specific features. This contributes to the understanding of end-of-life trajectories associated to advanced chronic illnesses.

ARTICLE SUMMARY

- This study innovatively explores the relationship between the end-of-life indicators used to identify patients with advanced chronic conditions and the three archetypal end-of-life trajectories: acute (typically cancer), intermittent (typically organ failure) and gradual dwindling (typically dementia or frailty).

- Knowing the behaviour of end-of-life indicators is helpful to deal with decision making.

- Dynamic variables are the most consistent to identify these patients transversally. Other variables allow defining clusters of patients with specific characteristics, contributing to the clinical end-of-life trajectories approach.

- These concepts could be useful for health professionals -for decision making purposes-, for policymakers -in the design of policies and healthcare devices-, as well as for researchers as starting point for future research.

- The limitations of this study are the heterogeneity in the collection of variables due the multiple assessments from all health care system resources; and the number of missing data in the nutritional variables.

MAIN TEXT

INTRODUCTION

Two new concepts can illuminate care provision for patients with advanced chronic conditions: early identification of patients with palliative care (PC) needs and, secondly, end-of-life trajectories associated with advanced chronic illnesses. This gives a conceptual framework to easier understand the different behaviours of patients from their early identification onwards.

Conceptual transitions, early identification and end-of-life indicators

The process of end of life is divided into two transitions[1] (figure 1). The first one, frequently some months or years before death, may constitute the starting of the process due to the appearance and recognition of some indicators or variables which make early identification easier; throughout the article we will refer to these patients with advanced chronic diseases and conditions, palliative care needs and limited life prognosis as a “Patients with advanced chronic conditions“ (PACC). The second transition, when terminal decline begins is simply described as patients in the last days or weeks of life.

Early identification of PACC has been shown to provide many benefits[2–4] and becomes necessary for the development of anticipatory PC planning.[5] At this point, however, the earlier we want to identify these patients, the more difficult it becomes to obtain certain prognostic variables.[6] Then, classic prognosis approaches, basically focused on organ variables, have limitations, particularly for geriatric patients with multiple chronic conditions.[7] For this reason, most prognostic tools have incorporated other general conditions from different domains (functional, nutritional and cognitive

status, emotional problems, geriatric syndromes, social vulnerability and others) (table 1) with solid death predictive values which have been proved to be reliable indicators of end of life situation[8] (table 2).

Variables and Domains		Disease specific tools				Early identification of patients with Palliative needs screening tools			Multidimensional indexes			Frailty indexes		
		PPS	BODE	SHFM	CHILD	PIG-GSF	SPICT	NECPAL	Walter	Flacker	MPI	CSHA FI	Share -FI	Edmon -ton
Diseases		-	S	S	S	S	S	S,P	S	S	-	S	-	-
Comorbidity		-	-	-	-	+	+	+	-	-	+	+	+	-
Functional	IADL	S	-	-	-	-	-	-	-	-	S	S	S	S
	ADL	S	S +/-	-	-	S,P	S,P	S,P	S	S,P	S	S	S	-
Nutritional		S	S	S	S	S,P	S,P	S,P	S	S	S,P	-	S	P
Cognitive		S	-	-	-	S	S	S,P	-	P	S	S,P	S	S
Emotional		-	-	-	-	-	-	S	-	-	-	S	S	S
Geriatric syndromes		-	-	-	-	-	-	+	-	S	+	+	+	+
Symptoms		-	+	-	-	-	-	-	-	+	-	-	+	-
Social situation		-	-	-	-	-	-	-	-	-	+	-	-	+
Use of resources		+	-	+	-	+	+	+	-	-	-	-	-	+

Table 1: Variables of different domains and prognostic tools: (**-**): Domain not included. (**+**): domain included **S**: Severity. **P**: Progression. **IADL**: instrumental activities of daily living. **ADL**: activities of daily living. **PPS**: Performance Status Scale[9] -for cancer-; **BODE**: BODE index[10] -for Chronic Obstructive Pulmonary disease-; **SHFM**: Seattle Heart Failure Model[11] –for heart failure-; **CHILD**: or the Child-Pugh's classification[12] -for Liver disease-. **PIG-GSF**: Prognostic Indicator Guidance of the Gold Standards Framework[13]; **SPICT**: Supportive & Palliative Care Indicators Tool;[14] **NECPAL**: NECPAL CCOMS-ICO tool.[15–17] **Walter**: Walter index;[18] **Flacker**: Flacker index;[19] **MPI**: Multidimensional Prognostic Index.[20] **CSHA-FI**: Canadian Study of Health and Aging-Frailty Index;[21] **SHARE-FI**: Survey of Health, Ageing and Retirement in Europe –Frailty Index;[22] **Edmonton**: Edmonton Frail Scale.[23]

DOMAIN	EVIDENCE
Functional	Functional status has a more important predictive value of death risk than prognosis or other markers related to disease. Additionally, it has been proved to be the most significant isolated factor of mortality prediction on elderly in-patients, even beyond serious disease markers.[24] [25] There exists a significant association among age, gender and dependency, as well as there is relation among dependency, morbidity and mortality. Dependency could be, thus, used as predictive of both.[26] Even though there is also relation among functional decline, cognitive decline and emotional status, physical decline in the previous 6 months results the best predictive factor of mortality for the following year.[27] Not only has the static measure of functionality (severity) proved to have association with mortality. A study performed among patients in post-acute situation, proved that progression of functional and nutritional variables have independent statistic and clinical prognostic value.[28]

Nutritional	Undernourishment is tightly associated with mortality,[29–32] especially if there is lean body-mass loss,[33] and with bad health results: infections, multiple admittance, in-patients stays, pressure ulcers risk, etc.
Cognitive	Measuring cognitive function should be included in end-of-life patients' assessment. [34] It is well known that people with dementia, particularly the oldest, present significantly more frailty situation.[35]
Emotional Problems	There is a bidirectional association between depressive syndrome and end-of-life.[36] In fact, it has been proved[37] that the three variables related to death the most among elderly inpatients were dependency in ADL, cognitive dysfunction and presence of depressive symptoms (measure at day 90 and at year 2)
Geriatric Syndromes	Although some studies suggest a cause relationship between mortality and some geriatric syndromes– delirium,[38,39] dysphagia,[40] pressure ulcers[41] and repetitive falls-, [42] authors do specify that more research is necessary to reach more concluding results. This idea is corroborated by Kane.[43]
Symptoms	Symptoms such as anorexia and dyspnoea are related to mortality, especially in cancer patients,[44] but also in other chronic diseases: Dyspnoea predicts mortality and is a proxy for underlying diseases, most often of heart and lung,[45] and is associated with mortality in a severity-dependent manner.[46] Anxiety is associated with increased risk of mortality in coronary heart disease.[47] Pain is not an independent predictor of mortality.[48,49]
Social Vulnerability	The frailty of a certain population is strongly correlated to its economic level: in rich countries, frailty prevalence is lower and frail people live longer.[50] If we assess death risk in relation to social vulnerability among geriatric patients, the risk of absolute death is associated to the increase in social vulnerability -including loneliness and social isolation-:[51] Andrew et al[52] found that among people with low social vulnerability, death at 5 years was 10.8%, in comparison to 32.5% for those patients with higher social vulnerability; such difference of absolute death (22%) is clinically relevant. Indeed, orderly assessment of social vulnerability could predict negative health outcomes. Social context is also associated with disability before death: low-income patients suffer from a higher functional decline and disability during the 2 years prior to death than rich ones.[53]
Use of resources	It is well known that use of resources is mostly concentrated in the last months of life, independently of death age.[54] Unplanned admissions and frequent emergency users are at increased risk for death;[55] readmission rates also were associated with a higher mortality.[56]

Table 2: General conditions related to death

The evaluation of these variables - both main disease and other additional general conditions-, has shown the need for complementing the static vision (severity) with the analysis of dynamic behaviour (progression),[6] given the evidence that changing variables have proved to have more prognostic implications than those variables that remain stable.[28,57,58]

This prognostic approach aims at improving decision making processes and patients outcomes;[57] however, professionals still have difficulties finding unequivocal prognostic variables[7] - prognosis will always be uncertain-,[59] since end of life processes are multifactorial and strictly individual at the same time. Such uncertainty becomes more evident when we try to move from population models to individual

assessment and, it is strongly conditioned by the difficulty of establishing the situational diagnosis of a specific patient:[6] what moment of his/her vital trajectory is this person going through? How much reserve does he/she have? Is he/she really in end-of-life situation? How close to dying is he/she? Given this scenario, we suggest a new conceptual transition, moving from "prognostic variables" (correlation between variables and mortality, obtained from epidemiological analysis and from a population point of view) to "end-of-life indicators associated with a limited life prognosis and PC needs":[5] what variables are present? Which level of severity and progression do they perform? Do these variables lead us to think this person might benefit from palliative care?

Learning from the characteristics and behaviour of these indicators as the basis of individual situational diagnosis (figure 1) should help healthcare professionals make better clinical decisions, according to patients' values and preferences.[60]

End-of-life trajectories

Lunney et al. described three distinct illnesses trajectories of functional decline at the end of life in 2003[24] (figure 1) describing the typical dynamic patterns of a group of patients classified according to their main advanced chronic disease. Later, Murray et al.[61] highlighted the clinical implications of end-of-life trajectories by presenting trajectories as a framework to help professionals and patients facing the uncertainty of having an advanced chronic condition, and how to avoid "prognostic paralysis" Firstly, he explained that these trajectories may help clinicians to better plan care to meet their patients' multidimensional needs, and help patients and carers cope with their situation. Secondly, he pointed at the possibility that different models of care may be necessary to reflect and tackle patients' different experiences and needs. Finally, he suggested to explore the concept of multi-dimensional end-of-life trajectories, realising that the different dimensions of need may have different patterns of decline.

Hypothesis and objectives

We have analysed the data of a cohort of patients with advanced chronic conditions and PC needs identified with the NECPAL CCOMS-ICO© tool.[15–17] Subjects were mostly around the first end-of-life transition. This study revises the conceptual intersection between the end-of-life trajectories described and the end-of-life indicators which constitute the tool.

There might be a common denominator in the behaviour of some of these indicators that would allow us to identify PACC at a point in time. However, we hypothesize that there also exist distinguishing features in other indicators that support the conceptual model of end-of-life trajectories beyond the functional variables that describe such trajectories. This is why we have analysed the characteristics and distribution of the indicators related to end of life. Indicators have been arranged by domain (functional, nutritional and cognitive status, emotional problems, geriatric syndromes, social vulnerability and others) and according to their static (severity) and dynamic (progression) behaviour, for patients that could be included in each of the three end-of-life trajectories associated with advanced chronic illnesses.

METHODS

Methods, which have been extensively described elsewhere,[17] are consistent with the STROBE recommendations.[62] This study was formally approved by the ethical research committees of institutions involved in its execution (2010/PREVOsona: P10/65 and EO65).

Study design and Setting

Cross-sectional study of patients identified in a previous population-based study.[17] The study was conducted in the Spanish district of Osona, Barcelona, a mixed urban-rural district with a population of 156,087 residents, 21.4% of whom are aged >65 years, and annual mortality rate of 8.81 per 1000 inhabitants. Three selected primary care services and an acute care hospital, an intermediate care centre and four nursing homes serving these primary care services agreed to participate.

Eligibility criteria and participant selection

Case selection was undertaken from November 2010 to October 2011. Patient recruitment was conducted by doctors and nurses in each participating health care facility using the NECPAL CCOMS-ICO© tool. This tool has four categories of indicators: (a) the 'surprise question'; (b) choice/demand or need of PC approach; (c) general clinical indicators of severity and progression, including co-morbidity and resource use; and (d) disease-specific indicators. "NECPAL+" patients were defined as being surprise-question answer "no" (I wound not be surprised if they died) and having at least one subsequent positive category. There were no exclusion criteria.

Variables and sources of information

In the selected cohort, we evaluated the indicators included in the NECPAL CCOMS-ICO© tool (table 3), which were retrieved, if available, from patient's clinical records by the investigator team after interviewing health-care professionals to respond to categories 1 and 2, and indicators to be answered by clinical judgement in category 3.

In order to reduce systematic error, all definitions, procedures –including data collection- and measures were standardized and followed according to the study operations manual.

DOMAIN	SEVERITY	PROGRESSION (in the last 6 months):
FUNCTIONAL MARKERS	Serious established functional dependence Barthel score< 25, ECOG > 2 OR Karnofsky score < 50%)	Loss of 2 or more ADL's even though there is adequate therapeutic intervention OR Clinical Perception of functional decline (sustained, intense /severe, progressive, irreversible) not related to concurrent conditions
NUTRITIONAL MARKERS	Serum albumin < 2.5 g/dl, not related to acute episodes of unbalance	Weight loss > 10% or Clinical Perception of nutritional decline (sustained, intense/severe, progressive, irreversible) not related to concurrent conditions
COGNITIVE	Unable to dress, wash or eat without assistance (GDS/FAST 6c), urinary and faecal incontinence (GDS/FAST 6d-e) or unable to communicate meaningfully -6 or less intelligible words- (GDS/FAST 7)	Loss of 2 or more ADL's in the last 6 months, despite adequate therapeutic intervention (invaluable in hyperacute situation due to concurrent processes) or difficulty swallowing, or denial to eat, in patients who will not receive enteral or parenteral nutrition
EMOTIONAL	Presence of **emotional distress** with psychological symptoms (sustained, intense/severe, progressive) not related to acute concurrent conditions	
GERIATRIC SYNDROMES (in the last 6 months)	Persistent pressure ulcers (stage III–IV), Recurrent infections (> 1), Delirium, Persistent Dysphagia, Falls (> 2)	
ADVANCED DISEASE CRITERIA	**Cancer** *(one single criterion)*	○ Confirmed diagnosis of metastatic cancer who present low response or contraindication of specific treatment, progressive outbreak during treatment or metastatic affectation of vital organs ○ Significant functional deteriorating (Palliative Performance Status < 50%) ○ Persistent, troublesome symptoms, despite optimal treatment of underlying condition(s)
	Chronic pulmonary disease *(two or more criteria)*	○ Breathlessness at rest or on minimal exertion between exacerbations ○ Difficult physical or psychological symptoms despite optimal tolerated therapy ○ FEV1 <30% or criteria of restricted severe deficit: VFC < 40% / DLCO < 40% ○ Accomplishment of oxygen therapy at home criteria ○ Recurrent hospital admissions (> 3 admissions in 12 months due to exacerbations).
	Chronic heart disease *(two or more criteria)*	○ Heart failure NYHA stage III or IV, severe valve disease or inoperable coronary artery disease ○ Shortness of breath at rest or minimal exertion ○ Difficult physical or psychological symptoms despite optimal tolerated ○ Ejection fraction severely affected (< 30%) or severe pulmonary hypertension (> 60 mmHg) ○ Renal failure (GFR < 30 l/min) ○ Repeated hospital admissions with symptoms of heart failure/ischemic heart disease (> 3 last year)
	Serious chronic liver disease *(one single criterion)*	○ Advanced Cirrhosis: stage Child C, MELD-Na score > 30 or with one or more of the following medical complications: diuretic resistant ascites, hepato-renal syndrome or upper gastrointestinal bleeding due to portal hypertension with failed response to treatment ○ Hepatocellular carcinoma: present, in stage C or D (BCLC)
	Serious chronic renal disease *(one single criterion)*	○ Serious renal failures (GFR < 15) in patients to whom substitutive treatment or transplant is contraindicated
	Chronic neurological diseases (1): CVA *(one single criterion)*	○ During acute and sub-acute phases (< 3 months post-stroke): persistent vegetative or minimal conscious state > 3 days ○ During the chronic phase (> 3 months post-stroke): repeated medical complications (aspiration pneumonia, pyelonephritis, recurrent febrile episodes, pressure ulcers stage 3-4 or dementia with severe criteria post-stroke
	Chronic neurological diseases (2): motor neurone diseases, Múltiple Sclerosis & Parkinson (two or more criteria)	○ Progressive deterioration in physical and/or cognitive function despite optimal therapy ○ Complex and difficult symptoms ○ Speech problems with increasing difficulty communicating ○ Progressive Dysphagia ○ Recurrent aspiration pneumonia, breathless or respiratory failure
	Dementia *(two or more of the following criteria)*	○ Severity criteria: GDS/FAST 6c or more. ○ Progression criteria: loss of 2 or more ADL's in the last 6 months, despite adequate therapeutic intervention or difficulty swallowing, or denial to eat, in patients who will not receive enteral or parenteral nutrition ○ Use of resources criteria: multiple admissions (> 3 in 12 months, due to concurrent processes – aspiration pneumonia, pyelonephritis, sepsis, etc.- that cause functional and/or cognitive decline)
Others	**Co-morbidity**	Charlson index
	Additional Factors on use of resources	○ 2 or more urgent (unplanned) hospital (or skilled nursing facilities) admissions due to chronic disease in the last year ○ Need of complex/intense continuing care, either at an institution or at home
	Palliative Care approach	○ Choice/demand by patient or family: Have either the patient with advanced disease or the main caregiver requested, in explicit or implicit manner, palliative/comfort treatments exclusively or suggest limitation of therapeutic effort or reject specific treatments or those with curative purposes. ○ Need of Palliative Care: healthcare professionals consider that the patient **requires** palliative

	care or palliative treatment at this moment.

Table 3: Description of NECPAL CCOMS-ICO tool variables. **FEV1**: forced expiratory volume in one second. **FVC**: Forced vital capacity. **DLCO**: diffusing capacity of the lung for carbon monoxide. **NYHA**: New York Heart Association. **GFR**: Glomerular Filtration Rate. **BCLC**: Barcelona-Clinic Liver Cancer. **CVA**: Cerebrovascular accident.

Variables & Diseases

We evaluated the distribution of the variables by classifying persons according to the presence of severity and/or progression criteria of main disease (cancer, chronic pulmonary disease, chronic heart disease, serious chronic liver disease, serious chronic renal disease, chronic neurological diseases, dementia). We refer to the group of patients identified as being NECPAL + without severity and/or disease progression criteria as "Advanced frailty patients without advanced disease criteria".

Variables and End-of-life Trajectories.

We organized the illnesses according to the described end-of-life trajectories: cancer, organ failure (including lung, heart, hepatic and renal disease) and dementia. As for neurologic diseases, we put together primary neurodegenerative/Alzheimer and neurodegenerative diseases such as Parkinson and Amyotrophic Lateral Sclerosis for easier analysis purposes, given that their clinical evolution tends to be similar to dementia.

Statistical methods

The sample was analysed through descriptive and inferential analysis. We performed contrasts of proportions by using contingency tables between the variables and the end-of-life trajectories; for the categorical variables, a Xi-squared analysis was performed, and for the quantitative variables, an analysis of the variance (ANOVA analysis) was performed. SPSS 21 version was the software used.

RESULTS

Participants

782 participants (38.5 % men; 61.5% women; mean age: 80.89) were recruited from different levels of the whole health system. None of them presented severity and progression criteria for two concomitant organs. The appendix shows the results for each individual disease.

Main results

Functional progression (31.5% loss ≥2ADL's, 44.3% clinical perception) and nutritional criteria (particularly clinical perception, 30.7%) were the variables more constantly associated with end-of-life identification in all patients (table 4). Emotional distress (21.9%) and some geriatric syndromes (11.2% falls and 15.7% delirium) were also present, but less frequently and without statistically significant differences among the four groups. Generally, families perceived more palliative needs than the patients and professionals.

				END OF LIFE TRAJECTORY								
		ALL patients		Cancer		Organ failure (Pulmonary + heart + liver + renal)		Dementia + Chronic neurological diseases		Advanced frailty -No advanced disease criteria-		p
DOMAIN		n=782		n= 76 (9.7%)		N=126 (16.1%)		n=203 (26%)		n=377 (48.2%)		
		n	%	n	%	n	%	n	%	n	%	
FUNCTIONAL	S (Barthel <25)	147	22.2	3	4.5	6	5.3	101	49.7	37	10.6	<0.005
	S (Barthel mean)	59.6 (+/32.4)		79.9 (+/-24.9)		74.3 (+/-24.9)		31.74 (+/-28.1)		67.05 (+/-27.9)		<0.005
	P (loss ≥2ADL's)	243	31.5	33	43.4	38	30.6	63	31.03	109	29.4	0.121
	P (clinical perception)	343	44.3	45	59.2	54	42.9	84	41.4	160	43	0.050
NUTRITIO-NAL	S (albumin <2.5)	24	5.8	5	8.1	6	6.4	1	0.4	13	5.9	0.560
	P (Weight loss > 10%)	42	12.2	7	23.3	6	11.5	14	6.8	15	9.7	0.211
	P (clinical perception)	237	30.7	48	63.2	29	23	63	31.3	97	26.3	<0.005
COGNITIVE	S (GDS ≥6c)	169	21.9	0	0	0	0	169	83.2	0	0	<0.005
	P (loss ≥2ADL's)	68	8.7	na	na	na	na	68	33.5	na	na	<0.005

EMOTIONAL	Distress		165	**21.9**	20	**24.7**	28	**22.6**	33	**16.2**	84	**23.8**	0.134
GERIATRIC SYNDROMES	Pressure ulcers		34	**4.4**	3	**4**	1	**0.8**	19	**9.3**	11	**3**	**<0.005**
	Dysphagia		81	**10.4**	8	**10.8**	4	**3.2**	48	**23.6**	21	**5.6**	**<0.005**
	Falls >2		86	**11.2**	7	**9.5**	9	**7.3**	26	**12.8**	44	**12**	0.401
	Delirium		122	**15.7**	10	**13.2**	17	**13.5**	38	**18.7**	57	**15.3**	0.518
	Rec. infections		41	**5.3**	3	**4**	14	**11.2**	8	**3.9**	16	**4.3**	**0.015**
OTHERS	Comorbidity (Charlson mean)		**3.23** (+/-2.9)		**5.34** (+/-2.6)		**3.38** (+/-2.1)		**2.28** (+/-1.7)		**3.07** (+/-2.2)		**<0.005**
	Use of resour-ces	Unplanned admissions	**0.55** (+/-1.0)		**0.64** (+/-0.9)		**1.0** (+/-1.3)		**0.22** (+/-0.5)		**0.5** (+/-1.15)		**<0.005**
		Complex care	145	**19.2**	26	**35.1**	27	**22.1**	28	**13.8**	64	**17.9**	**<0.005**
	Palliative care approach	Choice/dem and patient	44	**5.6**	13	**17.1**	7	**5.6**	3	**1.4**	21	**5.6**	**<0.005**
		Choice/dem and family	209	**26.7**	30	**39.5**	30	**23.8**	69	**34.0**	80	**21.5**	**<0.005**
		Need (Healthcare professionals)	121	**15.5**	36	**47.4**	21	**16.9**	27	**13.3**	37	**10**	**<0.005**
	Age (mean)		**80.89** (+/-11.9)		**79.9** (+/-24.0)		**77.7** (+/-13.4)		**82.99** (+/-9.7)		**82.6** (+/-11.3)		**<0.005**
	Sex	Male	301	**38.5**	44	**57.9**	66	**52.4**	50	**24.6**	141	**37.4**	**<0.005**
		Women	481	**61.5**	32	**42.1**	60	**47.6**	153	**75.4**	236	**62.6**	

Table 4. **Distribution of variables per end-of-life trajectory;** % valid patients (missing patients excluded). **S**: Severity. **P**: Progression. **IADL**: instrumental activities of daily living. **ADL**: activities of daily living. na: not applicable

The functional severity criteria, Barthel index median, cognitive severity criteria, some geriatric syndromes such as decubitus ulcers, dysphagia or repetition infections, comorbidity, use of resources, election criteria, demand and need of PC, and age and gender showed statistically significant differences ($p< 0.005$) in the classification per trajectories performed.

Patients with *advanced cancer* rarely presented with functional severity criteria (4.5%). For these patients, the presence of nutritional progression criteria was more major than in the other groups (clinical perception: 63.2%). There was a high need of complex cures (35.1%), as well as demand and need of PC from the patients (17.1%), relatives (39.5 %) and professionals (47.4%).

Patients with *advanced organ disease* – all of them with main disease severity and progression criteria- presented less parameters of general severity and progression than the rest of trajectories and less percentage of geriatric

syndromes. In contrast, they presented a larger percentage of systemic infections (11.2%) and more unplanned admittances than the other groups.

Patients with *advanced dementia and chronic neurological diseases* presented severity criteria, both functional (49.7%) and cognitive (83.2%), and geriatric syndromes: ulcers (9.3%), persistent dysphagia (23.6%), repetitive falls (12.8%) and confusion syndrome (18.7%). These patients presented less need of resources than the other groups and there was a low perception of palliative needs among the professionals (13.3%) compared to relatives (34%).

48.2% of the whole patients presented palliative needs (NECPAL +) even though they did not present severity and progression criteria for any chronic disease. In this group *("Advanced frailty patients with no advanced disease criteria"),* we confirmed the importance of multiple variables of the different domains. However, their presence was not outstanding, not due to excess or defect, as for their behaviour in the other three groups. Professionals had low perceptions that these patients had palliative needs.

DISCUSSION

Key results

There is a series of common indicators in the identification of the PACC. Dynamic variables seem to be more discriminating than static ones.[28] Functional and nutritional progression criteria, in the first place, and emotional distress and some geriatric syndromes, though less significantly, may become relevant indicators of need, mainly regarding functional loss.[57,58]

Beyond the described parameters, we consider that there are no unique and definite indicators to identify PACC, since only a low percentage of patients present most of the

variables. This fact has two relevant implications: 1. Identifying PACC requires a multidimensional evaluation including a wide range of variables; and 2. The behaviour differences of these variables in the diverse groups (cancer, organ disease and dementia/advanced neurologic disease) support the conceptual model of end-of-life trajectories. This model seems to be consistent beyond the described functional dimension: in many of the other dimensions (nutritional, cognitive, geriatric syndromes and use of resources), the behaviour is also different among the diverse groups.

In this sense, regarding the behaviour differences of the variables in the different end-of-life trajectories, the low prevalence of patients with *advanced cancer* and functional severity criteria is remarkable. This is due to faster decline of these patients.[9,64,65] The impact of undernourishment as an important marker of end of life in cancer patients is also consistent with literature.[66–69] For patients with *advanced organ diseases*, there are more unplanned admittances, probably because of episodes of acute failure or recurrent infections, in keeping with the trajectory classically described cohort.[24,56,70–77] As for patients with *dementia and other neurological diseases* the criteria of disease severity (frequently based on the functional repercussions of the severity), determine the identification of end-of-life situation.[78,79] This fact, together with the presence of multiple geriatric syndromes, can help professionals understand the situation.[43] The slow and progressive process of decline, without too many unbalance episodes, determines less use of resources and, probably, less perception of palliative needs from the professionals, in contrast to the relatives' view. It was remarkable that in a particularly disease-centred clinical context, practically half of the cohort *("Advanced frailty patients with no advanced disease criteria")* did not present advanced disease criteria, but identified as persons with advanced chronic conditions and PC needs at the same time.

The analysis endorses the conceptual approach of end-of-life trajectories associated to advance chronic illnesses. However, complexity frequently exceeds such view, since some patients may embrace one or more trajectories.[80,81] This is due to an extremely heterogeneous behaviour of the variables over time and the severity among different patients. Given that frailty is the most frequent condition among elderly patients in end-of-life situation,[82] a rational clinical approach to these patients could be done from frailty, not understood as an independent entity defining only one of the end-of-life trajectories, but as a quantitative measurement system to determine the reserve level of the patient. Such reserve would act as the basis for a situational diagnosis. It may be that with frailty patients, the other non-physical trajectories of need may be important to monitor clinically, as they may show more dynamic needs for care. Analysis –determinant for the frailty degree and the end of life situation- shows that most variables are present in the three end-of-life trajectories previously described, although they behave differently; more research will be needed to substantiate this claim.

Finally, cancer and non-cancer patients present physical decline and significant psychosocial difficulties and all these patients could benefit from PC provision.[83] However, healthcare professionals are less willing to provide a palliative approach for the non-cancer group.[84] This might be because the end-of-life trajectory is less predictable for these patients.[85]

Strengths and Limitations

The study was carried out with 100% of participation from healthcare professionals and settings that needed to be involved. A standardised case identification methodology followed in all settings and a high level of commitment from all participants.

The study has some limitations. This study was based on multiple health professionals' assessment and routine data. This might have determined heterogeneity when retrieving variables, based on subjective perception. Additionally, a problem of over identification with the tool cannot be dismissed, due to the high number of "Advanced frailty patients with no advanced disease criteria". We are currently monitoring the mortality of this cohort to confirm or reject this hypothesis.

There was a significant number of missing nutritional variables requiring an objective measure (47.2% due to Albumin or 56% due to weight loss) – *see online appendix* -. This fact emphasizes some discordance between the importance of measuring the nutritional state according to scientific evidence[29–32] and the real clinical practice; we wonder whether using other parameters in the evaluation of undernourishment, such as body-mass Index or Mini Nutritional Assessment[63] results would have improved. Some of the variables described in the background section, such as social, vulnerability or symptoms, were not included in the NECPAL CCOMS-ICO© tool. Thus, these could not been assessed in the current study; similarly the progression criteria for dementia could only be assessed for patients with severity criteria of dementia.

Generalizability & Future trends

More studies are needed to corroborate these data. However, the results described are a useful basis for future research on the early identification of patients with advanced chronic conditions for integrated palliative care. Suggested topics to be developed include:

a) The cohort corresponds to persons identified a priori as PACC and, presumably, in end-of-life situation. It will be necessary, however, to analyse the behaviour

of these variables in relation to mortality. We are currently monitoring the cohort at 24 months.

b) Given the large prevalence of advanced frailty patients, new frameworks[6] based on knowledge on geriatrics and PC background will be necessary. In fact, these two areas already share methods regarding care process:[86] team work, multidimensional assessment, care provision based on objectives and preferences, psychosocial and caregivers support. More shared research between palliative medicine, geriatricians, primary care and public health doctors will be necessary for further progress in this area.

c) The conceptual link between the need of multidimensional evaluation of PACC and the high prevalence of advanced frailty patients with no advanced disease criteria can be found in the evaluation of the level of reserve of these patients. Frailty indexes,[22,87–90] already proved to have a strong association with mortality, will probably become the gold Standard for situational diagnosis, since they allow to quantify people's health reserves from a universal and objective point of view.

CONCLUSIONS

Learning from the behaviour of end-of-life indicators helps deal with the clinical complexity arising from the difficulties of situational diagnosis and decision making.

Dynamic variables most consistently identify PACC and PC needs, regardless of the patient's end-of-life trajectory. Additionally, the analysis of the rest of variables allows us to define clusters of patients with specific characteristics. This contributes to the clinical utility of the end-of-life trajectories approach.

Almost half of the cohort, although identified as PACC, did not have severe or progression advanced disease. To explore in detail the behaviour of the variables in these patients will help to provide them patient-centred care.

OTHER INFORMATION

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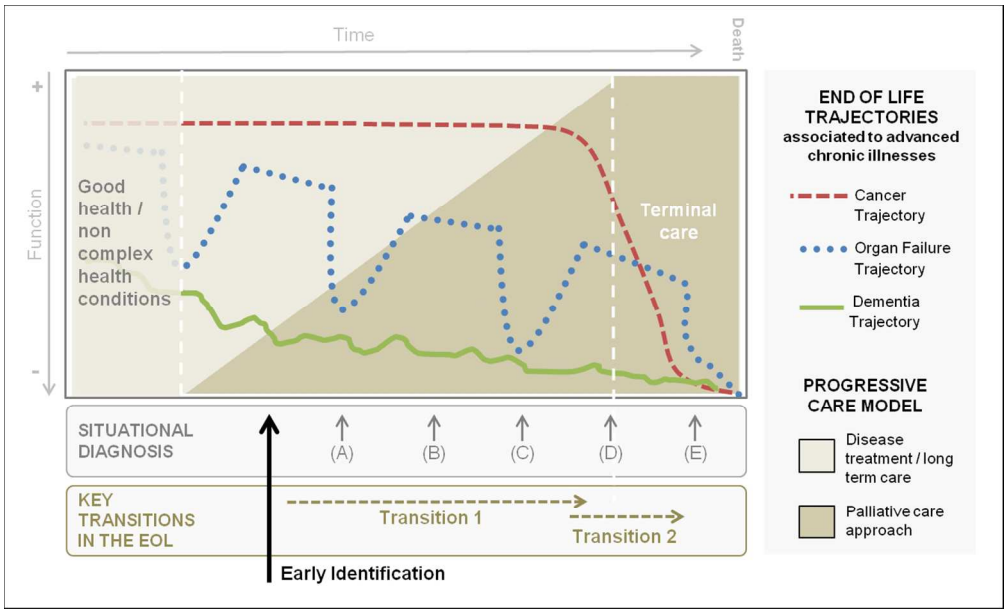

Figure 1: Key transitions and end of life trajectories. Three end-of-life trajectories are described: the first clinical trajectory, typically associated with cancer, features a stable and/or low decline phase with a severe decline in the last weeks. The second one features gradual decline, with acute episodes usually related to concomitant processes and disease evolution and partial recovery; this trajectory corresponds to patients with advanced organ diseases, such as heart, liver and renal failure and chronic obstructive pulmonary disease. Finally, the third trajectory shows a progressive slow-decline, typically related to frail or dementia patients. Early identification of palliative care needs becomes the starting point for transition 1. Situational diagnosis refers to the evaluation and assessment of patients that allows healthcare professionals determine patients' health degree (A, B, C, D or E) and identify entrance to Transition 2 (D) or last days-hours situation, instead (E); this situational diagnosis is indispensable to establish the objectives of care in this progressive care model in a decision-making process shared by professionals, patients and their families.
Conceptual transitions, early
226x136mm (150 x 150 DPI)

DOMAIN	DISEASE		ALL			Cancer		Chronic pulmonary disease		Chronic heart disease		Serious chronic liver disease		Serious chronic renal disease		Chronic neurological diseases		Dementia		No advanced disease criteria	
			n=782			n=76 (9.7%)		n= 43 (5.5%)		n= 63 (8.1%)		n= 9 (1.1%)		n= 11 (1.4%)		n=31 (4%)		n=172 (22%)		n=377 (48.2%)	
			n v	n m	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
FUNCTIONAL	S (Barthel <25)		147 662	120	22.2	3	4.5	0	0	6	10.2	0	0	0	0	12	40	89	52.4	37	10.6
	S (Barthel mean)		59.6 (+/32.4) 731	51		79.9 (+/-24.9)		75.38 (+/-21.9)		71.44 (+/-28.5)		84.8 (+/-17.4)		74.4 (+/-15.1)		36.17 (+/-30)		30.95 (+/-27.8)		67.05 (+/-27.9)	
	P (loss ≥2ADL's)		243 771	11	31.5	33	43.4	11	26.2	19	29.7	4	44.4	0	0	14	45.2	49	29.2	109	29.4
	P (clinical perception)		343 774	8	44.3	45	59.2	21	48.8	24	36.9	4	44.4	7	63.6	22	71	62	36.3	160	43
NUTRITIO-NAL	S (albumin <2.5)		24 413	369	5.8	5	8.1	0	0	0	0	6	66.7	0	0	0	0	1	2.8	13	5.9
	P (Weight loss > 10%)		42 344	438	12.2	7	23.3	2	8.7	2	9.5	2	33.3	0	0	2	15.4	12	13	15	9.7
	P Clinical Perception		237 771	11	30.7	48	63.2	8	18.6	14	21.5	4	44.4	3	27.3	6	19.4	57	33.5	97	26.3
COGNITIVE	S (GDS ≥6c)		169 772	10	21.9	0	0	0	0	0	0	0	0	0	0	0	0	169	98.3	0	0
	P (loss ≥2ADL's)		68 782	0	8.7	na	na	na	na	na	na	na	na	na	na	na	na	68	39.5	0	0
EMOTIONAL	Distress		165 753	29	21.9	20	24.7	5	11.9	17	26.6	2	22.2	4	36.4	11	36.7	22	12.9	84	23.8
GERIATRIC SYNDROMES	Pressure ulcers		34 773	9	4.4	3	4	1	2.3	0	0	0	0	0	0	5	16.1	14	8.2	11	3
	Dysphagia		81 779	3	10.4	8	10.8	2	4.7	2	3.1	0	0	0	0	15	48.4	33	19.2	21	5.6
	Falls >2		86 768	14	11.2	7	9.5	1	2.3	6	9.4	1	11.1	1	9.1	5	16.1	21	12.3	44	12
	Delirium		122 777	5	15.7	10	13.2	4	9.3	8	12.3	3	33.3	2	18.2	6	19.4	32	18.6	57	15.3
	Recurrent infections		41 774	8	5.3	3	4	11	25.6	2	3.1	1	11.1	0	0	1	3.2	7	4.1	16	4.3
OTHERS	Comorbidity (Charlson mean)		3.23 (+/-2.9) 683	99		5.34 (+/-2.6)		2.81 (+/-1.7)		3.14 (+/-1.9)		5 (+/-2.8)		5.18 (+/-2.4)		2.14 (+/-2.0)		2.32 (+/-1.6)		3.07 (+/-2.2)	
	Use of resources	Unplanned admissions	0.55 (+/-1.0) 686	96		0.64 (+/-0.9)		1.09 (+/-1.1)		0.86 (+/-1.3)		1.89 (+/-1.6)		0.73 (+/-0.9)		0.24 (+/-0.6)		0.21 (+/-0.4)		0.5 (+/-1.1)	
		Complex care	145 755	27	19.2	26	35.1	12	27.9	8	12.9	2	22.2	5	50	10	34.5	18	10.6	64	17.9
	Palliative care approach	Choice/dem and patient	44 786	6	5.6	13	17.1	2	4.7	5	7.7	0	0	4	36.4	2	6.4	1	0.6	21	5.6
		Choice/dem and family	209 782	0	26.7	30	39.5	11	25.6	13	20	2	22.2	0	0	5	16.2	64	37.3	80	21.5
		Need (Healthcare professionals)	121 776	6	15.5	36	47.4	7	16.3	10	15.6	3	33.3	1	10	4	12.9	23	13.5	37	10
	Age (mean)		80.89 (+/-11.9) 782	0		79.92 (+/-24.0)		79.09 (+/-9.9)		78.25 (+/-14.4)		67.56 (+/-16.0)		76.45 (+/-13.4)		71.74 (+/-15.6)		85.01 (+/-6.5)		82.62 (+/-11.3)	
	Sex	Male	301 782	0	38.5	44	57.9	31	72.1	26	40	6	66.7	5	45.5	16	51.6	34	19.8	141	37.4
		Women	481 782	0	61.5	32	42,1	12	27.9	39	60	3	33.3	6	54.5	15	48.4	138	80.2	236	62.6

Distribution of variables according to presence of disease severity and/or progression criteria; **v**: % valid patients . **m**: missing patients. **S**: Severity. **P**: Progression. **IADL**: instrumental activities of daily living. **ADL**: activities of daily living. **na**: not applicable

STROBE Statement—checklist of items that should be included in reports of observational studies

Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of indicators related to end-of-life trajectories.

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract p.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found p. 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p. 6-9, T1, T2 and F1.
Objectives	3	State specific objectives, including any prespecified hypotheses p. 10
Methods		
Study design	4	Present key elements of study design early in the paper p. 10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p. 10-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants p. 11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable p. 11-13, T3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group p. 11
Bias	9	Describe any efforts to address potential sources of bias

		p. 11
Study size	10	Explain how the study size was arrived at p. 10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why p. 11-13, T3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding p. 13
		(*b*) Describe any methods used to examine subgroups and interactions p. 13
		(*c*) Explain how missing data were addressed p. 13
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy NA
		(*e*) Describe any sensitivity analyses p. 13
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed p. 14
		(b) Give reasons for non-participation at each stage NA
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders p. 14, T4 and A1
		(b) Indicate number of participants with missing data for each variable of interest T4 and A1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures T4 and A1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included p. 14-16, T4 and A1
		(*b*) Report category boundaries when continuous variables were categorized NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p. 14-16, T4 and A1
Discussion		
Key results	18	Summarise key results with reference to study objectives p. 16-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias p. 18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p. 18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results p. 19-20
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p. 21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of prognostic indicators related to end-of-life trajectories

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TITLE PAGE

Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of prognostic indicators related to end-of-life trajectories.

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KEY WORDS: Advanced chronic conditions, End-of-life trajectories, Palliative care, Advanced Frailty, Health Status Indicators, Prognosis.

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ABSTRACT

Objectives: Two concepts have recently been rediscovered to improve the care of patients with advanced chronic conditions: early identification of palliative care needs and the three end-of-life trajectories in chronic illnesses (acute, intermittent and gradual dwindling). It is not clear (1) what indicators work best for this early identification and (2) if specific clinical indicators exist for each of these trajectories. The objectives of this study are to explore these two issues.

Setting: Three primary care services, an acute care hospital, an intermediate care centre and four nursing homes in a mixed urban-rural district in Barcelona, Spain.

Participants: 782 patients (61.5% women) with a positive NECPAL CCOMS-ICO© test, indicating they might benefit from a palliative care approach.

Outcome measures: The characteristics and distribution of the indicators of the NECPAL CCOMS-ICO© tool are analysed with respect to the three trajectories and have been arranged by domain (functional, nutritional and cognitive status, emotional problems, geriatric syndromes, social vulnerability and others) and according to their static (severity) and dynamic (progression) properties.

Results: The common indicators associated with early end-of-life identification are: functional (44.3%) and nutritional (30.7%) progression, emotional distress (21.9%) and geriatric syndromes (15.7% delirium, 11.2% falls). The rest of the indicators showed differences in the associations by illness trajectories ($p<0.05$). 48.2% of the total cohort was identified as advanced frailty patients with no advanced disease criteria.

Conclusions: Dynamic indicators are present in the three trajectories and are especially useful to identify patients with advanced chronic conditions for a progressive palliative care approach purpose. Most of the others indicators are typically associated with a specific trajectory. These findings can help clinicians improve the identification of patients for a palliative approach.

ARTICLE SUMMARY

- This study innovatively explores the relationship between end-of-life indicators used to identify patients with advanced chronic conditions and the three archetypal end-of-life trajectories: acute (typically cancer), intermittent (typically organ failure) and gradual dwindling (typically dementia or frailty).

- Analysing the characteristics of end-of-life indicators allows us to know which indicators most consistently identify patients for palliative care. It also provides data on the characteristics that most commonly occur in each end-of-life trajectory.

- The large number of identified patients with advanced chronic conditions but *with no advanced disease criteria* reveals that there is a real and not previously well described cohort of people with advanced frailty and palliative care needs.

- These concepts are useful for clinical decision-making, for policymakers in designing appropriate health services, as well as giving researchers a theoretical framework for future research.

- Study limitations include the heterogeneity in the collection of variables due to the multiple assessments from all health care system resources; and the number of missing data in some variables.

MAIN TEXT

INTRODUCTION

Two concepts can combine to illuminate care provision for patients with advanced chronic conditions: early identification of patients with palliative care (PC) needs and, secondly, end-of-life trajectories associated with advanced chronic illnesses. This gives a conceptual framework to understand the different characteristics of patients from their early identification for palliative care onwards.

Early identification of patients with palliative care needs

The modern approach to the end-of-life divides this into two transitions[1] (figure 1). The first transition, frequently some months or years before death, may constitute the starting of the process of identification of patients with palliative care needs, due to the appearance and recognition of some indicators or variables which make early identification easier. Throughout the article we will refer to these patients with advanced chronic diseases and conditions, palliative care needs and limited life prognosis as a “Patients with advanced chronic conditions“(PACC). The second transition -or “the last days or weeks of patient’s life”- starts when the terminal decline begins and corresponds to the out-moded paradigm of very late palliative care provision.

Early identification for palliative care has shown many benefits: it helps to clarify treatment preferences and goals of care, it improves quality of life and symptom control, it reduces distress, it allows less aggressive care, lowers spending, and may even lengthen survival.[2–4] Thus, to develop anticipatory or palliative care[5] becomes crucial during this first transition.

A certain degree of "prognostic approach" may be used with caution in the care of individual patients, and professionals still have difficulties finding unequivocal prognostic variables[6]. Prognosis will always imply a degree of uncertainty-,[7] since end of life processes are multifactorial and strictly individual at the same time. Besides, the earlier we want to identify these patients, the more difficult it becomes to obtain certain prognostic variables.[8]

Thus, although certain variables are broadly linked with mortality risks, there is no single prognostic indicator that identifies all patients who will die soon.[6] The classic prognosis approach focused on advanced chronic disease severity criteria has limitations: prognostic disease-centred variables, when used in isolation, have shown low prognostic capacity [9–14] particularly for geriatric patients with multiple chronic conditions.[6] The prognostic relevance of more general factors have proved to be more reliable indicators of end of life:[15] functional,[16–19] nutritional,[20–24] and cognitive status,[25,26] emotional problems,[27,28] geriatric syndromes -such delirium,[29,30] dysphagia,[31] pressure ulcers[32] and repetitive falls-,[33] symptoms –such dyspnoea,[34–36] and anxiety-,[37] social vulnerability,[38–41] or use of resources.[42–44]

Thus, most screening tools for identification of patients with Palliative needs[45] -e.g. the Prognostic Indicator Guidance of the Gold Standards Framework (PIG-GSF),[46] the Supportive & Palliative Care Indicators Tool (SPICT),[47] the RADboud indicators for PAlliative Care needs (RADPAC)[48] and the NECesidades PALiativas CCOMS-ICO tool (NECPAL CCOMS-ICO tool)-[49–51] have incorporated these general conditions from different domains in different degrees.

The evaluation of these variables -both disease specific and these other general factors-, has also shown the need for complementing the static status (severity) with an assessment of dynamic progression of decline.[8]

End-of-life trajectories

Lunney et al. described three distinct illnesses trajectories of functional decline at the end of life in 2003[52] (figure 1) illustrating the typical dynamic patterns of a group of patients classified according to their main chronic disease: the first clinical trajectory, typically associated to cancer, features a stable and/or low decline phase broken up by a severe decline in the last weeks. The second features gradual decline, with acute episodes usually related to concomitant processes and disease evolution and partial recovery; this trajectory corresponds to patients with advanced organ diseases such as heart, lung, renal or liver failure. Finally, the third trajectory shows a progressive slow-pace decline, typically related to dementia or frail patients.

Later, Murray et al.[53] highlighted the clinical implications of end-of-life trajectories by presenting trajectories as a framework to help professionals and patients facing the uncertainty of having an advanced chronic condition avoid “prognostic paralysis”. Firstly, these trajectories may help clinicians to better plan care to meet their patients’ changing needs, and help patients and caregivers to cope with their situation. Secondly, by pointing out at the possibility that different models of care may be necessary to reflect and tackle patients’ different experiences and needs. Thirdly, by graphing dimensional end-of-life trajectories, the different dimensions of need –physical, social, psychological and spiritual- may be identified and addressed.

Hypothesis and objectives

We hypothesize that there might be a common denominator in the characteristics of some indicators that would allow us to identify PACC at specific time points. On the other hand, distinguishing features may also exist in other indicators that support and develop the conceptual model of end-of-life trajectories.

Learning from the characteristics and evolution of these end-of-life indicators as the basis of the individual situational diagnosis[8] —understood as the assessment to determine patients' health degree and (or possible) closeness to end-of-life situation- (figure 1), can help clinicians to manage uncertainty and make better clinical decisions, according to patients' values and preferences.[54] In order to develop further knowledge on these indicators, we analysed the characteristics and distribution of the indicators related to end of life in a cohort of patients identified with the NECPAL CCOMS-ICO© tool.

METHODS

Our methods, as extensively described elsewhere,[51] are reported according to STROBE recommendations.[55] This study was formally approved by the ethical research committees of institutions involved in its execution (2010/PREVOsona: P10/65 and EO65).

Study design and Setting

Cross-sectional study of patients identified in a previous population-based study was conducted.[51] The study was conducted in the Spanish district of Osona, Barcelona, a mixed urban-rural district with a population of 156,087 residents, 21.4% of whom are aged >65 years, with an annual mortality rate of 8.81 per 1000 inhabitants. Three

selected primary care services and an acute care hospital, an intermediate care centre and four nursing homes serving these primary care services agreed to participate.

Eligibility criteria and participant selection

Case selection was undertaken from November 2010 to October 2011. There were no exclusion criteria. Patient recruitment was conducted by doctors and nurses in each participating health care facility using the NECPAL CCOMS-ICO© tool. NECPAL positive (+) patients were defined as being surprise-question[56] answer "no" (*"I would not be surprised if this patient were to die in the next 12 months"*) and having at least one subsequent positive category: (a) category 1: choice, request or need of PC approach (*have the patient or the main caregiver requested palliative / comfort treatments exclusively or suggest limitation of therapeutic effort? Healthcare professionals consider that the patient requires palliative care or palliative treatment at this moment?*); (b) category 2: general clinical prognostic indicators of severity and progression -including co-morbidity and resource use- (table 1); or (c) category 3: disease-specific prognostic indicators (table 2).

DOMAIN	SEVERITY	PROGRESSION (in the last 6 months):
FUNCTIONAL MARKERS	Serious established functional dependence Barthel score< 25, ECOG >2 or Karnofsky score < 50%)	Loss of 2 or more ADL's even though there is adequate therapeutic intervention or Clinical Perception of functional decline (sustained, intense /severe, progressive, irreversible) not related to concurrent conditions
NUTRITIONAL MARKERS	Serum albumin < 2.5 g/dl, not related to acute episodes of unbalance	Weight loss > 10% or Clinical Perception of nutritional decline (sustained, intense/severe, progressive, irreversible) not related to concurrent conditions
COGNITIVE	Unable to dress, wash or eat without assistance (GDS/FAST 6c), urinary and faecal incontinence (GDS/FAST 6d-e) or unable to communicate meaningfully -6 or less intelligible words- (GDS/FAST 7)	Loss of 2 or more ADL's in the last 6 months, despite adequate therapeutic intervention (invaluable in hyperacute situation due to concurrent processes) or difficulty swallowing, or denial to eat, in patients who will not receive enteral or parenteral nutrition
EMOTIONAL	Presence of emotional distress with psychological symptoms (sustained, intense/severe, progressive) not related to acute concurrent conditions	
GERIATRIC SYNDROMES (in the last 6 months)	Persistent pressure ulcers (stage III–IV), Recurrent infections (> 1), Delirium, Persistent Dysphagia, Falls (> 2)	
CO-MORBIDITY	Charlson index	

Additional factors on **USE OF RESOURCES**	○ 2 or more urgent (unplanned) hospital (or skilled nursing facilities) admissions due to chronic disease in the last year ○ Need of complex/intense continuing care, either at an institution or at home

Table 1: Category 2 of the NECPAL CCOMS-ICO© tool: General indicators of severity and progression. **ADL**: Activities of Daily Living. **ECOG**: Eastern Cooperative Oncology Group; **GDS/FAST**: Global Deterioration Scale / Functional Assessment Staging

CANCER *(one single criterion)*	○ Confirmed diagnosis of metastatic cancer who present low response or contraindication of specific treatment, progressive outbreak during treatment or metastatic affectation of vital organs ○ Significant functional deteriorating (Palliative Performance Status < 50%) ○ Persistent, troublesome symptoms, despite optimal treatment of underlying condition(s)
CHRONIC PULMONARY DISEASE *(two or more criteria)*	○ Breathlessness at rest or on minimal exertion between exacerbations ○ Difficult physical or psychological symptoms despite optimal tolerated therapy ○ FEV1 <30% or criteria of restricted severe deficit: FVC < 40% / DLCO < 40% ○ Accomplishment of oxygen therapy at home criteria ○ Recurrent hospital admissions (> 3 admissions in 12 months due to exacerbations).
CHRONIC HEART DISEASE *(two or more criteria)*	○ Heart failure NYHA stage III or IV, severe valve disease or inoperable coronary artery disease ○ Shortness of breath at rest or minimal exertion ○ Difficult physical or psychological symptoms despite optimal tolerated ○ Ejection fraction severely affected (< 30%) or severe pulmonary hypertension (> 60 mmHg) ○ Renal failure (GFR < 30 l/min) ○ Repeated hospital admissions with symptoms of heart failure/ischemic heart disease (> 3 last year)
SERIOUS CHRONIC LIVER DISEASE *(one single criterion)*	○ Advanced Cirrhosis: stage Child C, MELD-Na score > 30 or with one or more of the following medical complications: diuretic resistant ascites, hepato-renal syndrome or upper gastrointestinal bleeding due to portal hypertension with failed response to treatment ○ Hepatocellular carcinoma: present, in stage C or D (BCLC)
SERIOUS CHRONIC RENAL DISEASE *(one single criterion)*	○ Serious renal failures (GFR < 15) in patients to whom substitutive treatment or transplant is contraindicated
Chronic Neurological Diseases (1): CVA *(one single criterion)*	○ During acute and sub-acute phases (< 3 months post-stroke): persistent vegetative or minimal conscious state > 3 days ○ During the chronic phase (> 3 months post-stroke): repeated medical complications (aspiration pneumonia, pyelonephritis, recurrent febrile episodes, pressure ulcers stage 3-4 or dementia with severe criteria post-stroke
Chronic neurological diseases (2): MOTOR NEURONE DISEASES, MÚLTIPLE SCLEROSIS & PARKINSON (two or more criteria)	○ Progressive deterioration in physical and/or cognitive function despite optimal therapy ○ Complex and difficult symptoms ○ Speech problems with increasing difficulty communicating ○ Progressive Dysphagia ○ Recurrent aspiration pneumonia, breathless or respiratory failure
DEMENTIA *(two or more of the following criteria)*	○ Severity criteria: GDS/FAST 6c or more. ○ Progression criteria: loss of 2 or more ADL's in the last 6 months, despite adequate therapeutic intervention or difficulty swallowing, or denial to eat, in patients who will not receive enteral or parenteral nutrition ○ Use of resources criteria: multiple admissions (> 3 in 12 months, due to concurrent processes –aspiration pneumonia, pyelonephritis, sepsis, etc.- that cause functional and/or cognitive decline)

Table 2: Category 3 of the NECPAL CCOMS-ICO© tool: disease-specific indicators. **ADL**: Activities of Daily Living. **BCLC**: Barcelona Clínic Liver Cancer. **CHILD**: Child-Pugh's classification. **CVA**: Cerebrovascular accident. **GDS/FAST**: Global Deterioration Scale / Functional Assessment Staging **GFR**: Glomerular Filtration Rate. **FEV1**: forced expiratory volume in one second. **FVC**: Forced vital capacity. **DLCO**: diffusing capacity of the lung for carbon monoxide. **MELD-Na**: Model for End-Stage Liver Disease **NYHA**: New York Heart Association. **GDS/FAST**: Global Deterioration Scale / Functional Assessment Staging

Variables and sources of information

In the selected cohort, we evaluated the indicators included in the NECPAL CCOMS-ICO© tool, which were retrieved, if available, from patient's clinical records by the investigator team or by clinical judgement after interviewing health-care professionals (including clinical variables and need, demand and choice requests). In order to reduce systematic error, all definitions, procedures –including data collection- and measures were standardized and followed according to the study operations manual.

Indicators were arranged by domain (functional, nutritional and cognitive status, emotional problems, geriatric syndromes, social vulnerability and others) and according to their static (severity) and dynamic (progression) characteristics, for patients in each of the three end-of-life trajectories associated with advanced chronic illnesses.

Indicators & Diseases

We evaluated the distribution of the indicators by classifying persons according to the presence of severity and/or progression criteria of main disease (cancer, chronic pulmonary disease, chronic heart disease, serious chronic liver disease, serious chronic renal disease, chronic neurological diseases, and dementia). We refer to the group of patients identified as being NECPAL (+) without severity and/or disease progression criteria as "Advanced frailty patients without advanced disease criteria".

Indicators and End-of-life Trajectories.

We organized the illnesses according to the described end-of-life trajectories: cancer, organ failure (including lung, heart, hepatic and renal disease) and dementia. As for neurologic diseases, we put together primary neurodegenerative/Alzheimer and neurodegenerative diseases such as Parkinson and Amyotrophic Lateral Sclerosis for

easier analysis purposes, given that their clinical evolution tends to be similar to dementia.

Statistical methods

Characteristics by domain were reported as average with standard deviation for continuous variables (Barthel, Charlson, unplanned admissions and age) or percentages for the categorical variables. All indicators were calculated for the entire sample and for each four categories of patients: Cancer, Organ Failure, Dementia/Chronic neurological diseases and Advance Frailty. We compared the proportions among the four groups using Chi-squared test for categorical variables. Differences for non-categorical variables were assessed using ANOVA test.

Analyses were performed with the Statistical Package for Social Sciences (SPSS), version 21.0. A two-sided p value < 0.05 was considered to indicate statistical significance.

RESULTS

Participants

A total number of 782 participants (38.5 % men; 61.5% women; mean age: 80.89) were recruited from different levels of the health system: 523 (66.9%) residents in the community, 154 (19.7%) in Nursing Homes, 55(7%) at the Intermediate Care Centre and 50 (6.4%) at the Acute Care Hospital; this distribution of patients among the diverse settings is representative of the population prevalence of these patients [51]. All participants were allocated to one trajectory presented severity and progression criteria for two concomitant organs. The appendix shows the results for each individual disease.

Main results

Functional progression (31.5% loss ≥2ADL's, 44.3% clinical perception) and nutritional criteria (particularly clinical perception, 30.7%) were the indicators most constantly associated with end-of-life identification in all patients (table 3). For the patients with Cancer, Organ Failure and Advanced Frailty, we could not determine if there were cognitive progression criteria (na), since this feature was only evaluated as a criterion for advanced dementia. Emotional distress (21.9%) and some geriatric syndromes (11.2% falls and 15.7% delirium) were also present, but less frequently and without statistically significant differences among the four groups. Generally, families perceived more palliative needs than the patients and professionals.

					END OF LIFE TRAJECTORY								
			ALL patients		Cancer		Organ failure (Pulmonary + heart + liver + renal)		Dementia + Chronic neurological diseases		Advanced frailty -No advanced disease criteria-		p-value*
			n=782		n= 76 (9.7%)		N=126 (16.1%)		n=203 (26%)		n=377 (48.2%)		
DOMAIN			n	%	n	%	n	%	n	%	n	%	
FUNCTIONAL	S (Barthel <25)		147	22.2	3	4.5	6	5.3	101	49.7	37	10.6	<0.005
	P (loss ≥2ADL's)		243	31.5	33	43.4	38	30.6	63	31.03	109	29.4	0.121
	P (clinical perception)		343	44.3	45	59.2	54	42.9	84	41.4	160	43	0.050
NUTRITIO-NAL	S (albumin <2.5)		24	5.8	5	8.1	6	6.4	1	0.4	13	5.9	0.560
	P (Weight loss > 10%)		42	12.2	7	23.3	6	11.5	14	6.8	15	9.7	0.211
	P (clinical perception)		237	30.7	48	63.2	29	23	63	31.3	97	26.3	<0.005
COGNITIVE	S (GDS/FAST ≥6c)		169	21.9	0	0	0	0	169	83.2	0	0	<0.005
	P (loss ≥2ADL's)		68	8.7	na	na	na	na	68	33.5	na	na	<0.005
EMOTIONAL	Distress		165	21.9	20	24.7	28	22.6	33	16.2	84	23.8	0.134
GERIATRIC SYNDROMES	Pressure ulcers		34	4.4	3	4	1	0.8	19	9.3	11	3	<0.005
	Dysphagia		81	10.4	8	10.8	4	3.2	48	23.6	21	5.6	<0.005
	Falls >2		86	11.2	7	9.5	9	7.3	26	12.8	44	12	0.401
	Delirium		122	15.7	10	13.2	17	13.5	38	18.7	57	15.3	0.518
	Rec. infections		41	5.3	3	4	14	11.2	8	3.9	16	4.3	0.015
OTHERS	Comorbidity *(Charlson average)*		3.23 (+/-2.9)		5.34 (+/-2.6)		3.38 (+/-2.1)		2.28 (+/-1.7)		3.07 (+/-2.2)		<0.005
	Use of resources	Unplanned admissions *(average, per year)*	0.55 (+/-1.0)		0.64 (+/-0.9)		1.0 (+/-1.3)		0.22 (+/-0.5)		0.5 (+/-1.15)		<0.005
		Complex care	145	19.2	26	35.1	27	22.1	28	13.8	64	17.9	<0.005

	Palliative care approach	Choice/dem and patient	44	**5.6**	13	**17.1**	7	**5.6**	3	**1.4**	21	**5.6**	**<0.005**
		Choice/dem and family	209	**26.7**	30	**39.5**	30	**23.8**	69	**34.0**	80	**21.5**	**<0.005**
		Need (Healthcare professionals)	121	**15.5**	36	**47.4**	21	**16.9**	27	**13.3**	37	**10**	**<0.005**
	Age (mean)		**80.89** (+/-11.9)		**79.9** (+/-24.0)		**77.7** (+/-13.4)		**82.99** (+/-9.7)		**82.6** (+/-11.3)		**<0.005**
	Sex	Male	301	**38.5**	44	**57.9**	66	**52.4**	50	**24.6**	141	**37.4**	**<0.005**
		Women	481	**61.5**	32	**42.1**	60	**47.6**	153	**75.4**	236	**62.6**	

Table 3. **Distribution of indicators per end-of-life trajectory.** %: percentage of patients with presence of the analysed variable with respect to the total of patients (once missing data excluded). **ADL**: activities of daily living. **GDS/FAST**: Global Deterioration Scale / Functional Assessment Staging **n**: number of valid patients for evaluation of variable. **na**: not applicable. * **p-values**: obtained from comparative analysis among the 4 groups described: Cancer, Organ failure, Dementia/Chronic neurological diseases i Advanced frailty. **P**: Progression criteria. **S**: Severity criteria.

The functional severity criteria, cognitive severity criteria, some geriatric syndromes such as decubitus ulcers, dysphagia or repetition infections, comorbidity, use of resources, election criteria, demand and need of PC, and age and gender showed statistically significant differences in the classification per trajectories performed.

Patients with *advanced cancer* rarely presented with functional severity criteria (4.5%). For these patients, the presence of nutritional progression criteria was more common than in the other groups (clinical perception: 63.2%). There was a high need of complex care (35.1%), as well as demand and need of PC from the patients (17.1%), relatives (39.5 %) and professionals (47.4%).

Patients with *advanced organ disease* –all had main disease severity and progression criteria- presented less parameters of general severity and progression than the rest of trajectories and less percentage of geriatric syndromes. In contrast, they presented a larger percentage of systemic infections (11.2%) and more unplanned admittances than the other groups.

Patients with *advanced dementia and chronic neurological diseases* presented severity criteria, both functional (49.7%) and cognitive (83.2%), and geriatric syndromes: ulcers (9.3%), persistent dysphagia (23.6%), repetitive falls (12.8%)

and delirium (18.7%). These patients presented less need of resources than the other groups and there was a low perception of palliative needs among the professionals (13.3%) compared to relatives (34%).

48.2% of the whole NECPAL(+) patients did not present severity and progression criteria for any chronic disease. In comparison with the other trajectories, no indicator in this group *("Advanced frailty patients with no advanced disease criteria") was* especially prevalent or relatively infrequent: for instance, these patients present more functional severity criteria (10.6%) then cancer (4.5%) and organ failure (5.3%) patients, but lower than patients with dementia (49.7%); they present less nutritional progression criteria (9.7%) than cancer (23.3%) and organ failure (11.5%) patients, but more than patients with dementia (6.8%); or they have more comorbidity (Charlson: 3.07) than patients with dementia (2.28), but less than Cancer (5.34) and Organ Failure (3.38) patients. Globally, professionals had low perceptions that these patients had palliative needs.

DISCUSSION

Key results

Dynamic indicators are more discriminating than static ones.[19] Functional and nutritional progression criteria (also cognitive progression could be included if there is delirium)[57] are also important, mainly regarding functional loss.[58,59] This fact is supported by the literature, given the evidence that changing variables have been shown to have better prognostic ability than those variables that remain stable.[19,58,59] Also emotional distress and some geriatric syndromes, though less significantly, have been shown to be useful indicators for early identification.

Beyond the described parameters, we consider that there are no unique and specific indicators to reliably identify PACC, since only a low percentage of patients present most of them. This fact has two implications: (a) Early identification of PACC requires a multidimensional evaluation including a wide range of indicators; and (b) The different characteristics of these indicators in the diverse groups (cancer, organ disease and dementia/advanced neurologic disease) support the conceptual model of end-of-life trajectories. This model seems to be consistent beyond the described functional dimension: in many of the other dimensions (nutritional, cognitive, geriatric syndromes and use of resources), the behaviour is also different among the groups.

Regarding the differences of the variables in the three end-of-life trajectories, the low prevalence of patients with *advanced cancer* and functional severity criteria is remarkable; this could be due to a faster decline of these patients in the second transition –if we assume that most patients of this cohort were stable-,[60–62] although it could also be due to a selection bias on the part of recruitment process. The impact of undernourishment as an important marker of end of life in cancer patients is also consistent with literature.[63–66] For patients with *advanced organ diseases*, there are more unplanned admittances, probably because of episodes of acute failure or infections, in keeping with the trajectory classically described cohort.[44,52,67–74] As for patients with *dementia and other neurological diseases* the criteria of disease severity (frequently based on the functional repercussions of the severity), determine the identification of end-of-life situation.[75,76] This fact, together with the presence of multiple geriatric syndromes, can help professionals in this process of identification.[77] The slow and progressive process of decline, determines less use of resources and, probably, less perception of palliative needs from the professionals, in contrast to the relatives' view. This analysis endorses the conceptual approach of typical trajectories of decline in advanced chronic illnesses.

However, with mutimorbidity the norm at the end of life, patients may embrace one or more trajectories.[78,79] This resulted in an extremely heterogeneous behaviour of the variables over time among different patients.

It was remarkable that in a particularly disease-centred clinical context, practically half of the cohort did not meet advanced disease criteria *("Advanced frailty patients with no advanced disease criteria")*, but identified as persons with advanced chronic conditions and PC needs at the same time (NECPAL+); it is estimated that 40% of deaths occur in frail older people who have no main overriding diagnosis.[80] This is relevant because it suggests that for early identification for palliative care it is essential to look beyond disease-centred variables and that multiple general indicators in different domains need to be considered.[81] Given that frailty is the most prevalent condition as people approach death,[82] a rational clinical approach to these patients would be to consider frailty not as an independent entity defining only one of the end-of-life trajectories, but as a quantitative measurement system to determine the reserve level of the patient. Such reserve would act as the basis for a "situational diagnosis". Analysis shows that most variables are present in the end-of-life trajectories, although they behave differently. It may be that with frail patients, the other non-physical trajectories of need may be important to monitor clinically, as they may show more dynamic needs for care. More research will be needed to substantiate this claim.

Finally, cancer and non-cancer patients present physical decline and significant psychosocial difficulties and all these patients could benefit from a palliative approach.[83] However, healthcare professionals currently identify less patients for a palliative approach for the non-cancer group.[84] This might be because the end-of-life trajectory is less predictable for these patients, but this should not stop identifying these patients according to these indicators, rather than professionals having "prognostic paralysis".[85]

Strengths and Limitations

The study was carried out with 100% of participation from healthcare professionals and settings invited. A standardised case identification methodology followed in all settings and a high level of commitment from all participants.

The study has limitations. Since this study was based on health professionals' assessment and routine data, patients' perspective was not included. Availability of quantitative data in clinical charts may have affected description of patients' characteristics. The study results may have also been affected by ageing population and strong influence of geriatric care in the area, as well as by length of the study window. Additionally, a problem of over identification with the tool cannot be dismissed, due to the high number of "Advanced frailty patients with no advanced disease criteria". We are currently monitoring the mortality of this cohort to confirm or reject this hypothesis.

There was a significant number of missing nutritional indicators requiring an objective measure (47.2% due to Albumin or 56% due to weight loss) –*see online appendix*-. This fact emphasizes some discordance between the importance of measuring the nutritional state according to scientific evidence[20–23] and the real clinical practice; we wonder whether using other parameters in the evaluation of undernourishment, such as body-mass Index or Mini Nutritional Assessment[86] results would be indicated. Some of the indicators described in the background section, such as social vulnerability or symptoms, were not included in the NECPAL CCOMS-ICO© tool. Thus, these could not been assessed in the study; similarly the progression criteria for dementia could only be assessed for patients with severity criteria of dementia.

The proposal of grouping neurologic diseases, including neurodegenerative diseases such as Parkinson and Amyotrophic Lateral Sclerosis with the group of primary

neurodegenerative/Alzheimer is arguable; however, it might have not effected final results, given the low number of patients (n=31, 4% of the total cohort).

Generalizability & Future trends

More studies are needed to corroborate these data. However, the results described are a useful basis for future research on the early identification of patients with advanced chronic conditions for integrated palliative care. Suggested topics to be developed include:

a) The cohort corresponds to persons identified a priori as PACC and, likely to die in the foreseeable future. It will be necessary, however, to analyse the behaviour of these variables in relation to mortality. We are currently monitoring the cohort at 24 months.

b) Given the large prevalence of advanced frailty patients, new frameworks[8] based on knowledge on geriatrics, primary care and palliative care are indicated. In fact, these three areas already share methods regarding care process:[87] team work, multidimensional assessment, patient-centred care, psychosocial and caregivers support. More shared research between these specialties and public health will best take this agenda forward together.

c) The conceptual link between the need of multidimensional evaluation of PACC and the high prevalence of advanced frailty patients with no advanced disease criteria can be found in the evaluation of the level of reserve of these patients. Frailty indexes,[88–92] already proved to have a strong association with mortality, may become the gold Standard for situational diagnosis, since they allow to quantify people's health reserves from a universal and objective point of view.

CONCLUSIONS

Learning from the behaviour of end-of-life indicators helps clinicians deal with the clinical complexity and innate prognostic uncertainties of this group of patients

There are indicators of palliative care need common to all types of trajectories, and others associated with specific trajectories: dynamic variables most consistently identify PACC and palliative care needs, regardless of the patient's end-of-life trajectory. Additionally, the analysis of the other indicators allows us to develop useful knowledge relating to how people die in different ways. To explore in detail the characteristics of the indicators in these patients will help to provide them patient-centred care.

Almost half of the cohort, although identified as PACC, did not have severe or progression advanced disease. This fact is particularly relevant and highlights the need of more research, probably by using new measuring systems for frailty, and the need of alternative conceptual models, probably by defining new end-of-life trajectories, in order to provide better end-of-life care to this great number of people.

OTHER INFORMATION

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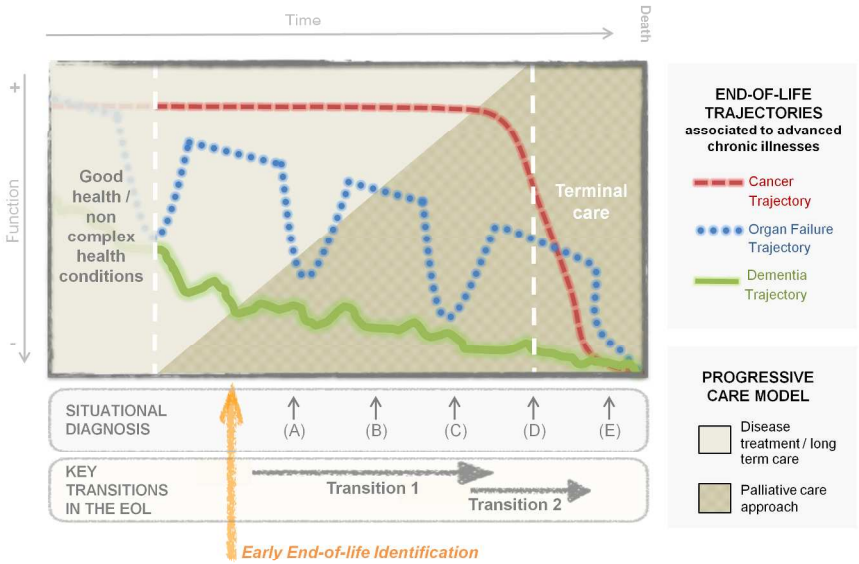

Figure 1: Key transitions and the three end-of-life trajectories. Early identification of palliative care needs becomes the starting point for transition 1. Situational diagnosis refers to the evaluation and assessment of patients that allows healthcare professionals determine patients' health degree (A, B, C, D or E) and identify entrance to Transition 2 (D) or last days-hours situation, instead (E); this situational diagnosis is indispensable to establish the objectives of care in this progressive care model in a decision-making process shared by professionals, patients and their families.

254x190mm (300 x 300 DPI)

DISEASE / DOMAIN			ALL			Cancer		Chronic pulmonary disease		Chronic heart disease		Serious chronic liver disease		Serious chronic renal disease		Chronic neurological diseases		Dementia		No advanced disease criteria	
			n=782			n=76 (9.7%)		n= 43 (5.5%)		n= 63 (8.1%)		n= 9 (1.1%)		n= 11 (1.4%)		n=31 (4%)		n=172 (22%)		n=377 (48.2%)	
			n v	n m	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
FUNCTIONAL	**S** (Barthel <25)		147 662	120	**22.2**	3	4.5	0	0	6	10.2	0	0	0	0	12	40	89	52.4	37	10.6
	S (Barthel average)		**59.6** (+/32.4) 731	51		79.9 (+/-24.9)		75.38 (+/-21.9)		71.44 (+/-28.5)		84.8 (+/-17.4)		74.4 (+/-15.1)		36.17 (+/-30)		30.95 (+/-27.8)		67.05 (+/-27.9)	
	P (loss ≥2ADL's)		243 771	11	**31.5**	33	43.4	11	26.2	19	29.7	4	44.4	0	0	14	45.2	49	29.2	109	29.4
	P (clinical perception)		343 774	8	**44.3**	45	59.2	21	48.8	24	36.9	4	44.4	7	63.6	22	71	62	36.3	160	43
NUTRITIO-NAL	**S** (albumin <2.5)		24 413	369	**5.8**	5	8.1	0	0	0	0	6	66.7	0	0	0	0	1	2.8	13	5.9
	P (Weight loss > 10%)		42 344	438	**12.2**	7	23.3	2	8.7	2	9.5	2	33.3	0	0	2	15.4	12	13	15	9.7
	P Clinical Perception		237 771	11	**30.7**	48	63.2	8	18.6	14	21.5	4	44.4	3	27.3	6	19.4	57	33.5	97	26.3
COGNITIVE	**S** (GDS/FAST ≥6c)		169 772	10	**21.9**	0	0	0	0	0	0	0	0	0	0	0	0	169	98.3	0	0
	P (loss ≥2ADL's)		68 782	0	**8.7**	na	na	na	na	na	na	na	na	na	na	na	na	68	39.5	0	0
EMOTIONAL	Distress		165 753	29	**21.9**	20	24.7	5	11.9	17	26.6	2	22.2	4	36.4	11	36.7	22	12.9	84	23.8
GERIATRIC SYNDROMES	Pressure ulcers		34 773	9	**4.4**	3	4	1	2.3	0	0	0	0	0	0	5	16.1	14	8.2	11	3
	Dysphagia		81 779	3	**10.4**	8	10.8	2	4.7	2	3.1	0	0	0	0	15	48.4	33	19.2	21	5.6
	Falls >2		86 768	14	**11.2**	7	9.5	1	2.3	6	9.4	1	11.1	1	9.1	5	16.1	21	12.3	44	12
	Delirium		122 777	5	**15.7**	10	13.2	4	9.3	8	12.3	3	33.3	2	18.2	6	19.4	32	18.6	57	15.3
	Recurrent infections		41 774	8	**5.3**	3	4	11	25.6	2	3.1	1	11.1	0	0	1	3.2	7	4.1	16	4.3
OTHERS	Comorbidity (Charlson mean)		**3.23** (+/-2.9) 683	99		5.34 (+/-2.6)		2.81 (+/-1.7)		3.14 (+/-1.9)		5 (+/-2.8)		5.18 (+/-2.4)		2.14 (+/-2.0)		2.32 (+/-1.6)		3.07 (+/-2.2)	
	Use of resources	Unplanned admissions (average per year)	**0.55** (+/-1.0) 686	96		0.64 (+/-0.9)		1.09 (+/-1.1)		0.86 (+/-1.3)		1.89 (+/-1.6)		0.73 (+/-0.9)		0.24 (+/-0.6)		0.21 (+/-0.4)		0.5 (+/-1.1)	
		Complex care	145 755	27	**19.2**	26	35.1	12	27.9	8	12.9	2	22.2	5	50	10	34.5	18	10.6	64	17.9
	Palliative care approach	Choice/dem and patient	44 786	6	**5.6**	13	17.1	2	4.7	5	7.7	0	0	4	36.4	2	6.4	1	0.6	21	5.6
		Choice/dem and family	209 782	0	**26.7**	30	39.5	11	25.6	13	20	2	22.2	0	0	5	16.2	64	37.3	80	21.5
		Need (Healthcare professionals)	121 776	6	**15.5**	36	47.4	7	16.3	10	15.6	3	33.3	1	10	4	12.9	23	13.5	37	10
	Age (mean)		**80.89** (+/-11.9) 782	0		79.92 (+/-24.0)		79.09 (+/-9.9)		78.25 (+/-14.4)		67.56 (+/-16.0)		76.45 (+/-13.4)		71.74 (+/-15.6)		85.01 (+/-6.5)		82.62 (+/-11.3)	
	Sex	Male	301 782	0	**38.5**	44	57.9	31	72.1	26	40	6	66.7	5	45.5	16	51.6	34	19.8	141	37.4
		Women	481 782	0	**61.5**	32	42,1	12	27.9	39	60	3	33.3	6	54.5	15	48.4	138	80.2	236	62.6

Distribution of variables according to presence of disease severity and/or progression criteria; *%: percentage of patients with presence of the analysed variable with respect to the total of patients. **ADL**: activities of daily living. **IADL**: instrumental activities of daily living. **GDS/FAST**: Global Deterioration Scale / Functional Assessment Staging **m**: missing patients. **n**: number of valid patients for evaluation of variable. **na**: not applicable. **v**: % valid patients

STROBE Statement—checklist of items that should be included in reports of observational studies

Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of indicators related to end-of-life trajectories.

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract p.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found p. 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p. 6-9, T1, T2 and F1.
Objectives	3	State specific objectives, including any prespecified hypotheses p. 10
Methods		
Study design	4	Present key elements of study design early in the paper p. 10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p. 10-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants p. 11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable p. 11-13, T3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group p. 11
Bias	9	Describe any efforts to address potential sources of bias

		p. 11
Study size	10	Explain how the study size was arrived at p. 10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why p. 11-13, T3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding p. 13
		(*b*) Describe any methods used to examine subgroups and interactions p. 13
		(*c*) Explain how missing data were addressed p. 13
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy NA
		(*e*) Describe any sensitivity analyses p. 13
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed p. 14
		(b) Give reasons for non-participation at each stage NA
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders p. 14, T4 and A1
		(b) Indicate number of participants with missing data for each variable of interest T4 and A1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures T4 and A1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included p. 14-16, T4 and A1
		(*b*) Report category boundaries when continuous variables were categorized NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p. 14-16, T4 and A1
Discussion		
Key results	18	Summarise key results with reference to study objectives p. 16-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias p. 18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p. 18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results p. 19-20
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p. 21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of prognostic indicators related to end-of-life trajectories

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Primary Subject Heading:	Palliative care
Secondary Subject Heading:	General practice / Family practice, Geriatric medicine, Health policy, Medical management, Patient-centred medicine
Keywords:	Advanced chronic conditions, End-of-life trajectories, Adult palliative care < PALLIATIVE CARE, Advanced Frailty, Health Status Indicators, Prognosis

TITLE PAGE

Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of prognostic indicators related to end-of-life trajectories.

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ABSTRACT

Objectives: Two innovative concepts have lately been developed to radically improve the care of patients with advanced chronic conditions: early identification of palliative care needs and the three end-of-life trajectories in chronic illnesses (acute, intermittent and gradual dwindling). It is not clear (1) what indicators work best for this early identification and (2) if specific clinical indicators exist for each of these trajectories. The objectives of this study are to explore these two issues.

Setting: Three primary care services, an acute care hospital, an intermediate care centre and four nursing homes in a mixed urban-rural district in Barcelona, Spain.

Participants: 782 patients (61.5% women) with a positive NECPAL CCOMS-ICO© test, indicating they might benefit from a palliative care approach.

Outcome measures: The characteristics and distribution of the indicators of the NECPAL CCOMS-ICO© tool are analysed with respect to the three trajectories and have been arranged by domain (functional, nutritional and cognitive status, emotional problems, geriatric syndromes, social vulnerability and others) and according to their static (severity) and dynamic (progression) properties.

Results: The common indicators associated with early end-of-life identification are: functional (44.3%) and nutritional (30.7%) progression, emotional distress (21.9%) and geriatric syndromes (15.7% delirium, 11.2% falls). The rest of the indicators showed differences in the associations per illness trajectories ($p<0.05$). 48.2% of the total cohort was identified as advanced frailty patients with no advanced disease criteria.

Conclusions: Dynamic indicators are present in the three trajectories and are especially useful to identify patients with advanced chronic conditions for a progressive palliative care approach purpose. Most of the others indicators are typically associated with a specific trajectory. These findings can help clinicians improve the identification of patients for a palliative approach.

ARTICLE SUMMARY

- This study innovatively explores the relationship between end-of-life indicators used to identify patients with advanced chronic conditions and the three archetypal end-of-life trajectories: acute (typically cancer), intermittent (typically organ failure) and gradual dwindling (typically dementia or frailty).

- Analysing the characteristics of end-of-life indicators allows us to know which indicators most consistently identify patients for palliative care. It also provides data on the characteristics that most commonly occur in each end-of-life trajectory.

- The large number of identified patients with advanced chronic conditions but *with no advanced disease criteria* reveals that there is a real and not previously well described cohort of people with advanced frailty and palliative care needs.

- These concepts are useful for clinical decision-making, for policymakers in designing appropriate health services, as well as giving researchers a theoretical framework for future research.

- Study limitations include the heterogeneity in the collection of variables due to the multiple assessments from all health care system resources; and the number of missing data in some variables.

MAIN TEXT

INTRODUCTION

Two concepts can be combined to illuminate care provision for patients with advanced chronic conditions: early identification of patients with palliative care (PC) needs and, secondly, end-of-life trajectories associated with advanced chronic illnesses. This gives a conceptual framework to understand the different characteristics of patients from their early identification for palliative care onwards.

Early identification of patients with palliative care needs

The modern approach to the end-of-life divides this into two transitions[1] (figure 1). The first one, frequently some months or years before death, may constitute the starting of the process of identification of patients with palliative care needs, due to the appearance and recognition of some indicators or variables which make early identification easier. Throughout the article we will refer to these patients with advanced chronic diseases and conditions, palliative care needs and limited life prognosis as a “Patients with advanced chronic conditions“(PACC). The second transition -or “the last days or weeks of patient’s life”- starts when the terminal decline begins and corresponds to the out-moded paradigm of very late palliative care provision.

Early identification for palliative care has shown many benefits: it helps to clarify treatment preferences and goals of care, it improves quality of life and symptom control, it reduces distress, it allows less aggressive care, lower spending, and may even lengthen survival.[2–4] Thus, to develop anticipatory palliative care[5] becomes crucial during this first transition.

A certain degree of prognostic approach may be used with caution in the care of individual patients, and professionals still have difficulties finding unequivocal prognostic variables[6]. Prognosis will always imply a degree of uncertainty-,[7] since end of life processes are multifactorial and strictly individual at the same time. Besides, the earlier we want to identify these patients, the more difficult it becomes to obtain certain prognostic variables.[8]

Thus, although certain variables are broadly linked with mortality risks, there is no single prognostic indicator that identifies all patients who will die soon.[6] The classic prognosis approach focused on advanced chronic disease severity criteria has limitations: prognostic disease-centred variables, when used in isolation, have shown low prognostic capacity[9–14] particularly for geriatric patients with multiple chronic conditions.[6] Other general factors have proved to be more reliable end-of-life prognostic indicators than disease centred-variables:[15] functional,[16–19] nutritional,[20–24] and cognitive status,[25,26] emotional problems,[27,28] geriatric syndromes -such delirium,[29,30] dysphagia,[31] pressure ulcers[32] and repetitive falls-,[33] symptoms –such as dyspnoea,[34–36] and anxiety-,[37] social vulnerability,[38–41] or use of resources.[42–44]

Thus, most screening tools for identification of patients with palliative care needs[45] -e.g. the Prognostic Indicator Guidance of the Gold Standards Framework (PIG-GSF),[46] the Supportive & Palliative Care Indicators Tool (SPICT),[47] the RADboud indicators for PAlliative Care needs (RADPAC)[48] and the NECesidades PALiativas CCOMS-ICO tool (NECPAL CCOMS-ICO tool)-[49–51] have incorporated these general conditions from different domains in different degrees.

The evaluation of these variables -both disease specific and these other general factors- has also shown the need for complementing the static status (severity) with an assessment of dynamic progression of decline.[8]

End-of-life trajectories

In 2003, Lunney et al. described three distinct illnesses trajectories of functional decline at the end of life[52] (figure 1) illustrating the typical dynamic patterns of a group of patients classified according to their main chronic disease: the first clinical trajectory, typically associated to cancer, features a stable and/or low decline phase broken up by a severe decline in the last weeks. The second features gradual decline, with acute episodes usually related to concomitant processes and disease evolution and partial recovery; this trajectory corresponds to patients with advanced organ diseases such as heart, lung, renal or liver failure. Finally, the third trajectory shows a progressive slow-pace decline, typically related to dementia or frail patients.

Later, Murray et al.[53] highlighted the clinical implications of end-of-life trajectories by presenting trajectories as a framework to help professionals and patients facing the uncertainty of having an advanced chronic condition avoid a prognostic paralysis. Firstly, these trajectories may help clinicians to better plan care to meet their patients' changing needs, and help patients and caregivers to cope with their situation. Secondly, by pointing out that different models of care may be necessary to reflect and tackle patients' different experiences and needs. Thirdly, by graphing dimensional end-of-life trajectories, the different dimensions of need –physical, social, psychological and spiritual- may be identified and addressed.

Hypothesis and objectives

We hypothesize that there might be a common denominator in the characteristics of some indicators that would allow us to identify PACC at specific time points. On the other hand, distinguishing features may also exist in other indicators that support and develop the conceptual model of end-of-life trajectories.

Learning from the characteristics and evolution of these end-of-life indicators as the basis of the individual situational diagnosis[8] —understood as the assessment to determine patients' health degree and (or possible) closeness to end-of-life situation- (figure 1), can help clinicians to manage uncertainty and make better clinical decisions, according to patients' values and preferences.[54] In order to develop further knowledge on these indicators, we analysed the characteristics and distribution of the indicators related to end of life in a cohort of patients identified with the NECPAL CCOMS-ICO© tool.

METHODS

Our methods, as extensively described elsewhere,[51] are reported according to the STROBE recommendations.[55] This study was formally approved by the ethical research committees of institutions involved in its execution (2010/PREVOsona: P10/65 and EO65).

Study design and Setting

A cross-sectional study of patients identified in a previous population-based study was conducted.[51] The study was conducted in the Spanish district of Osona, Barcelona, a mixed urban-rural district with a population of 156,087 residents, 21.4% of whom are aged >65 years, with an annual mortality rate of 8.81 per 1000 inhabitants. Three

selected primary care services and an acute care hospital, an intermediate care centre and four nursing homes serving these primary care services agreed to participate.

Eligibility criteria and participant selection

Case selection was undertaken from November 2010 to October 2011. There were no exclusion criteria. Patient recruitment was made using the NECPAL CCOMS-ICO© tool through the healthcare records and by interviews with healthcare professionals (doctors and nurses). "NECPAL positive (+)" patients were defined as being surprise-question[56] answer "no" (*"I would not be surprised if this patient were to die in the next 12 months"*) and having at least one subsequent positive category: (a) category 1: choice, request or need of PC approach (*has the patient or the main caregiver requested palliative / comfort treatments exclusively or suggests limitation of therapeutic effort? Healthcare professionals consider that the patient requires palliative care or palliative treatment at this moment?*); (b) category 2: general clinical prognostic indicators of severity and progression -including co-morbidity and resource use- (table 1); or (c) category 3: disease-specific prognostic indicators (table 2).

DOMAIN	SEVERITY	PROGRESSION (in the last 6 months):
FUNCTIONAL MARKERS	Serious established functional dependence Barthel score< 25, ECOG >2 or Karnofsky score < 50%)	Loss of 2 or more ADL's even though there is adequate therapeutic intervention OR Clinical Perception of functional decline (sustained, intense /severe, progressive, irreversible) not related to concurrent conditions
NUTRITIONAL MARKERS	Serum albumin < 2.5 g/dl, not related to acute episodes of unbalance	Weight loss > 10% or Clinical Perception of nutritional decline (sustained, intense/severe, progressive, irreversible) not related to concurrent conditions
COGNITIVE	Unable to dress, wash or eat without assistance (GDS/FAST 6c), urinary and faecal incontinence (GDS/FAST 6d-e) or unable to communicate meaningfully -6 or less intelligible words- (GDS/FAST 7)	Loss of 2 or more ADL's in the last 6 months, despite adequate therapeutic intervention (invaluable in hyperacute situation due to concurrent processes) or difficulty swallowing, or denial to eat, in patients who will not receive enteral or parenteral nutrition
EMOTIONAL	Presence of emotional distress with psychological symptoms (sustained, intense/severe, progressive) not related to acute concurrent conditions	
GERIATRIC SYNDROMES (in the last 6 months)	Persistent pressure ulcers (stage III–IV), Recurrent infections (> 1), Delirium, Persistent Dysphagia, Falls (> 2)	
CO-MORBIDITY	Charlson index	

Additional factors on **USE OF RESOURCES**	○ 2 or more urgent (unplanned) hospital (or skilled nursing facilities) admissions due to chronic disease in the last year ○ Need of complex/intense continuing care, either at an institution or at home

Table 1: Category 2 of the NECPAL CCOMS-ICO© tool: General indicators of severity and progression. **ADL**: Activities of Daily Living. **ECOG**: Eastern Cooperative Oncology Group; **GDS/FAST**: Global Deterioration Scale / Functional Assessment Staging

CANCER *(one single criterion)*	○ Confirmed diagnosis of metastatic cancer who present low response or contraindication of specific treatment, progressive outbreak during treatment or metastatic affectation of vital organs ○ Significant functional deteriorating (Palliative Performance Status < 50%) ○ Persistent, troublesome symptoms, despite optimal treatment of underlying condition(s)
CHRONIC PULMONARY DISEASE *(two or more criteria)*	○ Breathlessness at rest or on minimal exertion between exacerbations ○ Difficult physical or psychological symptoms despite optimal tolerated therapy ○ FEV1 <30% or criteria of restricted severe deficit: VFC < 40% / DLCO < 40% ○ Accomplishment of oxygen therapy at home criteria ○ Recurrent hospital admissions (> 3 admissions in 12 months due to exacerbations).
CHRONIC HEART DISEASE *(two or more criteria)*	○ Heart failure NYHA stage III or IV, severe valve disease or inoperable coronary artery disease ○ Shortness of breath at rest or minimal exertion ○ Difficult physical or psychological symptoms despite optimal tolerated ○ Ejection fraction severely affected (< 30%) or severe pulmonary hypertension (> 60 mmHg) ○ Renal failure (GFR < 30 l/min) ○ Repeated hospital admissions with symptoms of heart failure/ischemic heart disease (> 3 last year)
SERIOUS CHRONIC LIVER DISEASE *(one single criterion)*	○ Advanced Cirrhosis: stage Child C, MELD-Na score > 30 or with one or more of the following medical complications: diuretic resistant ascites, hepato-renal syndrome or upper gastrointestinal bleeding due to portal hypertension with failed response to treatment ○ Hepatocellular carcinoma: present, in stage C or D (BCLC)
SERIOUS CHRONIC RENAL DISEASE *(one single criterion)*	○ Serious renal failures (GFR < 15) in patients to whom substitutive treatment or transplant is contraindicated
Chronic Neurological Diseases (1): CVA *(one single criterion)*	○ During acute and sub-acute phases (< 3 months post-stroke): persistent vegetative or minimal conscious state > 3 days ○ During the chronic phase (> 3 months post-stroke): repeated medical complications (aspiration pneumonia, pyelonephritis, recurrent febrile episodes, pressure ulcers stage 3-4 or dementia with severe criteria post-stroke
Chronic neurological diseases (2): MOTOR NEURONE DISEASES, MÚLTIPLE SCLEROSIS & PARKINSON (two or more criteria)	○ Progressive deterioration in physical and/or cognitive function despite optimal therapy ○ Complex and difficult symptoms ○ Speech problems with increasing difficulty communicating ○ Progressive Dysphagia ○ Recurrent aspiration pneumonia, breathless or respiratory failure
DEMENTIA *(two or more of the following criteria)*	○ Severity criteria: GDS/FAST 6c or more. ○ Progression criteria: loss of 2 or more ADL's in the last 6 months, despite adequate therapeutic intervention or difficulty swallowing, or denial to eat, in patients who will not receive enteral or parenteral nutrition ○ Use of resources criteria: multiple admissions (> 3 in 12 months, due to concurrent processes –aspiration pneumonia, pyelonephritis, sepsis, etc.- that cause functional and/or cognitive decline)

Table 2: Category 3 of the NECPAL CCOMS-ICO© tool: disease-specific indicators. **FEV1**: forced expiratory volume in one second. **FVC**: Forced vital capacity. **DLCO**: diffusing capacity of the lung for carbon monoxide. **NYHA**: New York Heart Association. **GFR**: Glomerular Filtration Rate. **BCLC**: Barcelona-Clinic Liver Cancer. **CVA**: Cerebrovascular accident.

Variables and sources of information

In the selected cohort, we evaluated the indicators included in the NECPAL CCOMS-ICO© tool, which were retrieved, if available, from patient's clinical records by the investigator team or by clinical judgement after interviewing health-care professionals (including clinical variables and need, demand and choice requests). In order to reduce systematic error, all definitions, procedures –including data collection- and measures were standardized and followed according to the study operations manual.

Indicators were arranged by domain (functional, nutritional and cognitive status, emotional problems, geriatric syndromes, social vulnerability and others) and according to their static (severity) and dynamic (progression) characteristics, for patients in each of the three end-of-life trajectories associated with advanced chronic illnesses.

Indicators & Diseases

We evaluated the distribution of the indicators by classifying persons according to the presence of severity and/or progression criteria of the main disease (cancer, chronic pulmonary disease, chronic heart disease, serious chronic liver disease, serious chronic renal disease, chronic neurological diseases, and dementia). We refer to the group of patients identified as being NECPAL (+) without severity and/or disease progression criteria as "Advanced frailty patients without advanced disease criteria".

Indicators and End-of-life Trajectories.

We organized the illnesses according to the described end-of-life trajectories: cancer, organ failure (including lung, heart, hepatic and renal disease) and dementia. As for neurologic diseases, we put together primary neurodegenerative/Alzheimer and neurodegenerative diseases such as Parkinson and Amyotrophic Lateral Sclerosis for easier analysis purposes, given that their clinical evolution tends to be similar to dementia.

Statistical methods

Characteristics by domain were reported as averages with standard deviations for continuous variables (Barthel, Charlson, unplanned admissions and age) or percentages for the categorical variables. All indicators were calculated for the entire sample and for each four categories of patients: Cancer, Organ Failure, Dementia/Chronic neurological diseases and Advanced Frailty. We compared the proportions among the four groups using Chi-squared test for categorical variables. Differences for non-categorical variables were assessed using ANOVA tests.

Analyses were performed with the Statistical Package for Social Sciences (SPSS), version 21.0. A two-sided p value <0.05 was considered to indicate statistical significance.

RESULTS

Participants

A total number of 782 NECPAL positive (+) patients (38.5 % men; 61.5% women; mean age: 80.89) were recruited from different levels of the health system: 523 (66.9%) residents in the community, 154 (19.7%) in Nursing Homes, 55 (7%) at the Intermediate Care Centre and 50 (6.4%) at the Acute Care Hospital; this distribution of patients among the diverse settings is representative of the population prevalence of these patients [51]. All participants were allocated to one trajectory presented severity and progression criteria for two concomitant organs. The appendix shows the results for each individual disease.

Main results

Functional progression (31.5% loss ≥2ADL's, 44.3% clinical perception) and nutritional criteria (particularly clinical perception, 30.7%) were the indicators most constantly associated with end-of-life identification in all patients (table 3). For the patients with

cancer, organ failure and advanced frailty, we could not determine if there were cognitive progression criteria (na), since this feature was only evaluated as a criterion for advanced dementia. Emotional distress (21.9%) and some geriatric syndromes (11.2% falls and 15.7% delirium) were also present, but less frequently and without statistically significant differences among the four groups. Generally, families perceived more palliative needs than the patients and professionals.

					END OF LIFE TRAJECTORY								
			ALL patients		Cancer		Organ failure (Pulmonary + heart + liver + renal)		Dementia + chronic neurological diseases		Advanced frailty -No advanced disease criteria-		p-value*
DOMAIN			n=782		n= 76 (9.7%)		N=126 (16.1%)		n=203 (26%)		n=377 (48.2%)		
			n	%	n	%	n	%	n	%	n	%	
FUNCTIONAL	S (Barthel <25)		147	22.2	3	4.5	6	5.3	101	49.7	37	10.6	<0.005
	P (loss ≥2ADL's)		243	31.5	33	43.4	38	30.6	63	31.03	109	29.4	0.121
	P (clinical perception)		343	44.3	45	59.2	54	42.9	84	41.4	160	43	0.050
NUTRITIO-NAL	S (albumin <2.5)		24	5.8	5	8.1	6	6.4	1	0.4	13	5.9	0.560
	P (Weight loss > 10%)		42	12.2	7	23.3	6	11.5	14	6.8	15	9.7	0.211
	P (clinical perception)		237	30.7	48	63.2	29	23	63	31.3	97	26.3	<0.005
COGNITIVE	S (GDS ≥6c)		169	21.9	0	0	0	0	169	83.2	0	0	<0.005
	P (loss ≥2ADL's)		68	8.7	na	na	na	na	68	33.5	na	na	<0.005
EMOTIONAL	Distress		165	21.9	20	24.7	28	22.6	33	16.2	84	23.8	0.134
GERIATRIC SYNDROMES	Pressure ulcers		34	4.4	3	4	1	0.8	19	9.3	11	3	<0.005
	Dysphagia		81	10.4	8	10.8	4	3.2	48	23.6	21	5.6	<0.005
	Falls >2		86	11.2	7	9.5	9	7.3	26	12.8	44	12	0.401
	Delirium		122	15.7	10	13.2	17	13.5	38	18.7	57	15.3	0.518
	Rec. infections		41	5.3	3	4	14	11.2	8	3.9	16	4.3	0.015
OTHERS	Comorbidity *(Charlson average)*		3.23 (+/-2.9)		5.34 (+/-2.6)		3.38 (+/-2.1)		2.28 (+/-1.7)		3.07 (+/-2.2)		<0.005
	Use of resources	Unplanned admissions *(average, per year)*	0.55 (+/-1.0)		0.64 (+/-0.9)		1.0 (+/-1.3)		0.22 (+/-0.5)		0.5 (+/-1.15)		<0.005
		Complex care	145	19.2	26	35.1	27	22.1	28	13.8	64	17.9	<0.005
	Palliative care approach	Choice/dem and patient	44	5.6	13	17.1	7	5.6	3	1.4	21	5.6	<0.005
		Choice/dem and family	209	26.7	30	39.5	30	23.8	69	34.0	80	21.5	<0.005
		Need (Healthcare professionals)	121	15.5	36	47.4	21	16.9	27	13.3	37	10	<0.005
	Age (mean)		80.89 (+/-11.9)		79.9 (+/-24.0)		77.7 (+/-13.4)		82.99 (+/-9.7)		82.6 (+/-11.3)		<0.005
	Sex	Male	301	38.5	44	57.9	66	52.4	50	24.6	141	37.4	<0.005
		Women	481	61.5	32	42.1	60	47.6	153	75.4	236	62.6	

Table 3. **Distribution of indicators per end-of-life trajectory.** %: percentage of patients with presence of the analysed variable with respect to the total of patients (once missing data excluded). **ADL**: activities of daily living. **IADL**: instrumental activities of daily living. **. n**: number of valid patients for evaluation of variable. **na**: not applicable. **p-values**: obtained from comparative analysis among the 4 groups described: Cancer, Organ failure, Dementia/Chronic neurological diseases i Advanced frailty. **P**: Progression criteria. **S**: Severity criteria.

The functional severity criteria, cognitive severity criteria, some geriatric syndromes such as decubitus ulcers, dysphagia or repetition infections, comorbidity, use of resources, election criteria, demand and need of PC, and age and gender showed statistically significant differences in the classification per trajectories performed.

Patients with *advanced cancer* rarely presented with functional severity criteria (4.5%). For these patients, the presence of nutritional progression criteria was more common than in the other groups (clinical perception: 63.2%). There was a high need of complex care (35.1%), as well as demand and need of PC from the patients (17.1%), relatives (39.5 %) and professionals (47.4%).

Patients with *advanced organ disease* –all had main disease severity and progression criteria- presented less parameters of general severity and progression than the rest of trajectories and a lower percentage of geriatric syndromes. In contrast, they presented a larger percentage of systemic infections (11.2%) and more unplanned admissions than the other groups.

Patients with *advanced dementia and those with chronic neurological diseases* presented severity criteria, both functional (49.7%) and cognitive (83.2%), and geriatric syndromes: ulcers (9.3%), persistent dysphagia (23.6%), repetitive falls (12.8%) and delirium (18.7%). These patients presented less need of resources than the other groups and there was a low perception of palliative needs among the professionals (13.3%) compared to relatives (34%).

48.2% of the whole NECPAL(+) patients did not present severity and progression criteria for any chronic disease. In comparison with the other trajectories, no indicator in this group *("Advanced frailty patients with no advanced disease criteria") was* especially prevalent or relatively infrequent: for instance, these patients present more functional severity criteria (10.6%) than cancer (4.5%) and organ failure (5.3%) patients, but lower than patients with dementia (49.7%); they present less nutritional progression criteria (9.7%) than cancer (23.3%) and organ failure (11.5%) patients, but more than patients with dementia (6.8%); or they have more comorbidities (Charlson: 3.07) than patients with dementia (2.28), but less than cancer (5.34) and organ failure (3.38) patients. Globally, professionals had low perceptions that these patients had palliative needs.

DISCUSSION

Key results

Dynamic indicators are more discriminating than static ones.[19] Functional and nutritional progression criteria (also cognitive progression could be included if there is delirium)[57] are also important, mainly regarding functional loss.[58,59] This fact is supported by the literature, given the evidence that changing variables have been shown to have better prognostic ability than those variables that remain stable.[19,58,59] Also emotional distress and some geriatric syndromes, though less significantly, have been shown to be useful indicators for early identification.

Beyond the described parameters, we consider that there are no unique and specific indicators to reliably identify PACC, since only a low percentage of patients present most of them. This fact has two implications: (a) Early identification of PACC requires a multidimensional evaluation including a wide range of indicators; and (b) The different

characteristics of these indicators in the diverse groups (cancer, organ disease and dementia/advanced neurologic disease) support the conceptual model of end-of-life trajectories. This model seems to be consistent beyond the described functional dimension: in many of the other dimensions (nutritional, cognitive, geriatric syndromes and use of resources), the behaviour is also different among the groups.

Regarding the differences of the variables in the three end-of-life trajectories, the low prevalence of patients with *advanced cancer* and functional severity criteria is remarkable; this could be due to a faster decline of these patients in the second transition –if we assume that most patients of this cohort were stable-,[60–62] although it could also be due to a selection bias on the part of recruitment process. The impact of undernourishment as an important marker of end of life in cancer patients is also consistent with literature.[63–66] For patients with *advanced organ diseases*, there are more unplanned admissions, probably because of episodes of acute failure or infections, in keeping with the trajectory classically described cohort.[44,52,67–74] As for patients with *dementia or with other neurological diseases* the criteria of disease severity (frequently based on the functional repercussions of the severity), determine the identification of the end-of-life situation.[75,76] This fact, together with the presence of multiple geriatric syndromes, can help professionals in this process of identification.[77] The slow and progressive process of decline determines less use of resources and, probably, less perception of palliative care needs from the professionals, in contrast to the relatives' view. This analysis endorses the conceptual approach of typical trajectories of decline in advanced chronic illnesses.

However, with mutimorbidity the norm at the end of life, patients may embrace one or more trajectories.[78,79] This resulted in an extremely heterogeneous behaviour of the variables over time among different patients.

It was remarkable that in a particularly disease-centred clinical context, practically half of the cohort did not meet advanced disease criteria *("Advanced frailty patients with no advanced disease criteria")*, but were identified as persons with advanced chronic conditions and PC needs at the same time (NECPAL+); it is estimated that 40% of deaths occur in frail older people who have no main overriding diagnosis.[80] This is relevant because it suggests that for early identification for palliative care it is essential to look beyond disease-centred variables and that multiple general indicators in different domains need to be considered.[81] Given that frailty is the most prevalent condition as people approach death,[82] a rational clinical approach to these patients would be to consider frailty not as an independent entity defining only one of the end-of-life trajectories, but as a quantitative measurement system to determine the reserve level of the patient. Such reserve would act as the basis for a "situational diagnosis". Analysis shows that most variables are present in the end-of-life trajectories, although they behave differently. It may be that with frail patients, the other non-physical trajectories of need may be important to monitor clinically, as they may show more dynamic needs for care.[83] More research will be needed to substantiate this claim.

Finally, cancer and non-cancer patients present physical decline and significant psychosocial difficulties and all these patients could benefit from a palliative care approach. However, healthcare professionals currently identify less patients for a palliative approach for the non-cancer group.[84] This might be because the end-of-life trajectory is less predictable for these patients, but this should not stop identifying these patients according to these indicators, rather than professionals having a prognostic paralysis.[85]

Strengths and Limitations

The study was carried out with 100% of participation from healthcare professionals and settings invited. A standardised case identification methodology was followed in all settings and a high level of commitment from all participants was gained.

The study has limitations. Since this study was based on health professionals' assessment and routine data, patients' perspectives were not included. Availability of quantitative data in clinical charts may have affected description of patients' characteristics. The study results may have also been affected by the ageing population and strong influence of geriatric care in the area, as well as by length of the study window. Additionally, a problem of over identification with the tool cannot be dismissed, due to the high number of *"Advanced frailty patients with no advanced disease criteria"*. We are currently monitoring the mortality of this cohort to confirm or reject this hypothesis.

There was a significant number of missing nutritional indicators requiring an objective measure (47.2% due to Albumin or 56% due to weight loss) *–see online appendix-*. This fact emphasizes some discordance between the importance of measuring the nutritional state according to scientific evidence[20–23] and the real clinical practice; we wonder whether using other parameters in the evaluation of undernourishment, such as body-mass Index or Mini Nutritional Assessment[86] results would be indicated. Some of the indicators described in the background section, such as social vulnerability or symptoms, were not included in the NECPAL CCOMS-ICO© tool. Thus, these could not be assessed in the study; similarly the progression criteria for dementia could only be assessed for patients with severity criteria of dementia.

The proposal of grouping neurologic diseases, including neurodegenerative diseases such as Parkinson and Amyotrophic Lateral Sclerosis with the group of primary neurodegenerative/Alzheimer is arguable; however, it might have not effected final results, given the low number of patients (n=31, 4% of the total cohort).

Generalizability & Future trends

More studies are needed to corroborate these data. However, the results described are a useful basis for future research on the early identification of patients with advanced chronic conditions for integrated palliative care. Suggested topics to be developed include:

a) The cohort corresponds to persons identified a priori as PACC and, likely to die in the foreseeable future. It will be necessary, however, to analyse the behaviour of these variables in relation to mortality. We are currently monitoring the cohort at 24 months.

b) Given the large prevalence of advanced frailty patients, new frameworks[8] and tools[87] based on knowledge on geriatrics, primary care and palliative care are indicated. In fact, these three areas already share methods regarding care process:[88] team work, multidimensional assessment, patient-centred care, psychosocial and caregivers support. More shared research between these specialties and public health will best take this agenda forward together.

c) The conceptual link between the need of multidimensional evaluation of PACC and the high prevalence of advanced frailty patients with no advanced disease criteria can be found in the evaluation of the level of reserve of these patients. Frailty indexes,[89–93] already proved to have a strong association with mortality, may become the gold Standard for situational diagnosis, since they allow to quantify people's health reserves from a universal and objective point of view.

CONCLUSIONS

Learning from the behaviour of end-of-life indicators helps clinicians deal with the clinical complexity and innate prognostic uncertainties of this group of patients.

There are indicators of palliative care needs common to all types of trajectories, and others associated with specific trajectories: dynamic variables most consistently identify PACC and palliative care needs, regardless of the patient's end-of-life trajectory. Additionally, the analysis of the other indicators allows us to develop useful knowledge relating to how people die in different ways. To explore in detail the characteristics of the indicators in these patients will help to provide them with patient-centred care.

Almost half of the cohort, although identified as PACC, did not have severe or progression advanced disease. This fact is particularly relevant and highlights the need for more research, probably by using new measuring systems for frailty, and the need of alternative conceptual models, probably by defining new end-of-life trajectories, in order to provide better end-of-life care to this great number of people.

OTHER INFORMATION

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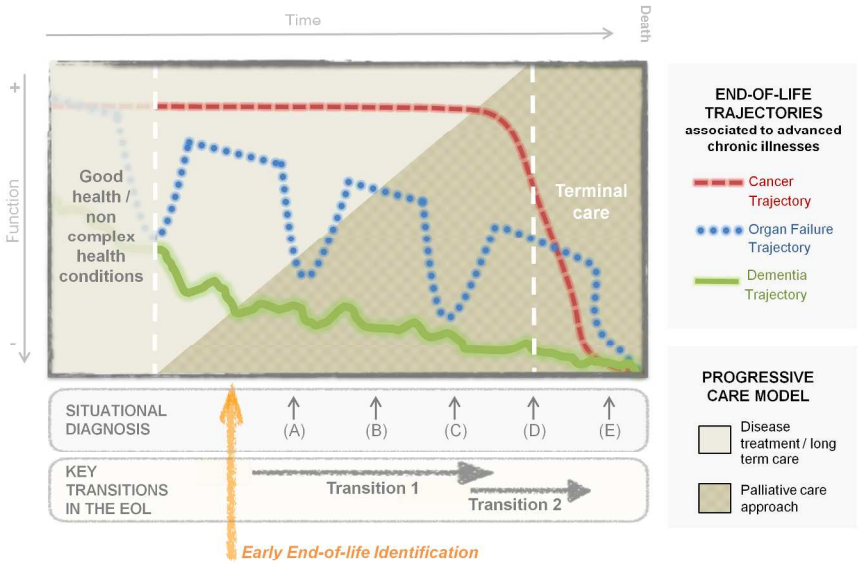

Figure 1: Key transitions and the three end-of-life trajectories. Early identification of palliative care needs becomes the starting point for transition 1. Situational diagnosis refers to the evaluation and assessment of patients that allows healthcare professionals determine patients' health degree (A, B, C, D or E) and identify entrance to Transition 2 (D) or last days-hours situation, instead (E); this situational diagnosis is indispensable to establish the objectives of care in this progressive care model in a decision-making process shared by professionals, patients and their families.

254x190mm (300 x 300 DPI)

DISEASE / DOMAIN			ALL			Cancer		Chronic pulmonary disease		Chronic heart disease		Serious chronic liver disease		Serious chronic renal disease		Chronic neurological diseases		Dementia		No advanced disease criteria	
			n=782			n=76 (9.7%)		n= 43 (5.5%)		n= 63 (8.1%)		n= 9 (1.1%)		n= 11 (1.4%)		n=31 (4%)		n=172 (22%)		n=377 (48.2%)	
			n v	n m	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
FUNCTIONAL	**S** (Barthel <25)		147 662	120	**22.2**	3	4.5	0	0	6	10.2	0	0	0	0	12	40	89	52.4	37	10.6
	S (Barthel average)		**59.6** (+/32.4) 731	51		79.9 (+/-24.9)		75.38 (+/-21.9)		71.44 (+/-28.5)		84.8 (+/-17.4)		74.4 (+/-15.1)		36.17 (+/-30)		30.95 (+/-27.8)		67.05 (+/-27.9)	
	P (loss ≥2ADL's)		243 771	11	**31.5**	33	43.4	11	26.2	19	29.7	4	44.4	0	0	14	45.2	49	29.2	109	29.4
	P (clinical perception)		343 774	8	**44.3**	45	59.2	21	48.8	24	36.9	4	44.4	7	63.6	22	71	62	36.3	160	43
NUTRITIO-NAL	**S** (albumin <2.5)		24 413	369	**5.8**	5	8.1	0	0	0	0	6	66.7	0	0	0	0	1	2.8	13	5.9
	P (Weight loss > 10%)		42 344	438	**12.2**	7	23.3	2	8.7	2	9.5	2	33.3	0	0	2	15.4	12	13	15	9.7
	P Clinical Perception		237 771	11	**30.7**	48	63.2	8	18.6	14	21.5	4	44.4	3	27.3	6	19.4	57	33.5	97	26.3
COGNITIVE	**S** (GDS/FAST ≥6c)		169 772	10	**21.9**	0	0	0	0	0	0	0	0	0	0	0	0	169	98.3	0	0
	P (loss ≥2ADL's)		68 782	0	**8.7**	na	na	na	na	na	na	na	na	na	na	na	na	68	39.5	0	0
EMOTIONAL	Distress		165 753	29	**21.9**	20	24.7	5	11.9	17	26.6	2	22.2	4	36.4	11	36.7	22	12.9	84	23.8
GERIATRIC SYNDROMES	Pressure ulcers		34 773	9	**4.4**	3	4	1	2.3	0	0	0	0	0	0	5	16.1	14	8.2	11	3
	Dysphagia		81 779	3	**10.4**	8	10.8	2	4.7	2	3.1	0	0	0	0	15	48.4	33	19.2	21	5.6
	Falls >2		86 768	14	**11.2**	7	9.5	1	2.3	6	9.4	1	11.1	1	9.1	5	16.1	21	12.3	44	12
	Delirium		122 777	5	**15.7**	10	13.2	4	9.3	8	12.3	3	33.3	2	18.2	6	19.4	32	18.6	57	15.3
	Recurrent infections		41 774	8	**5.3**	3	4	11	25.6	2	3.1	1	11.1	0	0	1	3.2	7	4.1	16	4.3
OTHERS	Comorbidity (Charlson mean)		**3.23** (+/-2.9) 683	99		5.34 (+/-2.6)		2.81 (+/-1.7)		3.14 (+/-1.9)		5 (+/-2.8)		5.18 (+/-2.4)		2.14 (+/-2.0)		2.32 (+/-1.6)		3.07 (+/-2.2)	
	Use of resources	Unplanned admissions (average per year)	**0.55** (+/-1.0) 686	96		0.64 (+/-0.9)		1.09 (+/-1.1)		0.86 (+/-1.3)		1.89 (+/-1.6)		0.73 (+/-0.9)		0.24 (+/-0.6)		0.21 (+/-0.4)		0.5 (+/-1.1)	
		Complex care	145 755	27	**19.2**	26	35.1	12	27.9	8	12.9	2	22.2	5	50	10	34.5	18	10.6	64	17.9
	Palliative care approach	Choice/dem and patient	44 786	6	**5.6**	13	17.1	2	4.7	5	7.7	0	0	4	36.4	2	6.4	1	0.6	21	5.6
		Choice/dem and family	209 782	0	**26.7**	30	39.5	11	25.6	13	20	2	22.2	0	0	5	16.2	64	37.3	80	21.5
		Need (Healthcare professionals)	121 776	6	**15.5**	36	47.4	7	16.3	10	15.6	3	33.3	1	10	4	12.9	23	13.5	37	10
	Age (mean)		**80.89** (+/-11.9) 782	0		79.92 (+/-24.0)		79.09 (+/-9.9)		78.25 (+/-14.4)		67.56 (+/-16.0)		76.45 (+/-13.4)		71.74 (+/-15.6)		85.01 (+/-6.5)		82.62 (+/-11.3)	
	Sex	Male	301 782	0	**38.5**	44	57.9	31	72.1	26	40	6	66.7	5	45.5	16	51.6	34	19.8	141	37.4
		Women	481 782	0	**61.5**	32	42,1	12	27.9	39	60	3	33.3	6	54.5	15	48.4	138	80.2	236	62.6

Distribution of variables according to presence of disease severity and/or progression criteria; *%: percentage of patients with presence of the analysed variable with respect to the total of patients. **ADL**: activities of daily living. **IADL**: instrumental activities of daily living. **GDS/FAST**: Global Deterioration Scale / Functional Assessment Staging **m**: missing patients. **n**: number of valid patients for evaluation of variable. **na**: not applicable. **v**: % valid patients

STROBE Statement—checklist of items that should be included in reports of observational studies

Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of indicators related to end-of-life trajectories.

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract p.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found p. 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p. 6-9, T1, T2 and F1.
Objectives	3	State specific objectives, including any prespecified hypotheses p. 10
Methods		
Study design	4	Present key elements of study design early in the paper p. 10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p. 10-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants p. 11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable p. 11-13, T3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group p. 11
Bias	9	Describe any efforts to address potential sources of bias

		p. 11
Study size	10	Explain how the study size was arrived at p. 10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why p. 11-13, T3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding p. 13
		(*b*) Describe any methods used to examine subgroups and interactions p. 13
		(*c*) Explain how missing data were addressed p. 13
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy NA
		(*e*) Describe any sensitivity analyses p. 13
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed p. 14
		(b) Give reasons for non-participation at each stage NA
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders p. 14, T4 and A1
		(b) Indicate number of participants with missing data for each variable of interest T4 and A1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures T4 and A1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included p. 14-16, T4 and A1
		(*b*) Report category boundaries when continuous variables were categorized NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p. 14-16, T4 and A1
Discussion		
Key results	18	Summarise key results with reference to study objectives p. 16-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias p. 18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p. 18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results p. 19-20
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p. 21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.