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Frailty Degree and Illness Trajectories in Older People towards the End-of-life: a Prospective Observational Study

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Abstract

Objectives: To assess the degree of frailty in older people with different advanced diseases and its relationship with end-of-life illness trajectories and survival.

Methods: Prospective, observational study, including all patients admitted to the Acute Geriatric Unit of the University Hospital of Vic (Barcelona, Spain) during 12 consecutive months in 2014 - 2015. The Frail-VIG index, based on 22 questions assessing 25 different deficits, was used to quantify frailty degree, and participants with palliative care needs were identified using the NECPAL tool. Participants were classified according to their Frail-VIG index scores into 4 groups (i.e., no frailty, mild frailty, moderate frailty, and advanced frailty) and their dominant illness trajectory and followed for up to 2 years, until 2017.

Results: Of the 590 persons with a mean (SD) age of 86.4 (5.6) years recruited, 260 (44.1%) were identified as people with palliative care needs, distributed into cancer (n=31, 11.9%), organ failure (n=79, 30.4%), dementia (n=86, 33.1%), and multimorbidity (n=64, 24.6%) categories. Regardless of the illness trajectory, all 260 people had some degree of frailty, mostly advanced frailty (n=184, 70.8%), and 220 (84.6%) died within two years. The survival curves showed a significant relationship between frailty degree and survival (X^2=69.9, p<0.0001) and differences in the frailty degree between the four illness trajectories (X^2=12.1, p=0.007), revealing different patterns of survival decline according to the frailty degree.

Conclusions: Advanced frailty occurs in all illness trajectories in older people. Frailty indexes may be useful to assess end-of-life older people, regardless of their trajectory.

The survival pattern of people with multimorbidity could support the description of a new composite illness trajectory.

Keywords: Frailty, palliative care, mortality, multimorbidity, longitudinal study

Strengths and Limitations of this Study

- To our knowledge, this is the first study that evaluated the degree of frailty (no frailty, mild frailty, moderate frailty, and advanced frailty) using a frailty index in patients with different advanced illness trajectories.
- This is a real-life study, using tools routinely applied in the Acute Geriatric Unit conducting this study: the NECPAL, to identify people with palliative care needs, and the Frail-VIG index, to measure the degree of frailty and personalization of the interventions.
- In this context, assessing frailty degree may contribute to establish a common language between geriatric and palliative knowledge, with the goal of providing a better care for older people with palliative care needs, specially those in the first end-of-life transition.
- The use of a single computer system collecting the mortality status reported by all health providers prevented loss of patients and missing data, increasing the accuracy of the results.
- Study limitations include bias in the study population towards older patients and a study sample with particular sociodemographic characteristics, due to the limited area covered by the participating hospital, potentially limiting the generalizability of the results.

INTRODUCTION

The model of care for patients with advanced chronic conditions is currently shifting towards a new paradigm, characterized by early identification of persons with any disease or chronic condition who would benefit from palliative care [1,2]—this corresponds to the first transition in palliative care. Despite the benefits of this early identification,[3]the increasing number of people with palliative care needs, together with their high heterogeneity regarding age, needs, diseases, and chronic illnesses, poses novel challenges for early identification and assessment of these patients.[4,5] Indeed, the progression towards the end of life is conditioned by multiple variables and is strictly individual: not all people age in the same way nor reach the final situation with the same circumstances or needs.[6]

In the context of this new paradigm of "early palliative care", some authors have pointed to frailty as a crucial concept for persons needing palliative care —particularly older people with multimorbidity—, their caregivers, and healthcare professionals, to learn to manage the uncertainty and complexity of these end-of-life situations.[7–9] Given the relationship between mortality and frailty,[10] the concept of frailty has been proposed as a criterion useful in the three key steps ensuring good palliative care,[5,6,11,12] including 1) early identification of persons in end-of-life situation (particularly in cases of advanced frailty); 2) multidimensional assessment and situational diagnosis; and 3) drafting an advanced care plan and sharing decision-making.

Regardless of the proposed uses of frailty as an indicator, palliative care and geriatrics have traditionally used this concept, albeit with different perspectives.[8] In the setting of palliative care, frailty has equated to the third end-of-life trajectory and defined as the gradual decline in physical function, typically associated with dementia.[13,14] In

contrast, from the geriatric perspective, frailty is rather a multidimensional clinical entity defined as a vulnerability state against stressing factors due to limited compensatory mechanisms.[15] Of the multiple instruments developed to assess frailty, frailty indexes (i.e., the ratio between accumulated deficits in a given person and the total possible deficits) may have utility in identifying people with frailty for end-of-life care across all disease groups.[8,16]

A better understanding of how to provide the best palliative care for frail older people has become an international priority,[17] and the concept of frailty is increasingly acknowledged as a cornerstone in the assessment and care of persons in an end-of-life situation and needing palliative care.[15,18] However, a consensus on how to use the concept of frailty to provide palliative care to end-of-life people remains to be established.[15,19] In this study, aimed at improving the care of end-of-life people in general, we tested the hypothesis that all end-of-life people are significantly frail irrespective of their underlying diseases and that their frailty is measurable and related to their prognosis.

METHODS

Study Design and Participants

This was a prospective, observational study, including all patients admitted to the Acute Geriatric unit (AGU) at the University Hospital of Vic (Barcelona, Spain) during 12 consecutive months (January 2014 – January 2015. The University Hospital of Vic is a 200-bed acute care hospital covering a population area of 156,000 inhabitants. Admission criteria to the AGU were age ≥ 85 years, cognitive decline, and/or end-of-life situation; no exclusion criteria were defined. The methods, including study design, variables, data

sources, and study size have been described in a previous study conducted in the same setting.[20] The study results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[21] All patients and family relatives of patients with advanced dementia situation (GDS ≥ 6) signed the written informed consent for participation before any data was recorded. The study protocol was approved by the Ethics Committee of the University Hospital of Vic (2,014,850 PR80); this study was conducted in accordance with the Helsinki Declaration and the local Personal Data Protection Law (LOPD 15/1999).

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Variables and Data Sources

Frailty was assessed using the Frail-VIG index, a tool consisting in 22 questions to assess 25 deficits commonly associated with age and adverse health outcomes, based on the cumulative deficit model of frailty. The Frail-VIG index is a continuous variable ranging from 0 to 1 and classified into 4 groups: no frailty (Frail-VIG index score <0.2), mild frailty (Frail-VIG index score 0.2-0.35), moderate frailty (Frail-VIG index score 0.36-0.5), and advanced frailty (Frail-VIG index score >0.5) [20]. End-of-life people were identified using the NECPAL tool, a validated tool for the early identification of the need for palliative care among individuals with limited life expectancy.[22,23] End-of-life people were classified into the 3 archetypal end-of-life trajectories according to the

severity and/or progression criteria for their main underlying disease: cancer, organ failure (including chronic pulmonary disease, chronic heart disease, serious chronic liver disease, and serious chronic renal disease), and dementia (including other chronic neurological diseases). People with palliative care needs without a predominant advanced disease were identified as "multimorbidity" group or trajectory, since all had 2 or more underlying chronic conditions.

After inclusion of the last patient in the study (i.e., last admitted patient in the AGU before January 15th, 2015) and before starting data analysis in 2017, patients were followed for up to 24 months (2015 - beginning 2017). Information regarding the patient status after the 24-month follow-up period was obtained from the Shared Medical Record in Catalonia (HC3), a sole electronic database accessible to all healthcare providers in Catalonia that allows healthcare professionals to reliably determine whether a patient is “active” (alive) or deceased (including date of death).[24]

Statistical Analysis

Qualitative variables were presented as frequencies and percentages, whereas quantitative variables were presented as the mean and the standard deviation (SD). Qualitative variables were compared using the Pearson’s chi-squared test. The relationship between frailty degree and survival has been evaluated using the C-statistics (to analyze the concordance), the log-rank test (to evaluate the association) and the ROC curves (to measure the prognostic capability of mortality at 24 months). Survival curves were plotted using the Kaplan-Meier estimator, and compared using the log-rank test. The significance level for all analyses was set at a two-sided α=0.05. The descriptive statistics analysis of the variables was performed using the SPSS software program (IBM; Chicago,

IL; USA), and the survival analysis was performed using the Survival, pROC, and RMS packages from the R project (https://www.r-project.org).

RESULTS

Patient Characteristics and End-of-life Status

The study included 590 patients with a mean (SD, range) age of 86.4 (5.6, 48-105) years, of whom 339 (57.5%) were women. Based on the Frail-VIG index scores, 543 (92%) patients showed some degree of frailty, with 111 (18.8%), 207 (35.1%), and 225 (38.1%) patients showing mild, moderate and advanced frailty, respectively. Of the 590 patients included, 53 (8.9%) died during hospitalization, and 260 (44.1%) were identified as end-of-life people; of these, 31 (11.9%), 79 (30.4%), 86 (33.1%), and 64 (24.6%) were classified in cancer, organ failure, dementia, and multimorbidity illness trajectories, respectively.

Relationship between End-of-life Status and Patient Characteristics

End-of-life people and non-end-of-life people had similar mean age (86.3 and 86.5 years, respectively) and sex frequencies (54.6% and 59.7% females, respectively), but differed in the distribution among the 4 frailty groups: all end-of-life people (260) and 283 (85.8%) of the 330 non-end-of-life people were frail to some extent, with 252 (96.9%) and 180 (54.5%) showing moderate or advanced frailty in the end-of-life people and non-end-of-life people group, respectively. Table 1 summarizes the frequencies of end-of-life and non-end-of-life people across the various frailty categories.

Table 1. Classification of study patients according to the Frail-VIG index scores

and end-of-life status (n=590), n (%)

	No frail	Mild Frailty	Moderate Frailty	Advanced Frailty
EOLp	0 (0)	8 (3.1)	68 (26.1)	184 (70.8)
NonEOLp	47 (14.3)	103 (31.2)	139 (42.1)	41 (12.4)

EOLp: End-of-life people, NonEOLp: Non End-of-life people

Correspondingly, median Frail-VIG index scores were significantly higher in end-of-life compared to non-end-of-life people: 0.56 and 0.36, respectively ($p<0.001$). In end-of-life people, the predominant frailty degree was persistently advanced for all end-of-life trajectory categories: cancer, organ failure, dementia, and multimorbidity (range 68-75%) (Table 2). All end-of-life people in the multimorbidity trajectory (n=64) were classified in the moderate and advanced frailty groups.

Table 2. Classification of end-of-life people according to Frail-VIG index scores and end-of-life trajectory (n=260), n (%)

	No frail	Mild Frailty	Moderate Frailty	Advanced Frailty	Total
Cancer	0 (0)	3 (9.7)	7 (22.6)	21 (67.7)	31 (11.9)
Organ Failure	0 (0)	4 (5.1)	20 (25.3)	55 (69.6)	79 (30.4)

Dementia	0 (0)	1 (1.1)	25 (29.1)	60 (69.8)	86 (33.1)
Multimorbidity	0 (0)	0 (0)	16 (25.0)	48 (75.0)	64 (24.6)
Total	0 (0)	8 (3.1)	68 (26.1)	184 (70.8)	260

Relationship between Frailty Degree and Survival

During the 2-year follow up period, a total of 338 (57.3%) study patients died. Mortality was significantly higher in end-of-life people than in non-end-of-life people: 220 (84.6%) and 118 (35.7%), respectively ($p<0.001$). The log-rank test comparing the survival curves of each frailty degree revealed significant differences in the overall population ($X^2 = 423$, $p < 0.0001$), end-of-life people ($X^2 = 69.9$, $p<0.0001$), and non-end-of-life people ($X^2 = 122$, $p<0.0001$) (Figure 1). Correspondingly, the C coefficient for concordance between the survival time and the Frail-VIG score was 0.8, indicating that higher scores of the Frail-VIG index are associated with lower survival.

Survival curves differed among the different end-of-life trajectories, including the 3 archetypal end-of-life trajectories and the multimorbidity trajectory ($X^2=12.1$, $p=0.007$), revealing different patterns of survival decline according to the frailty degree (Figure 2). Specifically, the presence of moderate or advanced frailty resulted in important differences in survival in dementia and multimorbidity end-of-life trajectory patients, but not in cancer end-of-life trajectory ones. Also, regardless of the frailty groups, deaths in the cancer end-of-life trajectory accumulated quickly, whereas in the other trajectories accumulated more progressively. The frequencies of death at the end of the 2-year follow-up period for each trajectory in end-of-life people are presented in Table 3.

Table 3. Status of end-of-life people according to the Frail-VIG index scores and end-of-life trajectory after the 2-year follow-up (n=260), n (%)

	n	Status	Mild Frailty	Moderate Frailty	Advanced Frailty	Total
Cancer	31	Dead	2 (6.5)	7 (22.6)	21 (67.7)	30 (96.8)
		Alive	1 (3.2)	0 (0)	0 (0)	1 (3.2)
Organ Failure	79	Dead	2 (2.5)	16 (20.2)	54 (68.4)	72 (91.1)
		Alive	2 (2.5)	4 (5.1)	1 (1.3)	7 (8.9)
Dementia	86	Dead	1 (1.2)	6 (6.9)	55 (64.0)	62 (72.1)
		Alive	0 (0)	19 (22.1)	5 (5.8)	24 (27.9)
Multimorbidity	64	Dead	0 (0)	8 (12.5)	48 (75.0)	56 (87.5)
		Alive	0 (0)	8 (12.5)	0 (0)	8 (12.5)

Prognosis Value of the Frail-VIG Index

The prognostic value of the Frail-VIG index for the end-of-life people (expressed as the AUC of the ROC analysis) was 0.87 (95% CI:0.83-0.92) after one year and 0.87 (95%

CI:0.84-0.92) after two years of follow-up. Of the 184 end-of-life people with advanced frailty (Frail-VIG index score > 0.5), 178 (96.7%) had died at two years of follow-up. The AUC differed among each of the faour end-of-life trajectories: cancer (1 and 0.93), organ failure (0.86 and 0.90), dementia (0.92 and 0.92) and multimorbidity (0.91 and 0.94), after one and two years of follow-up, respectively. Regarding the sensitivity and specificity of the Frail-VIG index as prognosis factor of mortality, the most sensitive and specific cut-off was 0.5 at both one and two years after follow-up, showing a sensitivity of 0.81 and 0.85 and a specificity of 0.83 and 0.81, respectively.

DISCUSSION

In this prospective, observational study including 590 patients admitted at an Acute Geriatric unit (AGU), we found that all older patients were frail towards the end of life (the prevalence of moderate-to-advanced frailty was 97% among people within an end-of-life trajectory and 55% outside it). Furthermore, advanced frailty was the predominant frailty category (ranged 68 to 75%) for all end-of-life trajectories: cancer, organ failure, dementia, and multimorbidity. Overall, the Frail-VIG index had a high capacity to predict death at one and two years (AUC 0.87), albeit to a different extent for the end-of-life categories cancer, organ failure, dementia and multimorbidity (AUC was always >0.86 for mortality at either one or two years). This finding confirms the hypothesis that the degree of frailty is related to prognosis regardless of the illness trajectory.

The characteristics and outcomes of the cohort assessed in this study, which included all patients admitted to an Acute Geriatric unit (AGU), were similar to those previously reported. All the persons assessed in this study had a Frail-VIG index score <0.8, similar to previous studies showing that the theoretical maximum score is 0.7. According to these studies, the accumulation of 2/3 of all possible deficits (Frailty index score >0.7) results

in death due to the person's inability to overcome more deficits, a phenomenon defined as system failure.[25,26] Likewise, similar to previous studies in other populations, the mortality rate in our cohort was nearly 100% for the end of life people with frailty index score >0.5.[26,27]

Furthermore, we provide evidence showing that frailty, measured using the Frail-VIG index, significantly influenced survival irrespective of the advanced illness and end-of-life trajectory. In spite of this general influence, the survival curves according to the frailty degree followed different patterns for the four end-of-life trajectories, enabling the description of different frailty or deficit accumulation end-of-life trajectories according to the main disease. Thus, in end-of-life people with cancer, mortality rates were high regardless of the frailty degree (moderate or advanced), leading to the hypothesis, similar to recent studies, that cancer patients have a catastrophic accumulation of deficits.[28] In contrast, end-of-life people with dementia showed different mortality rates according to their frailty degree and died progressively, likely due to the natural history of the disease, suggesting a slower accumulation of deficits. People with multimorbidity and advanced frailty shows a survival profile similar to people with cancer, while those with moderate frailty have a survival rate more similar to people with dementia. Finally, persons with an organ disease would accumulate deficits in episodes, even though prospective studies with serial frailty indexes would be required to test this hypothesis.

In this regard, similar to recent studies describing different trajectories according to the evolution of the social, spiritual or psychological situation of end-of-life people,[3] prospective studies following the degree of frailty using electronic frailty indexes have described three different trajectories (i.e., rapidly rising frailty, moderately increasing frailty, and stable frailty).[28] Even though more studies would be required to describe

different end-of-life frailty trajectories, the fact that each end-of-life trajectory resulted in different mortality curves supports a dynamic view of end-of-life people.

The traditional association of frailty to the "third end-of-life trajectory" (i.e., dementia) [13,14] has probably been influenced by the lack of specific prognostic instruments for persons in this trajectory, unlike those in the cancer [29,30] or organ disease [31,32] trajectories. Our results regarding the high prevalence of frailty in all end-of-life trajectories support the validity of the concept that frailty may be present in all trajectories beyond the dementia trajectory. In addition to expanding the concept of frailty, our study underscores the need to consider a further development of the end-of-life trajectories. Of the 260 people who were identified as people in end-of-life situation, 24.6% did not have severity criteria for a single disease, although all of them had at least 2 chronic conditions. The identification of this cluster of people with advanced frailty and multimorbidity can help provide them early palliative care, and the benefits derived from it.[33,34]

Moreover, the fact that the concept of frailty is valid for all end-of-life trajectories grants practical uses of quantitative frailty assessment in the management and identification of end-of-life people.[8] First, assessment and quantification of frailty using a frailty index, which is suitable to synthesize the results of a multidimensional evaluation, can be useful to validate the identification of people in an end-of-life situation;[12] secondly, due to its ability to discriminate between different degrees of severity, frailty indexes can be very useful to healthcare professionals for the situational diagnosis of the first and second end-of-life transition,[6,12] and monitorization of end-of-life people evolution;[35,36] and finally, quantification of frailty would enable palliative care customization [37,38] and engage people, caregivers and healthcare professionals in sharing decision-making and advance care planning.

The results of this study should be interpreted in the context of some limitations, particularly regarding the generalizability of the results. Firstly, the recruitment strategy based on an AGU solely was likely to enrich our study sample with older patients and consequently, the results of this study may be only applicable to older patients. Secondly, although the study site was a reference hospital covering an area of 156,000 inhabitants, the sociodemographic characteristics of our sample might not match those of the overall population. Finally, the analysis of end-of-life people frailty across the various end-of-life trajectory categories importantly reduced the number of patients in each group, thus limiting the statistical power of these analyses. However, despite the reduced number of patients in some groups, our analysis yielded statistically significant results. In spite of its limitations, to our knowledge, this study is the first to evaluate the degree of frailty using a frailty index in patients identified as end-of-life people. Frailty was evaluated in a cohort of geriatric patients, including end-of-life and non-end-of-life people, and the data for this study was collected during routine geriatric assessment, as opposed to previous studies that used electronic health record data to evaluate the degree of frailty.[39] Moreover, the single computer information system of Catalonia (HC3) that collects the medical records and mortality status of all patients reported by all health providers prevented loss of patients up to follow-up.[24] Consequently, the lack of missing data due to the HC3 system, along with the use of standard and validated tools to identify end-of-life people (NECPAL) and to measure frailty (Frail-VIG index) increased the accuracy of the results obtained from this study. The early identification of people needing palliative care and the more accurate definition of the various end-of-life trajectories opened the door to a novel perspective of palliative care.[40] In this regard, the use of frailty as an overarching concept in the assessment of all people in an end-of-

life situation —at least of those with a multimorbid profile— might contribute to go one step further in this novel approach to palliative care.

CONCLUSIONS

Our results showed that all end-of-life people were frail (mostly with advanced frailty) irrespective of the end-of-life trajectory. Their degree of frailty, measured using the Frail-VIG index, influenced mortality. This indicates a close relationship between frailty, end-of-life status, and mortality for all people who die. Measuring frailty using a frailty index could be useful in routine practice for healthcare professionals to understand the heterogeneous nature of people needing palliative care and tailor their care to the patient's needs. The survival pattern of people with multimorbidity could support the description of a composite illness trajectory for this patient group.

DECLARATIONS

Ethics Approval and Consent to Participate

All patients and family relatives of patients with advanced dementia situation (GDS $\geq$ 6) signed the written informed consent for participation before any data was recorded. The study protocol was approved by the Ethics Committee of the University Hospital of Vic (2,014,850 PR80). This study was conducted in accordance with the Helsinki Declaration and the local Personal Data Protection Law (LOPD 15/1999).

Consent for publication

Not applicable.

Data Sharing

The anonymized datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

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Author's contributions

JAN, AT, JCM, and XGB were responsible for the conception and design of the study. JAN coordinated and substantially contributed to the data collection. JCM and RO performed the statistical analysis. All authors (JAN, SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) were involved in interpretation of data. JAN wrote the initial draft of the manuscript and all the other authors (SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) critically revised the manuscript. All authors (JAN, SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) have provided approval for the final version of the manuscript submitted for publication and agree to be accountable for all aspects of the work.

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REFERENCES

1 Boyd K, Murray SSA. Recognising and managing key transitions in end of life care. *BMJ* 2010;**341**:c4863.

2 Gomez-Batiste X, Martinez-Munoz M, Blay C, *et al.* Identifying patients with chronic conditions in need of palliative care in the general population: development of the NECPAL tool and preliminary prevalence rates in Catalonia. *BMJ Support Palliat Care* 2013;**3**:300–8.

3 Murray SA, Kendall M, Mitchell G, *et al.* Palliative care from diagnosis to death. *BMJ* 2017;**356**:j878.

4 Kimbell B, Murray SA, Macpherson S BK. Embracing inherent uncertainty in advanced illness. *BMJ Br Med J* 2016;**354:i3802**.

5 Gómez-Batiste X, Blay C, Broggi MA, *et al.* Ethical Challenges of Early Identification of Advanced Chronic Patients in Need of Palliative Care. *J Palliat Care* 2018;**33**:247–51.

6 Amblàs-Novellas J, Espaulella J, Rexach L et al, *et al.* Frailty, severity, progression and shared decision-making: A pragmatic framework for the challenge of clinical complexity at the end of life. *Eur Geriatr Med* 2015;**6**:189–194.

7 Cardona-Morrell M, Lewis E, Suman S, *et al.* Recognising older frail patients near the end of life: What next? *Eur J Intern Med* 2017;**45**:84–90.

8 Koller K, Rockwood K. Frailty in older adults: Implications for end-of-life care. *Cleve Clin J Med* 2013;**80**:168–74.

9 Stow D, Spiers G, Matthews FE, *et al.* What is the evidence that people with frailty have needs for palliative care at the end of life? A systematic review and narrative synthesis. *Palliat Med* 2019;**33**:399–414.

10 Mousa A, Savva GM, Mitnitski A, *et al.* Is frailty a stable predictor of mortality across time? Evidence from the Cognitive Function and Ageing Studies. *Age Ageing* 2018;**47**:721–7.

11 Pialoux T, Goyard J, Hermet R. When frailty should mean palliative care. *J Nurs Educ Pract* 2013;**3**:75–84.

12 Pollack LR, Goldstein NE, Gonzalez WC, *et al.* The Frailty Phenotype and Palliative Care Needs In Older Survivors of Critical Illness Lauren. *J Am Geriatr Soc* 2018;**65**:1168–75.

13 Lunney JR, Lynn J, Foley DJ, *et al.* Patterns of functional decline at the end of life. *JAMA* 2003;**289**:2387–92.

14 Murray S a, Boyd K, Sheikh A. Palliative care in chronic illness. *BMJ* 2005;**330**:611–2.

15 Rodríguez-Mañas L, Féart C, Mann G, *et al.* Searching for an operational definition of frailty: A delphi method based consensus statement. the frailty operative definition-consensus conference project. *Journals Gerontol - Ser A Biol Sci Med Sci* 2013;**68**:62–7.

16 Cesari M, Gambassi G, van Kan GA, *et al.* The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing* 2014;**43**:10–2.

17 Bone AE, Morgan M, Maddocks M, *et al.* Developing a model of short-term

integrated palliative and supportive care for frail older people in community settings: perspectives of older people, carers and other key stakeholders. *Age Ageing* 2016;**45**:863–73.

18 Cesari M, Prince M, Thiyagarajan JA, *et al.* Frailty: An Emerging Public Health Priority. *J Am Med Dir Assoc* 2016;**17**:188–92.

19 Moorhouse P, Rockwood K, Morley JE, *et al.* Frailty Consensus: A Call to Action. *J Am Med Dir Assoc* 2013;**14**:392–7.

20 Amblàs-Novellas J, Martori JC, Espaulella J, *et al.* Frail-VIG index: a concise frailty evaluation tool for rapid geriatric assessment. *BMC Geriatr* 2018;**18**:29.

21 von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–7.

22 Gómez-Batiste X, Martínez-Muñoz M, Blay C, *et al.* Prevalence and characteristics of patients with advanced chronic conditions in need of palliative care in the general population: A cross-sectional study. *Palliat Med* 2014;**28**:302–11.

23 Gómez-Batiste X, Turrillas P, Tebé C, *et al.* NECPAL tool prognostication in advanced chronic illness: A rapid review and expert consensus. *BMJ Support Palliat Care* Published Online First: 2020. doi:10.1136/bmjspcare-2019-002126

24 Solans O, Gallego C, Garcia-Cuyas F, *et al.* Shared Medical Record, Personal Health Folder and Health and Social Integrated Care in Catalonia. In: *New Perspectives in Medical Records*. Springer, Cham 2017. 49–64.

25 Rockwood K, Mitnitski A. Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty. Clin. Geriatr. Med. 2011;**27**:17–26.

26 Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. *Mech Age Dev* 2006;**127**:494–6.

27 Rockwood K, Rockwood MRH, Mitnitski A. Physiological redundancy in older adults in relation to the change with age in the slope of a frailty index. *J Am Geriatr Soc* 2010;**58**:318–23.

28 Stow D, Matthews FE, Hanratty B. Frailty trajectories to identify end of life: A longitudinal population-based study. *BMC Med* 2018;**16**:1–7.

29 Evans C, McCarthy M. Prognostic uncertainty in terminal care: can the Karnofsky index help? *Lancet (London, England)* 1985;**1**:1204–6.

30 Anderson F, Downing GM, Hill J, *et al.* Palliative Performance Scale (PPS): A new tool. *J Palliat Care* 1996;**12**:5–11.

31 van Dijk WD, van den Bemt L, van den Haak-Rongen S, *et al.* Multidimensional prognostic indices for use in COPD patient care. A systematic review. Respir. Res. 2011;**12**:151.

32 Walter LC, Brand RJ, Counsell SR, *et al.* Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA* 2001;**285**:2987–94.

33 Moine S, Murray SA, Boyd K, *et al.* Palliative care and the endless cycle of serious health-related suffering. Lancet. 2018;**392**:471–2.

34 Aldridge MD, Bradley EH. Epidemiology and patterns of care at the end of life: Rising complexity, shifts in care patterns and sites of death. *Health Aff* 2017;**36**:1175–83.

35 Gill TM, Gahbauer E a, Allore HG, *et al.* Transitions between frailty states among community-living older persons. *Arch Intern Med* 2006;**166**:418–23.

36 Liu ZY, Wei YZ, Wei LQ, *et al.* Frailty transitions and types of death in Chinese older adults: A population-based cohort study. *Clin Interv Aging* 2018;**13**:947–56.

37 The Picker Institute. *Patient - Centered Care 2015 : Scenarios , Vision , Goals & Next Steps*. 2004.

38 Cohen-Mansfield J, Skornick-Bouchbinder M, Brill S. Trajectories of End of Life: A Systematic Review. *Journals Gerontol - Ser B Psychol Sci Soc Sci* 2018;**73**:564–72.

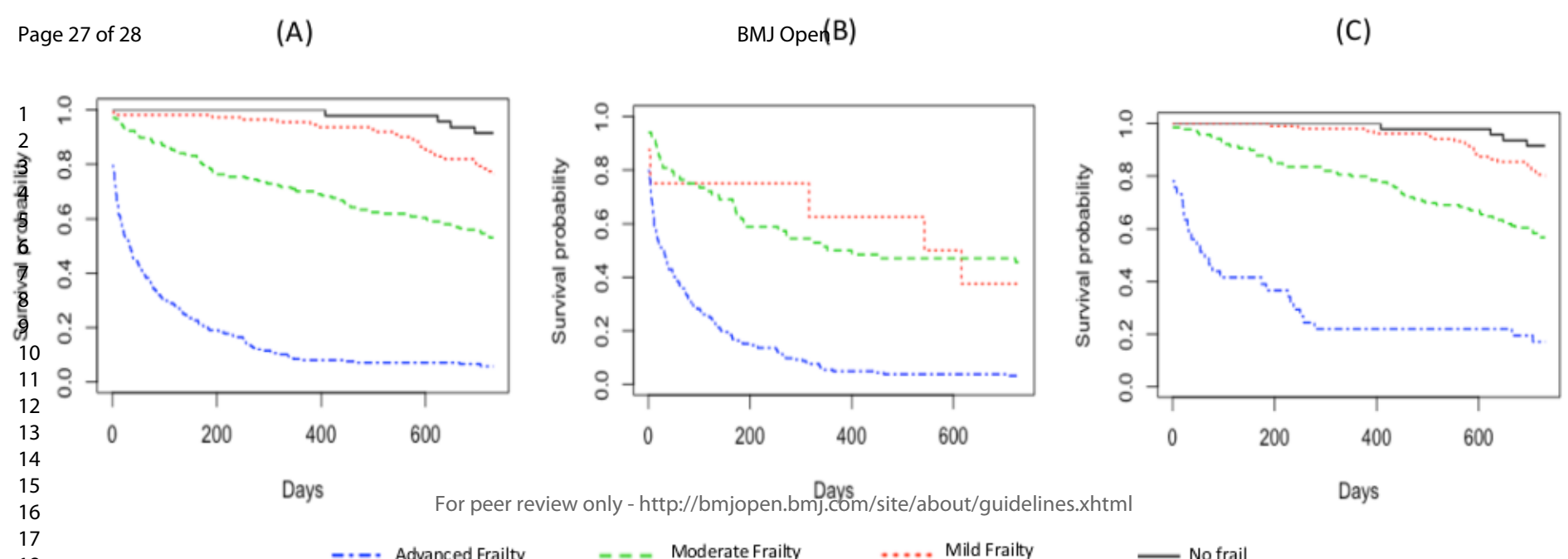
39 Clegg A, Bates C, Young J, *et al.* Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* 2016;**45**:353–60.

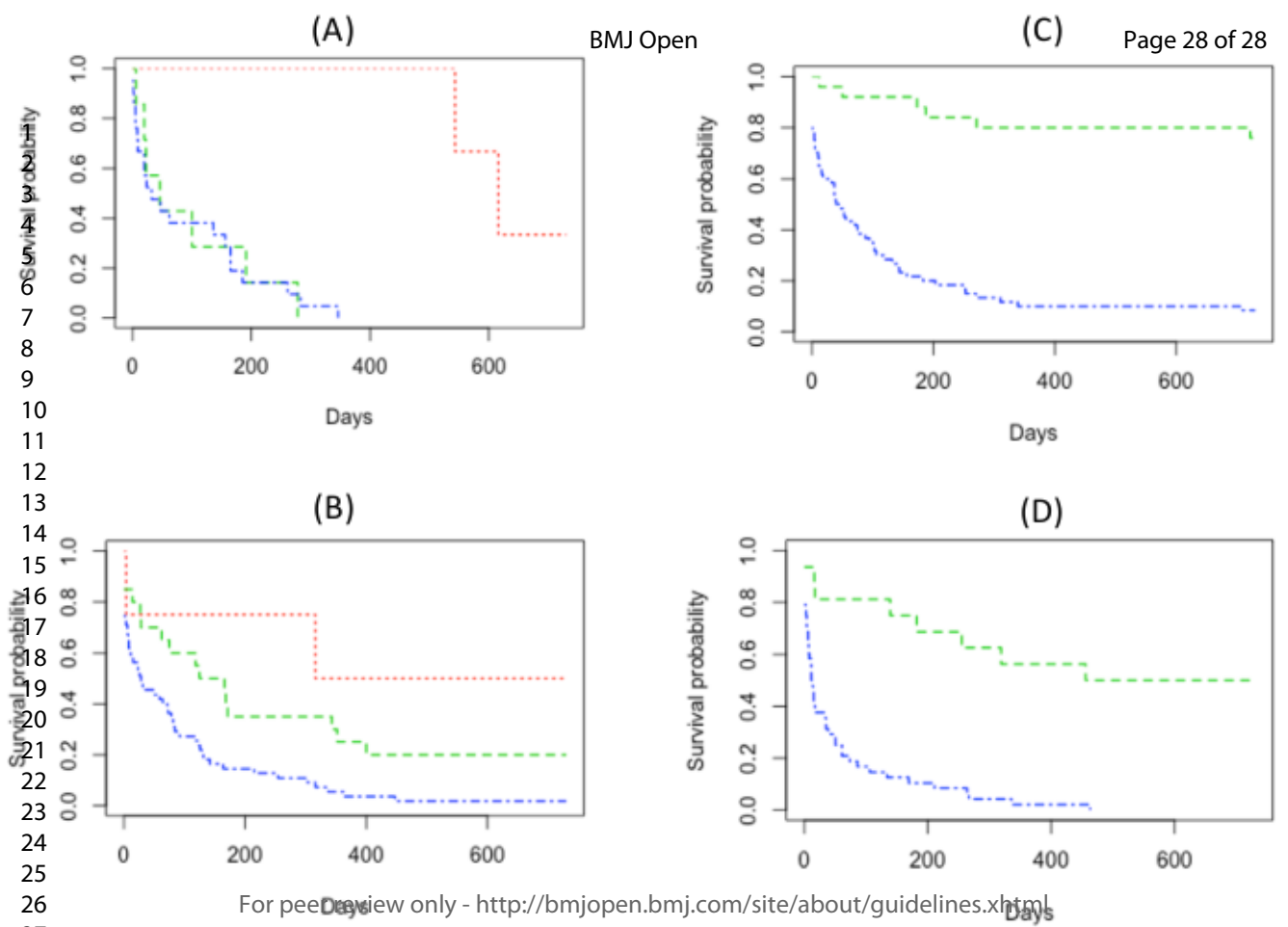
40 Amblàs-Novellas J, Murray SA, Espaulella J, *et al.* Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of prognostic indicators related to end-of-life trajectories. *BMJ Open* 2016;**6**:e012340.

FIGURE LEGENDS

Figure 1. Survival according to the degree of frailty in (A) the total study patients, (B) end-of-life people, and (C) Non End-of-life people.

Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.





STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6, 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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	7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
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	9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 11

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-13 7 N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
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	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
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	18

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

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Frailty degree and illness trajectories in older people towards the end-of-life: a prospective observational study

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Frailty Degree and Illness Trajectories in Older People towards the End-of-life: a Prospective Observational Study

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Abstract

Objectives: To assess the degree of frailty in older people with different advanced diseases and its relationship with end-of-life illness trajectories and survival.

Methods: Prospective, observational study, including all patients admitted to the Acute Geriatric Unit of the University Hospital of Vic (Barcelona, Spain) during 12 consecutive months (2014 – 2015). The Frail-VIG index, based on 22 questions assessing 25 deficits, was used to quantify frailty degree, and participants with palliative care needs were identified using the NECPAL tool. Participants were classified according to their Frail-VIG index scores into 4 groups (i.e., no frailty, mild frailty, moderate frailty, and advanced frailty) and their dominant illness trajectory and followed for up to 2 years. The relationship between frailty degree and survival was evaluated using the C-statistics and the ROC curves. Survival curves were plotted using the Kaplan-Meier estimator and compared using the log-rank test. A Cox proportional hazards model with the interaction between frailty degree and illness trajectories was calculated.

Results: Of the 590 persons with a mean (SD) age of 86.4 (5.6) years recruited, 260 (44.1%) were identified as people with palliative care needs, distributed into cancer (n=31, 11.9%), organ failure (n=79, 30.4%), dementia (n=86, 33.1%), and multimorbidity (n=64, 24.6%) categories. All 260 people identified as end-of-life had some degree of frailty, mostly advanced frailty (n=184, 70.8%), regardless of the illness trajectory, and 220 (84.6%) died within two years. Cox regression analyses showed that the effect of frailty degree on survival, whereby increased frailty was associated with decreased survival, depended on the illness trajectories (p<0.01 for all the coefficients).

Conclusions: All older people towards the end-of-life are frail, mostly with advanced frailty. The degree of frailty, the different illness trajectories, and survival show a tight correlation. Frailty indexes may be useful to assess end-of-life older people, regardless of their trajectory.

Keywords: Frailty, palliative care, mortality, multimorbidity, longitudinal study

Strengths and Limitations of this Study

- To our knowledge, this is the first study that evaluated the degree of frailty using a frailty index in older patients with different advanced illness trajectories.
- This is a real-life study, using tools routinely applied in the Acute Geriatric Unit conducting this study: the NECPAL, to identify people with palliative care needs, and the Frail-VIG index, to measure the degree of frailty and personalization of the interventions.
- In this context, assessing frailty degree may contribute to establish a common language between geriatric and palliative knowledge, with the goal of providing a better care for older people with palliative care needs, specially those in the first end-of-life transition.
- The use of a single computer system collecting the mortality status reported by all health providers prevented loss of patients and missing data, increasing the accuracy of the results.
- The results from this study were obtained in a very old population, potentially limiting their generalizability and raising the need for further studies in younger populations.

INTRODUCTION

The model of care for patients with advanced chronic conditions is currently shifting towards a new paradigm, characterized by early identification of persons with any disease or chronic condition who would benefit from palliative care [1,2]—this corresponds to the first transition in palliative care. Despite the benefits of this early identification,[3]the increasing number of people with palliative care needs, together with their high heterogeneity regarding age, needs, diseases, and chronic illnesses, poses novel challenges for early identification and assessment of these patients.[4,5] Indeed, the progression towards the end of life is conditioned by multiple variables and is strictly individual: not all people age in the same way nor reach the final situation with the same circumstances or needs.[6]

In the context of this new paradigm of "early palliative care", some authors have pointed to frailty as a crucial concept for persons needing palliative care —particularly older people with multimorbidity—, their caregivers, and healthcare professionals, to learn to manage the uncertainty and complexity of these end-of-life situations.[7–9] Given the relationship between mortality and frailty,[10] the concept of frailty has been proposed as a criterion useful in the three key steps ensuring good palliative care,[5,6,11,12] including 1) early identification of persons in end-of-life situation (particularly in cases of advanced frailty); 2) multidimensional assessment and situational diagnosis; and 3) drafting an advanced care plan and sharing decision-making.

Regardless of the proposed uses of frailty as an indicator, palliative care and geriatrics have traditionally used this concept, albeit with different perspectives.[8] In the setting of palliative care, frailty has equated to the third end-of-life trajectory and defined as the gradual decline in physical function, typically associated with dementia.[13,14] In

contrast, from the geriatric perspective, frailty is rather a multidimensional clinical entity defined as a vulnerability state against stressing factors due to limited compensatory mechanisms.[15] Of the multiple instruments developed to assess frailty, frailty indexes (i.e., the ratio between accumulated deficits in a given person and the total possible deficits) may have utility in identifying people with frailty for end-of-life care across all disease groups.[8,16]

A better understanding of how to provide the best palliative care for frail older people has become an international priority[17] and, considering the increased difficulty of identifying dying people in very old age (>85 years),[18–20] the concept of frailty is increasingly acknowledged as a cornerstone in the assessment and care of persons in an end-of-life situation and needing palliative care.[15,21] However, a consensus on how to use the concept of frailty to provide palliative care to end-of-life people remains to be established.[15,22,23] In this study, aimed at improving the care of end-of-life older people, we assessed the degree of frailty in a geriatric cohort with different advanced diseases and its relationship with end-of-life illness trajectories and survival.

METHODS

Study Design and Participants

This was a prospective, observational study, including all patients admitted to the Acute Geriatric unit (AGU) at the University Hospital of Vic (Barcelona, Spain) during 12 consecutive months (January 2014 – January 2015. The University Hospital of Vic is a 200-bed acute care hospital covering a population area of 156,000 inhabitants. Admission criteria to the AGU were age ≥ 85 years, cognitive decline, and/or end-of-life situation; no exclusion criteria were defined. The methods, including study design, variables, data

sources, and study size have been described in a previous study.[24] The results of this subanalysis are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[25] All patients and family relatives of patients with advanced dementia situation (GDS $\geq$ 6) signed the written informed consent for participation before any data was recorded. The study protocol was approved by the Ethics Committee of the University Hospital of Vic (2,014,850 PR80); this study was conducted in accordance with the Helsinki Declaration and the local Personal Data Protection Law (LOPD 15/1999).

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Variables and Data Sources

Frailty was assessed using the Frail-VIG index, a tool consisting in 22 questions to assess 25 deficits commonly associated with age and adverse health outcomes, based on the cumulative deficit model of frailty. Fifteen of the 22 questions refer to chronic conditions, including geriatric conditions and syndromes. The Frail-VIG index is a continuous variable ranging from 0 to 1 and classified into 4 groups: no frailty (Frail-VIG index score <0.2), mild frailty (Frail-VIG index score 0.2-0.35), moderate frailty (Frail-VIG index score 0.36-0.5), and advanced frailty (Frail-VIG index score >0.5). In addition to its predicitive value, previous studies have shown the content, construct, criteria, and convergent-divergent construct validity of the frail-VIG index [24,26,27]. End-of-life

people were identified using the NECPAL tool, a validated tool for the early identification of the need for palliative care among individuals with limited life expectancy.[28–30] End-of-life people were classified into the 3 archetypal end-of-life trajectories according to the severity and/or progression criteria for their main underlying disease: cancer, organ failure (including chronic pulmonary disease, chronic heart disease, serious chronic liver disease, and serious chronic renal disease), and dementia (including other chronic neurological diseases). People with palliative care needs without a predominant advanced disease were identified as "multimorbidity" group or trajectory, since all had 2 or more underlying chronic conditions.

After inclusion of the last patient in the study (i.e., last admitted patient in the AGU before January 15th, 2015) and before starting data analysis in 2017, patients were followed for up to 24 months (2015 - beginning 2017). Information regarding the patient status after the 24-month follow-up period was obtained from the Shared Medical Record in Catalonia (HC3), a sole electronic database accessible to all healthcare providers in Catalonia that allows healthcare professionals to reliably determine whether a patient is “active” (alive) or deceased (including date of death).[31]

Statistical Analysis

Qualitative variables were presented as frequencies and percentages, whereas quantitative variables were presented as the mean and the standard deviation (SD). Qualitative variables were compared using the Pearson’s chi-squared test. The concordance between frailty degree and survival has been evaluated using the C-statistics and the ROC curves were used to assess the ability of the Frail-VIG index to predict survival at 24 months by measuring their AUC. Survival curves were plotted using the Kaplan-Meier estimator, and survival curves for each illness trajectory were compared using the log-rank test. A

Cox proportional hazards model with the interaction between frailty degree and illness trajectories was calculated. The assumption of proportional hazards was checked using the Schoenfeld residuals and a goodness-of-fit test. The significance level for all analyses was set at a two-sided α=0.05. The descriptive statistics analysis of the variables was performed using the SPSS software program (IBM; Chicago, IL; USA), and the survival analysis was performed using the *survival and pROC packages* from the R project (https://www.r-project.org).

RESULTS

Patient Characteristics and End-of-life Status

The study included 590 patients with a mean (SD, range) age of 86.4 (5.6, 48-105) years, of whom 339 (57.5%) were women. Based on the Frail-VIG index scores, 543 (92%) patients showed some degree of frailty, with 111 (18.8%), 207 (35.1%), and 225 (38.1%) patients showing mild, moderate and advanced frailty, respectively. Of the 590 patients included, 53 (8.9%) died during hospitalization, and 260 (44.1%) were identified as end-of-life people; of these, 31 (11.9%), 79 (30.4%), 86 (33.1%), and 64 (24.6%) were classified in cancer, organ failure, dementia, and multimorbidity illness trajectories, respectively.

Relationship between End-of-life Status and Patient Characteristics

End-of-life people and non-end-of-life people had similar mean age and sex frequencies, but differed in the distribution among the 4 frailty groups: all end-of-life people (260) and 283 (85.8%) of the 330 non-end-of-life people were frail to some extent, with 252 (96.9%) and 180 (54.5%) showing moderate or advanced frailty in the end-of-life people

and non- end-of-life people group, respectively. Table 1 summarizes the frequencies of end-of-life and non-end-of-life people across the various frailty categories and their main demographic characteristics.

Table 1. Classification of study patients according to the Frail-VIG index scores, demographic characteristics, and end-of-life status (n=590)

	Demographic characteristics		**Frailty Degree, *n (%)***			
	Age (years), *mean (SD)*	Sex (% of women)	Not frail	Mild Frailty	Moderate Frailty	Advanced Frailty
EOLp	86.3 (5.8)	54.6	0 (0)	8 (3.1)	68 (26.1)	184 (70.8)
NonEOLp	86.5 (5.4)	59.7	47 (14.3)	103 (31.2)	139 (42.1)	41 (12.4)

EOLp: End-of-life people, NonEOLp: Non End-of-life people; SD, standard deviation

Correspondingly, median Frail-VIG index scores were significantly higher in end-of-life compared to non-end-of-life people: 0.56 and 0.36, respectively ($p<0.001$). In end-of-life people, the predominant frailty degree was persistently advanced for all end-of-life trajectory categories: cancer, organ failure, dementia, and multimorbidity (range 68-75%) (Table 2). All end-of-life people in the multimorbidity trajectory (n=64) were classified in the moderate and advanced frailty groups.

Table 2. Classification of end-of-life people according to demographic characteristics, Frail-VIG index scores and end-of-life trajectory (n=260), n (%)

	Demographic characteristics		**Frailty degree, n (%)**				
	Age (years),	Sex (% of women)	Not frail	Mild Frailty	Moderate Frailty	Advanced Frailty	Total

	mean (SD)						
Cancer	85.7 (5.4)	45.2	0 (0)	3 (9.7)	7 (22.6)	21 (67.7)	31 (11.9)
Organ Failure	86.9 (5.3)	46.8	0 (0)	4 (5.1)	20 (25.3)	55 (69.6)	79 (30.4)
Dementia	85.4 (5.3)	65.1	0 (0)	1 (1.1)	25 (29.1)	60 (69.8)	86 (33.1)
Multimorbidity	86.9 (7.3)	54.7	0 (0)	0 (0)	16 (25.0)	48 (75.0)	64 (24.6)
Total	N/A	N/A	0 (0)	8 (3.1)	68 (26.1)	184 (70.8)	260

N/A, not applicable; SD, standard deviation

Relationship between Frailty Degree and Survival

During the 2-year follow up period, a total of 338 (57.3%) study patients died. Mortality was significantly higher in end-of-life people than in non-end-of-life people: 220 (84.6%) and 118 (35.7%), respectively ($p<0.001$). The log-rank test comparing the survival curves of each frailty degree revealed significant differences in the overall population ($X^2 = 423$, $p < 0.0001$), end-of-life people ($X^2 = 69.9$, $p<0.0001$), and non-end-of-life people ($X^2 = 122$, $p<0.0001$) (Figure 1). Correspondingly, the C coefficient for concordance between the survival time and the Frail-VIG score was 0.8, indicating that higher scores of the Frail-VIG index are associated with lower survival.

The frequencies of death at the end of the 2-year follow-up period for each trajectory in end-of-life people are presented in Table 3. Survival curves, plotted using the Kaplan-Meier model for each frailty category (i.e., mild, intermediate, and advanced), differed among the different end-of-life trajectories, revealing different patterns of survival decline according to the frailty degree (Figure 2). A Cox regression model with the interaction between Frail-VIG index and illness trajectories revealed that the effect of the frailty degree on survival ass associated with illness trajectories ($p<0.01$ for all the coefficients), even though the influence of illness trajectory progressively decreased as

the frailty degree increased (Figure 3). The proportional hazard assumption was supported by the Schoenfeld residuals (p>0.1 for both global and each covariate tests). The estimated hazard ratios for the Frail-VIG index were 1.61 for people with dementia (95% CI=1.43-1.81), 1.30 for people with organ failure (95% CI=1.18-1.43), 1.30 for people with multimorbidity (95% CI=1.18-1.42), and 1.13 for people with cancer (95% CI=1.02-1.25). These results show that for each additional deficit (i.e., 0.04 increase in the Frail-VIG index) the risk of death increased by 61.5%, 30.1%, 29.6% and 12.9% in people with dementia, organ failure, multimorbidity and cancer, respectively.

Table 3. Status of end-of-life people according to the Frail-VIG index scores and end-of-life trajectory after the 2-year follow-up (n=260), n (%)

	n	Status	Mild Frailty	Moderate Frailty	Advanced Frailty	Total
Cancer	31	Dead	2 (6.5)	7 (22.6)	21 (67.7)	30 (96.8)
		Alive	1 (3.2)	0 (0)	0 (0)	1 (3.2)
Organ Failure	79	Dead	2 (2.5)	16 (20.2)	54 (68.4)	72 (91.1)
		Alive	2 (2.5)	4 (5.1)	1 (1.3)	7 (8.9)
Dementia	86	Dead	1 (1.2)	6 (6.9)	55 (64.0)	62 (72.1)
		Alive	0 (0)	19 (22.1)	5 (5.8)	24 (27.9)
Multimorbidity	64	Dead	0 (0)	8 (12.5)	48 (75.0)	56 (87.5)
		Alive	0 (0)	8 (12.5)	0 (0)	8 (12.5)

Prognosis Value of the Frail-VIG Index

The prognostic value of the Frail-VIG index for the end-of-life people (expressed as the AUC of the ROC analysis) was 0.87 (95% CI:0.83-0.92) after one year and 0.87 (95% CI:0.84-0.92) after two years of follow-up. Of the 184 end-of-life people with advanced

frailty (Frail-VIG index score > 0.5), 178 (96.7%) had died at two years of follow-up. The AUC differed among each of the four end-of-life trajectories: cancer (1 and 0.93), organ failure (0.86 and 0.90), dementia (0.92 and 0.92) and multimorbidity (0.91 and 0.94), after one and two years of follow-up, respectively. Regarding the sensitivity and specificity of the Frail-VIG index as prognosis factor of mortality, the most sensitive and specific cut-off was 0.5 at both one and two years after follow-up, showing a sensitivity of 0.81 and 0.85 and a specificity of 0.83 and 0.81, respectively.

DISCUSSION

In this prospective, observational study including 590 patients admitted at an Acute Geriatric unit (AGU), we found that all older patients were frail towards the end of life (the prevalence of moderate-to-advanced frailty was 97% among people within an end-of-life trajectory and 55% outside it). Furthermore, advanced frailty was the predominant frailty category (ranged 68 to 75%) for all end-of-life trajectories: cancer, organ failure, dementia, and multimorbidity. Overall, the Frail-VIG index had a high capacity to predict death at one and two years (AUC 0.87), albeit to a different extent for the end-of-life categories cancer, organ failure, dementia and multimorbidity (AUC was always >0.86 for mortality at either one or two years). This finding confirms the hypothesis that the degree of frailty is related to prognosis regardless of the illness trajectory.

The characteristics and outcomes of the cohort assessed in this study, which included all patients admitted to an Acute Geriatric unit (AGU), were similar to those previously reported. All the persons assessed in this study had a Frail-VIG index score <0.8, similar to previous studies showing that the theoretical maximum score is 0.7. According to these studies, the accumulation of 2/3 of all possible deficits (Frailty index score >0.7) results in death due to the person's inability to overcome more deficits, a phenomenon defined

as system failure.[32,33] Likewise, similar to previous studies in other populations, the mortality rate at 1 to 2 years in our cohort was nearly 100% for the end of life people with frailty index score >0.5.[33,34]

Furthermore, we provide evidence showing that the degree of frailty significantly influenced survival irrespective of the advanced illness and end-of-life trajectory. In spite of this general influence, the survival curves according to the frailty degree followed different patterns for the four end-of-life trajectories, enabling the description of different frailty or deficit accumulation end-of-life trajectories according to the main disease, specially in the absence of advanced frailty. As the frailty degree increased, differences between trajectories decreased, resulting in a trend towards a compression of survival curves in advanced frailty situations where mortality is very high irrespective of the main advanced illness and end-of-life trajectory. Thus, in end-of-life people with cancer, mortality rates were high regardless of the frailty degree (moderate or advanced), leading to the hypothesis, similar to recent studies, that cancer patients have a catastrophic accumulation of deficits.[35] In contrast, end-of-life people with dementia showed different mortality rates according to their frailty degree and died progressively, likely due to the natural history of the disease, suggesting a slower accumulation of deficits. People with multimorbidity and advanced frailty shows a survival profile similar to people with cancer, while those with moderate frailty have a survival rate more similar to people with dementia. Finally, persons with an organ disease would accumulate deficits in episodes, even though prospective studies with serial frailty indexes would be required to test this hypothesis.

In this regard, similar to recent studies describing different trajectories according to the evolution of the social, spiritual or psychological situation of end-of-life people,[3] prospective studies following the degree of frailty using electronic frailty indexes have

described three different trajectories (i.e., rapidly rising frailty, moderately increasing frailty, and stable frailty).[35] Even though more studies would be required to describe different end-of-life frailty trajectories, the fact that each end-of-life trajectory resulted in different mortality curves supports a dynamic view of end-of-life people.

The traditional association of frailty to the "third end-of-life trajectory" (i.e., dementia) [13,14] has probably been influenced by the lack of specific prognostic instruments for persons in this trajectory, unlike those in the cancer [36,37] or organ disease [38,39] trajectories. Our results regarding the high prevalence of frailty in all end-of-life trajectories support the validity of the concept that frailty may be present in all trajectories beyond the dementia trajectory. In addition to expanding the concept of frailty, our study underscores the need to consider a further development of the end-of-life trajectories. Of the 260 people who were identified as people in end-of-life situation, 24.6% did not have severity criteria for a single disease, although all of them had at least 2 chronic conditions. The identification of this cluster of people with advanced frailty and multimorbidity can help provide them early palliative care, and the benefits derived from it.[40,41]

Frailty Indices based on a Comprehensive Geriatric Assessment, such as the Frail-VIG index, may help professionals address one of the current challenges in palliative care [18,19,42]: the identification, assessment, and management of older people (i.e., aged >80 years) with palliative care needs [20,43]. First, assessment and quantification of frailty degree, which is suitable to synthesize the results of a multidimensional evaluation, can be useful to validate the identification of people in an end-of-life situation;[12] secondly, due to its ability to discriminate between different degrees of severity, frailty indexes can be very useful to healthcare professionals for the situational diagnosis of the first and second end-of-life transition,[6,12] and monitorization of end-of-life people evolution;[44,45] and finally, quantification of frailty would enable palliative care

customization [46,47] and engage people, caregivers and healthcare professionals in sharing decision-making and advance care planning.

The results of this study should be interpreted in the context of some limitations, particularly regarding the generalizability of the results. Firstly, the recruitment strategy based on an AGU solely was likely to enrich our study sample with older patients, likely precluding the applicability of these study results to younger patients. Secondly, the analysis of end-of-life people frailty across the various end-of-life trajectory categories importantly reduced the number of patients in each group, thus limiting the statistical power of these analyses. However, despite the reduced number of patients in some groups, our analysis yielded statistically significant results. In spite of its limitations, to our knowledge, this study is the first to evaluate the degree of frailty using a frailty index in very old patients identified as end-of-life people. Frailty was evaluated in a cohort of geriatric patients, including end-of-life and non-end-of-life people, and the data for this study was collected during routine geriatric assessment, as opposed to previous studies that used electronic health record data to evaluate the degree of frailty.[48] Moreover, the single computer information system of Catalonia (HC3) that collects the medical records and mortality status of all patients reported by all health providers prevented loss of patients up to follow-up.[31] Consequently, the lack of missing data due to the HC3 system, along with the use of standard and validated tools to identify end-of-life people (NECPAL) and to measure frailty (Frail-VIG index) increased the accuracy of the results obtained from this study. The early identification of people needing palliative care and the more accurate definition of the various end-of-life trajectories opened the door to a novel perspective of palliative care.[49] In this regard, the use of frailty as an overarching concept in the assessment of all people in an end-of-life situation —at least of those with

a multimorbid profile— might contribute to go one step further in this novel approach to palliative care.

CONCLUSIONS

Our results showed that all end-of-life people were frail (mostly with advanced frailty) irrespective of the end-of-life trajectory. Their degree of frailty, measured using the Frail-VIG index, influenced mortality. This indicates a close relationship between frailty, end-of-life status, and mortality for all people who die. Measuring frailty using a frailty index could be useful in routine practice for healthcare professionals to understand the heterogeneous nature of people needing palliative care and tailor their care to the patient's needs. The survival pattern of people with multimorbidity could support the description of a composite illness trajectory for this patient group.

DECLARATIONS

Ethics Approval and Consent to Participate

All patients and family relatives of patients with advanced dementia situation (GDS $\geq$ 6) signed the written informed consent for participation before any data was recorded. The study protocol was approved by the Ethics Committee of the University Hospital of Vic (2,014,850 PR80). This study was conducted in accordance with the Helsinki Declaration and the local Personal Data Protection Law (LOPD 15/1999).

Consent for publication

Not applicable.

Data Sharing

The anonymized datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

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Author's contributions

JAN, AT, JCM, and XGB were responsible for the conception and design of the study. JAN coordinated and substantially contributed to the data collection. JCM and RO performed the statistical analysis. All authors (JAN, SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) were involved in interpretation of data. JAN wrote the initial draft of the manuscript and all the other authors (SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) critically revised the manuscript. All authors (JAN, SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) have provided approval for the final version of the manuscript submitted for publication and agree to be accountable for all aspects of the work.

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REFERENCES

1 Boyd K, Murray SSA. Recognising and managing key transitions in end of life care. *BMJ* 2010;**341**:c4863. doi:10.1136/bmj.c4863

2 Gomez-Batiste X, Martinez-Munoz M, Blay C, *et al.* Identifying patients with chronic conditions in need of palliative care in the general population: development of the NECPAL tool and preliminary prevalence rates in Catalonia. *BMJ Support Palliat Care* 2013;**3**:300–8. doi:10.1136/bmjspcare-2012-000211

3 Murray SA, Kendall M, Mitchell G, *et al.* Palliative care from diagnosis to death. *BMJ* 2017;**356**:j878. doi:10.1136/bmj.j878

4 Kimbell B, Murray SA, Macpherson S BK. Embracing inherent uncertainty in advanced illness. *BMJ Br Med J* 2016;**354:i3802**.

5 Gómez-Batiste X, Blay C, Broggi MA, *et al.* Ethical Challenges of Early Identification of Advanced Chronic Patients in Need of Palliative Care. *J Palliat Care* 2018;**33**:247–51. doi:10.1177/0825859718788933

6 Amblàs-Novellas J, Espaulella J, Rexach L et al, *et al.* Frailty, severity, progression and shared decision-making: A pragmatic framework for the challenge of clinical complexity at the end of life. *Eur Geriatr Med* 2015;**6**:189–194. doi:10.1016/j.eurger.2015.01.002

7 Cardona-Morrell M, Lewis E, Suman S, *et al.* Recognising older frail patients near the end of life: What next? *Eur J Intern Med* 2017;**45**:84–90. doi:10.1016/j.ejim.2017.09.026

8 Koller K, Rockwood K. Frailty in older adults: Implications for end-of-life care. *Cleve Clin J Med* 2013;**80**:168–74. doi:10.3949/ccjm.80a.12100

9 Stow D, Spiers G, Matthews FE, *et al.* What is the evidence that people with frailty have needs for palliative care at the end of life? A systematic review and narrative synthesis. *Palliat Med* 2019;**33**:399–414. doi:10.1177/0269216319828650

10 Mousa A, Savva GM, Mitnitski A, *et al.* Is frailty a stable predictor of mortality across time? Evidence from the Cognitive Function and Ageing Studies. *Age Ageing* 2018;**47**:721–7. doi:10.1093/ageing/afy077

11 Pialoux T, Goyard J, Hermet R. When frailty should mean palliative care. *J Nurs Educ Pract* 2013;**3**:75–84. doi:10.5430/jnep.v3n7p75

12 Pollack LR, Goldstein NE, Gonzalez WC, *et al.* The Frailty Phenotype and Palliative Care Needs In Older Survivors of Critical Illness Lauren. *J Am Geriatr Soc* 2018;**65**:1168–75. doi:10.1111/jgs.14799.The

13 Lunney JR, Lynn J, Foley DJ, *et al.* Patterns of functional decline at the end of life. *JAMA* 2003;**289**:2387–92. doi:10.1001/jama.289.18.2387

14 Murray S a, Boyd K, Sheikh A. Palliative care in chronic illness. *BMJ* 2005;**330**:611–2. doi:10.1136/bmj.330.7492.611

15 Rodríguez-Mañas L, Féart C, Mann G, *et al.* Searching for an operational definition of frailty: A delphi method based consensus statement. the frailty

operative definition-consensus conference project. *Journals Gerontol - Ser A Biol Sci Med Sci* 2013;**68**:62–7. doi:10.1093/gerona/gls119

16 Cesari M, Gambassi G, van Kan GA, *et al.* The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing* 2014;**43**:10–2. doi:10.1093/ageing/aft160

17 Bone AE, Morgan M, Maddocks M, *et al.* Developing a model of short-term integrated palliative and supportive care for frail older people in community settings: perspectives of older people, carers and other key stakeholders. *Age Ageing* 2016;**45**:863–73. doi:10.1093/ageing/afw124

18 Moriarity J, Rutter D, Ross PD, *et al.* End of life care for people with dementia living in care homes. 2012;:4p.

19 Dixon J, King D, Matosevic T, *et al.* Equity in the provision of palliative care in the UK: Review of evidence. 2015;:145.

20 Teggi D. Unexpected death in ill old age: An analysis of disadvantaged dying in the English old population. *Soc Sci Med* 2018;**217**:112–20. doi:10.1016/j.socscimed.2018.09.048

21 Cesari M, Prince M, Thiyagarajan JA, *et al.* Frailty: An Emerging Public Health Priority. *J Am Med Dir Assoc* 2016;**17**:188–92. doi:10.1016/j.jamda.2015.12.016

22 Moorhouse P, Rockwood K, Morley JE, *et al.* Frailty Consensus: A Call to Action. *J Am Med Dir Assoc* 2013;**14**:392–7. doi:http://dx.doi.org/10.1016/j.jamda.2013.03.022

23 British Geriatrics Society. End of Life Care in Frailty: Identification and

prognostication | British Geriatrics Society. https://www.bgs.org.uk/resources/end-of-life-care-in-frailty-identification-and-prognostication (accessed 29 Nov 2020).

24 Amblàs-Novellas J, Martori JC, Espaulella J, *et al.* Frail-VIG index: a concise frailty evaluation tool for rapid geriatric assessment. *BMC Geriatr* 2018;**18**:29. doi:10.1186/s12877-018-0718-2

25 von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–7. doi:10.1016/S0140-6736(07)61602-X

26 Amblàs-Novellas J, Martori JC, Molist Brunet N, *et al.* Frail-VIG index: Design and evaluation of a new frailty index based on the Comprehensive Geriatric Assessment. *Rev Esp Geriatr Gerontol* 2017;**52**:119–27. doi:10.1016/j.regg.2016.09.003

27 Moreno-Ariño M, Torrente Jiménez I, Cartanyà Gutiérrez A, *et al.* Assessing the strengths and weaknesses of the Clinical Frailty Scale through correlation with a frailty index. *Aging Clin Exp Res* 2020;**32**:2225–32. doi:10.1007/s40520-019-01450-w

28 Gómez-Batiste X, Martínez-Muñoz M, Blay C, *et al.* Prevalence and characteristics of patients with advanced chronic conditions in need of palliative care in the general population: A cross-sectional study. *Palliat Med* 2014;**28**:302–11. doi:10.1177/0269216313518266

29 Gómez-Batiste X, Turrillas P, Tebé C, *et al.* NECPAL tool prognostication in

advanced chronic illness: A rapid review and expert consensus. *BMJ Support Palliat Care* Published Online First: 2020. doi:10.1136/bmjspcare-2019-002126

30 CENTRAL CATALONIA CHRONICITY RESEARCH GROUP. Utility of NECPAL. https://en.c3rg.com/necpal (accessed 29 Nov 2020).

31 Solans O, Gallego C, Garcia-Cuyas F, *et al.* Shared Medical Record, Personal Health Folder and Health and Social Integrated Care in Catalonia. In: *New Perspectives in Medical Records*. Springer, Cham 2017. 49–64. doi:10.1007/978-3-319-28661-7_4

32 Rockwood K, Mitnitski A. Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty. Clin. Geriatr. Med. 2011;**27**:17–26. doi:10.1016/j.cger.2010.08.008

33 Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. *Mech Age Dev* 2006;**127**:494–6. doi:10.1016/j.mad.2006.01.002

34 Rockwood K, Rockwood MRH, Mitnitski A. Physiological redundancy in older adults in relation to the change with age in the slope of a frailty index. *J Am Geriatr Soc* 2010;**58**:318–23. doi:10.1111/j.1532-5415.2009.02667.x

35 Stow D, Matthews FE, Hanratty B. Frailty trajectories to identify end of life: A longitudinal population-based study. *BMC Med* 2018;**16**:1–7. doi:10.1186/s12916-018-1148-x

36 Evans C, McCarthy M. Prognostic uncertainty in terminal care: can the Karnofsky index help? *Lancet (London, England)* 1985;**1**:1204–6. doi:10.1016/s0140-6736(85)92876-4

37 Anderson F, Downing GM, Hill J, *et al.* Palliative Performance Scale (PPS): A new tool. *J Palliat Care* 1996;**12**:5–11.

38 van Dijk WD, van den Bemt L, van den Haak-Rongen S, *et al.* Multidimensional prognostic indices for use in COPD patient care. A systematic review. Respir. Res. 2011;**12**:151. doi:10.1186/1465-9921-12-151

39 Walter LC, Brand RJ, Counsell SR, *et al.* Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA* 2001;**285**:2987–94. doi:10.1001/jama.285.23.2987

40 Moine S, Murray SA, Boyd K, *et al.* Palliative care and the endless cycle of serious health-related suffering. Lancet. 2018;**392**:471–2. doi:10.1016/S0140-6736(18)31195-4

41 Aldridge MD, Bradley EH. Epidemiology and patterns of care at the end of life: Rising complexity, shifts in care patterns and sites of death. *Health Aff* 2017;**36**:1175–83. doi:10.1377/hlthaff.2017.0182

42 (NCPC) NC for PC. National Council for Palliative Care (NCPC) Briefing The Government ' s National Commitment For End Of Life Care. 2016.

43 PA C, GE G, DA R, *et al.* Prediction of appropriate timing of palliative care for older adults with non-malignant life-threatening disease: a systematic review. *Age Ageing* 2005;**34**. doi:10.1093/AGEING/AFI054

44 Gill TM, Gahbauer E a, Allore HG, *et al.* Transitions between frailty states among community-living older persons. *Arch Intern Med* 2006;**166**:418–23. doi:10.1001/archinte.166.4.418

45 Liu ZY, Wei YZ, Wei LQ, *et al.* Frailty transitions and types of death in Chinese older adults: A population-based cohort study. *Clin Interv Aging* 2018;**13**:947–56. doi:10.2147/CIA.S157089

46 The Picker Institute. *Patient - Centered Care 2015 : Scenarios , Vision , Goals & Next Steps*. 2004.

47 Cohen-Mansfield J, Skornick-Bouchbinder M, Brill S. Trajectories of End of Life: A Systematic Review. *Journals Gerontol - Ser B Psychol Sci Soc Sci* 2018;**73**:564–72. doi:10.1093/geronb/gbx093

48 Clegg A, Bates C, Young J, *et al.* Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* 2016;**45**:353–60. doi:10.1093/ageing/afw039

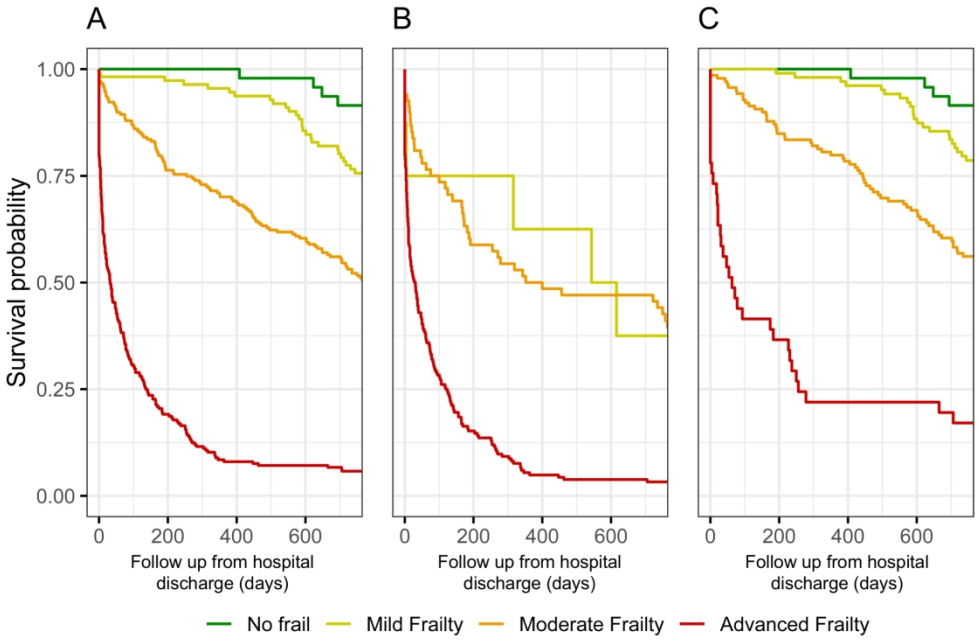
49 Amblàs-Novellas J, Murray SA, Espaulella J, *et al.* Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of prognostic indicators related to end-of-life trajectories. *BMJ Open* 2016;**6**:e012340. doi:10.1136/bmjopen-2016-012340

FIGURE LEGENDS

Figure 1. Survival according to the degree of frailty in (A) the total study patients, (B) end-of-life people, and (C) Non End-of-life people.

Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

Figure 3. Survival probability of end-of-life poeple in the different illness trajectories according to Frail-VIG index value: Frail-VIG index 0.44 (15th percentile) (A), Frail-VIG index 0.56 (median) (B) and Frail-VIG index 0.68 (90th percentile) (C).



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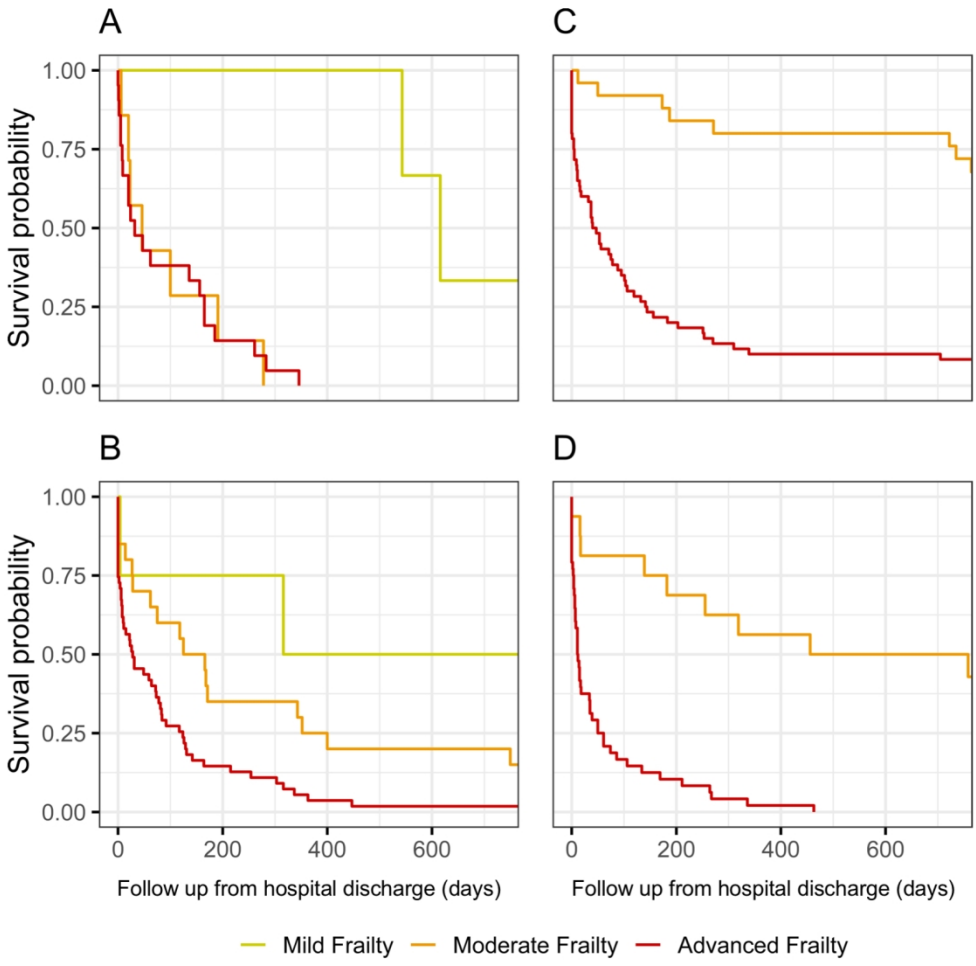

Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

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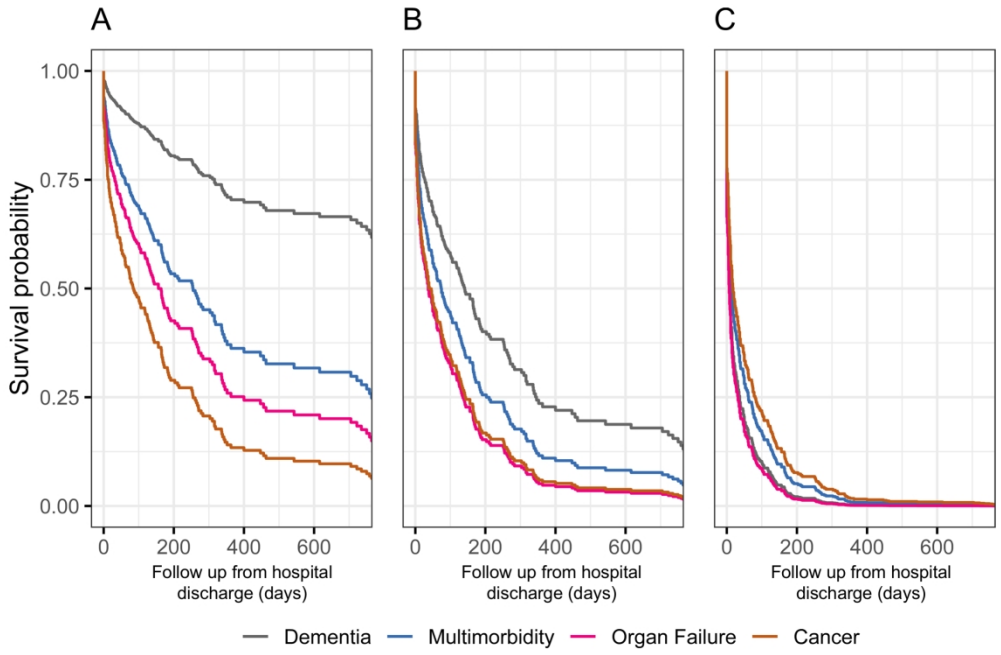

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874x564mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6, 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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	7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
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	9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 11

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-13 7 N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
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	15-16
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*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

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Frailty degree and illness trajectories in older people towards the end-of-life: a prospective observational study

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Frailty Degree and Illness Trajectories in Older People towards the End-of-life: a Prospective Observational Study

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Abstract

Objectives: To assess the degree of frailty in older people with different advanced diseases and its relationship with end-of-life illness trajectories and survival.

Methods: Prospective, observational study, including all patients admitted to the Acute Geriatric Unit of the University Hospital of Vic (Barcelona, Spain) during 12 consecutive months (2014 – 2015). The Frail-VIG index, based on 22 questions assessing 25 deficits, was used to quantify frailty degree, and participants with palliative care needs were identified using the NECPAL tool. Participants were classified according to their Frail-VIG index scores into 4 groups (i.e., no frailty, mild frailty, moderate frailty, and advanced frailty) and their dominant illness trajectory and followed for up to 2 years. The relationship between frailty degree and survival was evaluated using the C-statistics. Survival curves were plotted using the Kaplan-Meier estimator and compared using the log-rank test, and a Cox proportional hazards model with the interaction between frailty degree and illness trajectories was calculated.

Results: Of the 590 persons with a mean (SD) age of 86.4 (5.6) years recruited, 260 (44.1%) were identified as end-of-life people (EOLp), distributed into cancer (n=31, 11.9%), organ failure (n=79, 30.4%), dementia (n=86, 33.1%), and multimorbidity (n=64, 24.6%) categories. All 260 EOLp had some degree of frailty, mostly advanced frailty (n=184, 70.8%), regardless of the illness trajectory, and 220 (84.6%) died within two years. Survival curves differed between frailty degrees (p<0.0001) and revealed different patterns of survival decline in the different end-of-life trajectories. Cox regression analyses showed that each additional deficit was associated with a 61.5%, 30.1%, 29.6% and 12.9% increased risk of death in people with dementia, organ failure, multimorbidity and cancer, respectively, (p<0.01 for all the coefficients).

Conclusions: All older people towards the end-of-life in this study were frail, mostly with advanced frailty. The degree of frailty is related to survival across the different illness trajectories despite the differing survival patterns among trajectories. Frailty indexes may be useful to assess end-of-life older people, regardless of their trajectory.

Keywords: Frailty, palliative care, mortality, multimorbidity, longitudinal study

Strengths and Limitations of this Study

- To our knowledge, this is the first study that evaluated the degree of frailty using a frailty index in older patients with different advanced illness trajectories.
- This is a real-life study, using tools routinely applied in the Acute Geriatric Unit conducting this study: the NECPAL, to identify people with palliative care needs, and the Frail-VIG index, to measure the degree of frailty and personalization of the interventions.
- In this context, assessing frailty degree may contribute to establish a common language between geriatric and palliative knowledge, with the goal of providing a better care for older people with palliative care needs, specially those in the first end-of-life transition.
- The use of a single computer system collecting the mortality status reported by all health providers prevented loss of patients and missing data, increasing the accuracy of the results.
- The results from this study were obtained in a very old population and the frail VIG index lacks sufficient external validation, potentially limiting their generalizability and raising the need for further studies in younger populations.

INTRODUCTION

The model of care for patients with advanced chronic conditions is currently shifting towards a new paradigm, characterized by early identification of persons with any disease or chronic condition who would benefit from palliative care [1,2]—this corresponds to the first transition in palliative care. Despite the benefits of this early identification,[3]the increasing number of people with palliative care needs, together with their high heterogeneity regarding age, needs, diseases, and chronic illnesses, poses novel challenges for early identification and assessment of these patients.[4,5] Indeed, the progression towards the end of life is conditioned by multiple variables and is strictly individual: not all people age in the same way nor reach the final situation with the same circumstances or needs.[6]

In the context of this new paradigm of "early palliative care", some authors have pointed to frailty as a crucial concept for persons needing palliative care —particularly older people with multimorbidity—, their caregivers, and healthcare professionals, to learn to manage the uncertainty and complexity of these end-of-life situations.[7–9] Given the relationship between mortality and frailty,[10] the concept of frailty has been proposed as a criterion useful in the three key steps ensuring good palliative care,[5,6,11,12] including 1) early identification of persons in end-of-life situation (particularly in cases of advanced frailty); 2) multidimensional assessment and situational diagnosis; and 3) drafting an advanced care plan and sharing decision-making.

Regardless of the proposed uses of frailty as an indicator, palliative care and geriatrics have traditionally used this concept, albeit with different perspectives.[8] In the setting of palliative care, frailty has equated to the third end-of-life trajectory and defined as the gradual decline in physical function, typically associated with dementia.[13,14] In contrast, from the geriatric perspective, frailty is rather a multidimensional clinical entity

defined as a vulnerability state against stressing factors due to limited compensatory mechanisms.[15] Of the multiple instruments developed to assess frailty, frailty indexes (i.e., the ratio between accumulated deficits in a given person and the total possible deficits) may have utility in identifying people with frailty for end-of-life care across all disease groups.[8,16]

A better understanding of how to provide the best palliative care for frail older people has become an international priority[17] and, considering the increased difficulty of identifying dying people in very old age (>85 years),[18–20] the concept of frailty is increasingly acknowledged as a cornerstone in the assessment and care of persons in an end-of-life situation and needing palliative care.[15,21] However, a consensus on how to use the concept of frailty to provide palliative care to end-of-life people (EOLp) remains to be established.[15,22,23] In this study, aimed at improving the care of end-of-life older people, we assessed the degree of frailty in a geriatric cohort with different advanced diseases and its relationship with end-of-life illness trajectories and survival.

METHODS

Study Design and Participants

This was a prospective, observational study, including all patients admitted to the Acute Geriatric unit (AGU) at the University Hospital of Vic (Barcelona, Spain) during 12 consecutive months (January 2014 – January 2015). The University Hospital of Vic is a 200-bed acute care hospital covering a population area of 156,000 inhabitants. Admission criteria to the AGU, which were the criteria for inclusion in this study, were age ≥ 85 years, cognitive decline, and/or end-of-life situation; no exclusion criteria were defined. The methods, including study design, variables, data sources, and study size have been described in a previous study.[24] Of the patients included in this study (i.e., those

admitted to the AGU), those identified as non end-of-life were included in a control group of patients aged ≥ 85 years and/or with cognitive decline. The results of this subanalysis are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[25] All patients and family relatives of patients with advanced dementia situation (GDS ≥ 6) signed the written informed consent for participation before any data was recorded. The study protocol was approved by the Ethics Committee of the University Hospital of Vic (2,014,850 PR80); this study was conducted in accordance with the Helsinki Declaration and the local Personal Data Protection Law (LOPD 15/1999).

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Variables and Data Sources

Frailty was assessed using the Frail-VIG index, a tool consisting in 22 questions to assess 25 deficits commonly associated with age and adverse health outcomes, based on the cumulative deficit model of frailty. Fifteen of the 22 questions refer to chronic conditions, including geriatric conditions and syndromes. The Frail-VIG index is a continuous variable ranging from 0 to 1 and classified into 4 groups: no frailty (Frail-VIG index score <0.2), mild frailty (Frail-VIG index score 0.2-0.35), moderate frailty (Frail-VIG index score 0.36-0.5), and advanced frailty (Frail-VIG index score >0.5). In addition to its predicitive value, previous studies have shown the content, construct, criteria, and convergent-divergent construct validity of the Frail-VIG index [24,26–28]. EOLp were

identified using the NECPAL tool, a validated tool for the early identification of the need for palliative care among individuals with limited life expectancy.[29–31] EOLp were classified into the 3 archetypal end-of-life trajectories according to the severity and/or progression criteria for their main underlying disease: cancer, organ failure (including chronic pulmonary disease, chronic heart disease, serious chronic liver disease, and serious chronic renal disease), and dementia (including other chronic neurological diseases). People with palliative care needs without a predominant advanced disease were identified as "multimorbidity" group or trajectory, since all had 2 or more underlying chronic conditions.

After inclusion of the last patient in the study (i.e., last admitted patient in the AGU before January 15th, 2015) and before starting data analysis in 2017, patients were followed for up to 24 months (2015 - beginning 2017). Information regarding the patient status after the 24-month follow-up period was obtained from the Shared Medical Record in Catalonia (HC3), a sole electronic database accessible to all healthcare providers in Catalonia that allows healthcare professionals to reliably determine whether a patient is “active” (alive) or deceased (including date of death).[32]

Statistical Analysis

Qualitative variables were presented as frequencies and percentages, whereas quantitative variables were presented as the mean and the standard deviation (SD). Qualitative variables were compared using the Pearson’s chi-squared test. In the complete cohort, the concordance between frailty degree and survival was evaluated using the C-statistics and the Kaplain-Meier estimator was used to plot survival curves, which were compared using the log-rank test. In the group of people identified as end-of-life, survival curves for each illness trajectory were plotted using the Kaplan-Meier estimator and were compared using the log-rank test, and a Cox proportional hazards model with the interaction between

frailty degree and illness trajectories was calculated. The assumption of proportional hazards was checked using the Schoenfeld residuals and a goodness-of-fit test. The ROC curves were used to assess the ability of the Frail-VIG index to predict survival at one and two years by measuring their area under the receiver-operating curve (AUC) for the different illness trajectories. The significance level for all analyses was set at a two-sided α=0.05. The descriptive statistics analysis of the variables was performed using the SPSS software program (IBM; Chicago, IL; USA), and the survival analysis was performed using the *survival and pROC packages* from the R project (https://www.r-project.org).

RESULTS

Patient Characteristics and End-of-life Status

The study included 590 patients with a mean (SD, range) age of 86.4 (5.6, 48-105) years, of whom 339 (57.5%) were women. Based on the Frail-VIG index scores, 543 (92%) patients showed some degree of frailty, with 111 (18.8%), 207 (35.1%), and 225 (38.1%) patients showing mild, moderate and advanced frailty, respectively. Of the 590 patients included, 53 (8.9%) died during hospitalization, and 330 (55.9%) and 260 (44.1%) were identified as non-EOLp) and EOLp, respectively. Of the 260 EOLp, 31 (11.9%), 79 (30.4%), 86 (33.1%), and 64 (24.6%) were classified in cancer, organ failure, dementia, and multimorbidity illness trajectories, respectively.

Relationship between End-of-life Status and Patient Characteristics

EOLp and non-EOLp had similar mean age and sex frequencies, but differed in the distribution among the 4 frailty groups: all EOLp (260) and 283 (85.8%) of the 330 non-EOLp were frail to some extent, with 252 (96.9%) and 180 (54.5%) showing moderate or advanced frailty in the EOLp and non-EOLp group, respectively. Table 1 summarizes

the frequencies of EOLp and non-EOLp across the various frailty categories and their main demographic characteristics.

Table 1. Classification of study patients according to the Frail-VIG index scores, demographic characteristics, and end-of-life status (n=590)

	Demographic characteristics		**Frailty Degree, *n (%)***			
	Age (years), *mean (SD)*	Sex (% of women)	Not frail	Mild Frailty	Moderate Frailty	Advanced Frailty
EOLp	86.3 (5.8)	54.6	0 (0)	8 (3.1)	68 (26.1)	184 (70.8)
Non-EOLp	86.5 (5.4)	59.7	47 (14.3)	103 (31.2)	139 (42.1)	41 (12.4)

EOLp: End-of-life people, Non-EOLp: Non End-of-life people; SD, standard deviation

Correspondingly, median Frail-VIG index scores were significantly higher in EOLp compared to non-EOLp: 0.56 and 0.36, respectively (p<0.001). In EOLp, the predominant frailty degree was persistently advanced for all end-of-life trajectory categories: cancer, organ failure, dementia, and multimorbidity (range 68-75%) (Table 2). All EOLp in the multimorbidity trajectory (n=64) were classified in the moderate and advanced frailty groups.

Table 2. Classification of end-of-life people according to demographic characteristics, Frail-VIG index scores and end-of-life trajectory (n=260), n (%)

	Demographic characteristics		**Frailty degree, n (%)**				
	Age (years), *mean (SD)*	Sex (% of women)	Not frail	Mild Frailty	Moderate Frailty	Advanced Frailty	Total
Cancer	85.7 (5.4)	45.2	0 (0)	3 (9.7)	7 (22.6)	21 (67.7)	31 (11.9)
Organ Failure	86.9 (5.3)	46.8	0 (0)	4 (5.1)	20 (25.3)	55 (69.6)	79 (30.4)

Dementia	85.4 (5.3)	65.1	0 (0)	1 (1.1)	25 (29.1)	60 (69.8)	86 (33.1)
Multimorbidity	86.9 (7.3)	54.7	0 (0)	0 (0)	16 (25.0)	48 (75.0)	64 (24.6)
Total	N/A	N/A	0 (0)	8 (3.1)	68 (26.1)	184 (70.8)	260

N/A, not applicable; SD, standard deviation

Relationship between Frailty Degree and Survival

Of the complete cohort (EOLp and non-EOLp), 338 (57.3%) study patients died during the 2-year follow-up period. Mortality was significantly higher in EOLp than in non-EOLp: 220 (84.6%) and 118 (35.7%), respectively ($p<0.001$). The log-rank test comparing the survival curves of each frailty degree revealed significant differences in the overall population ($X^2 = 423$, $p<0.0001$), EOLp ($X^2 = 69.9$, $p<0.0001$), and non-EOLp ($X^2 = 122$, $p<0.0001$) (Figure 1). Correspondingly, the C coefficient for concordance between the survival time and the Frail-VIG score was 0.8, indicating that higher scores of the Frail-VIG index are associated with lower survival.

Relationship between Frailty Degree and Survival in End-of-Life People

The frequencies of death at the end of the 2-year follow-up period for each trajectory in EOLp are presented in Table 3. Survival curves, plotted using the Kaplan-Meier model for each frailty category (i.e., mild, intermediate, and advanced), differed among the different end-of-life trajectories, revealing different patterns of survival decline according to the frailty degree (Figure 2). A Cox regression model with the interaction between Frail-VIG index and illness trajectories revealed that the effect of the frailty degree on survival was associated with illness trajectories ($p<0.01$ for all the coefficients), even though the influence of illness trajectory progressively decreased as the frailty degree increased (Figure 3). The proportional hazard assumption was supported by the Schoenfeld residuals ($p>0.1$ for both global and each covariate tests). The estimated

hazard ratios for each additional deficit (i.e., a 0.04 increase in the Frail-VIG index) were 1.61 for people with dementia (95% CI=1.43-1.81), 1.30 for people with organ failure (95% CI=1.18-1.43), 1.30 for people with multimorbidity (95% CI=1.18-1.42), and 1.13 for people with cancer (95% CI=1.02-1.25). These results show that for each additional deficit (i.e., 0.04 increase in the Frail-VIG index) the risk of death increased by 61.5%, 30.1%, 29.6% and 12.9% in people with dementia, organ failure, multimorbidity and cancer, respectively.

Table 3. Status of end-of-life people according to the Frail-VIG index scores and end-of-life trajectory after the 2-year follow-up (n=260), n (%)

	n	Status	Mild Frailty	Moderate Frailty	Advanced Frailty	Total
Cancer	31	Dead	2 (6.5)	7 (22.6)	21 (67.7)	30 (96.8)
		Alive	1 (3.2)	0 (0)	0 (0)	1 (3.2)
Organ Failure	79	Dead	2 (2.5)	16 (20.2)	54 (68.4)	72 (91.1)
		Alive	2 (2.5)	4 (5.1)	1 (1.3)	7 (8.9)
Dementia	86	Dead	1 (1.2)	6 (6.9)	55 (64.0)	62 (72.1)
		Alive	0 (0)	19 (22.1)	5 (5.8)	24 (27.9)
Multimorbidity	64	Dead	0 (0)	8 (12.5)	48 (75.0)	56 (87.5)
		Alive	0 (0)	8 (12.5)	0 (0)	8 (12.5)

The ROC analysis of the Frail-VIG index for the EOLp showed an AUC of 0.87 (95% CI:0.83-0.92) after one year and 0.87 (95% CI:0.84-0.92) after two years of follow-up. Of the 184 EOLp with advanced frailty (Frail-VIG index score > 0.5), 178 (96.7%) had died at two years of follow-up. The AUC differed among each of the four end-of-life trajectories: cancer (1 and 0.93), organ failure (0.86 and 0.90), dementia (0.92 and 0.92) and multimorbidity (0.91 and 0.94), after one and two years of follow-up, respectively.

Despite these differences, the AUC remained high irrespective of the illness trajectory. Regarding the sensitivity and specificity of the Frail-VIG index as prognosis factor of mortality, the most sensitive and specific cut-off was 0.5 at both one and two years after follow-up, showing a sensitivity of 0.81 and 0.85 and a specificity of 0.83 and 0.81, respectively.

DISCUSSION

In this prospective, observational study including 590 patients admitted at an Acute Geriatric unit (AGU), we found that all older patients were frail towards the end of life (the prevalence of moderate-to-advanced frailty was 97% among people within an end-of-life trajectory and 55% outside it). Furthermore, advanced frailty was the predominant frailty category (ranged 68 to 75%) for all end-of-life trajectories: cancer, organ failure, dementia, and multimorbidity. Overall, the Frail-VIG index had a high capacity to predict death at one and two years (AUC 0.87), albeit to a different extent for the end-of-life categories cancer, organ failure, dementia and multimorbidity (AUC was always >0.86 for mortality at either one or two years). This finding confirms the hypothesis that the degree of frailty is related to prognosis regardless of the illness trajectory.

The characteristics and outcomes of the cohort assessed in this study, which included all patients admitted to an Acute Geriatric unit (AGU), were similar to those previously reported. All the persons assessed in this study had a Frail-VIG index score <0.8, similar to previous studies showing that the theoretical maximum score is 0.7. According to these studies, the accumulation of 2/3 of all possible deficits (Frailty index score >0.7) results in death due to the person's inability to overcome more deficits, a phenomenon defined as system failure.[33,34] Likewise, similar to previous studies in other populations, the mortality rate at 1 to 2 years in our cohort was nearly 100% for the EOLp with frailty index score >0.5.[34,35]

Furthermore, we provide evidence showing that the degree of frailty significantly influenced survival irrespective of the advanced illness and end-of-life trajectory. In spite of this general influence, the survival curves according to the frailty degree followed different patterns for the four end-of-life trajectories, enabling the description of different frailty or deficit accumulation end-of-life trajectories according to the main disease, specially in the absence of advanced frailty. As the frailty degree increased, differences between trajectories decreased, resulting in a trend towards a compression of survival curves in advanced frailty situations where mortality is very high irrespective of the main advanced illness and end-of-life trajectory. Thus, in EOLp with cancer, mortality rates were high regardless of the frailty degree (moderate or advanced), leading to the hypothesis, similar to recent studies, that cancer patients have a catastrophic accumulation of deficits.[36] In contrast, EOLp with dementia showed different mortality rates according to their frailty degree and died progressively, likely due to the natural history of the disease, suggesting a slower accumulation of deficits. People with multimorbidity and advanced frailty shows a survival profile similar to people with cancer, while those with moderate frailty have a survival rate more similar to people with dementia. Finally, persons with an organ disease would accumulate deficits in episodes, even though prospective studies with serial frailty indexes would be required to test this hypothesis.

In this regard, similar to recent studies describing different trajectories according to the evolution of the social, spiritual or psychological situation of EOLp,[3] prospective studies following the degree of frailty using electronic frailty indexes have described three different trajectories (i.e., rapidly rising frailty, moderately increasing frailty, and stable frailty).[36] Even though more studies would be required to describe different end-of-life frailty trajectories, the fact that each end-of-life trajectory resulted in different mortality curves supports a dynamic view of EOLp.

The traditional association of frailty to the "third end-of-life trajectory" (i.e., dementia) [13,14] has probably been influenced by the lack of specific prognostic instruments for persons in this trajectory, unlike those in the cancer [37,38] or organ disease [39,40] trajectories. Our results regarding the high prevalence of frailty in all end-of-life trajectories support the validity of the concept that frailty may be present in all trajectories beyond the dementia trajectory. In addition to expanding the concept of frailty, our study underscores the need to consider a further development of the end-of-life trajectories. Of the 260 people who were identified as people in end-of-life situation, 24.6% did not have severity criteria for a single disease, although all of them had at least 2 chronic conditions. The identification of this cluster of people with advanced frailty and multimorbidity can help provide them early palliative care, and the benefits derived from it.[41,42]

Frailty Indices based on a Comprehensive Geriatric Assessment, such as the Frail-VIG index, may help professionals address one of the current challenges in palliative care [18,19,43]: the identification, assessment, and management of older people (i.e., aged >80 years) with palliative care needs [20,44]. First, assessment and quantification of frailty degree, which is suitable to synthesize the results of a multidimensional evaluation, can be useful to validate the identification of people in an end-of-life situation;[12] secondly, due to its ability to discriminate between different degrees of severity, frailty indexes can be very useful to healthcare professionals for the situational diagnosis of the first and second end-of-life transition,[6,12] and monitorization of EOLp evolution;[45,46] and finally, quantification of frailty would enable palliative care customization [47,48] and engage people, caregivers and healthcare professionals in sharing decision-making and advance care planning.

The results of this study should be interpreted in the context of some limitations, particularly regarding the generalizability of the results. Firstly, the recruitment strategy

based on an AGU solely enriched our study sample with older patients, likely precluding the applicability of these study results to younger patients. Secondly, the analysis of EOLp frailty across the various end-of-life trajectory categories importantly reduced the number of patients in each group, thus limiting the statistical power of these analyses. However, despite the reduced number of patients in some groups, our analysis yielded statistically significant results. In spite of its limitations, to our knowledge, this study is the first to evaluate the degree of frailty using a frailty index in very old patients identified as EOLp. Frailty was evaluated in a cohort of geriatric patients, including EOLp and non-EOLp, and the data for this study was collected during routine geriatric assessment, as opposed to previous studies that used electronic health record data to evaluate the degree of frailty.[49] Moreover, the single computer information system of Catalonia (HC3) that collects the medical records and mortality status of all patients reported by all health providers prevented loss of patients up to follow-up.[32] Consequently, the lack of missing data due to the HC3 system, along with the use of standard and validated tools to identify EOLp (NECPAL) and to measure frailty (Frail-VIG index) increased the accuracy of the results obtained from this study. The early identification of people needing palliative care and the more accurate definition of the various end-of-life trajectories opened the door to a novel perspective of palliative care.[50] In this regard, the use of frailty as an overarching concept in the assessment of all people in an end-of-life situation —at least of those with a multimorbid profile— might contribute to go one step further in this novel approach to palliative care.

CONCLUSIONS

Our results showed that all end-of-life people were frail (mostly with advanced frailty) irrespective of the end-of-life trajectory. Their degree of frailty, measured using the Frail-VIG index, influenced mortality. This indicates a close relationship between frailty, end-

of-life status, and mortality for all people who die. Measuring frailty using a frailty index could be useful in routine practice for healthcare professionals to understand the heterogeneous nature of people needing palliative care and tailor their care to the patient's needs. The survival pattern of people with multimorbidity could support the description of a composite illness trajectory for this patient group.

DECLARATIONS

Ethics Approval and Consent to Participate

All patients and family relatives of patients with advanced dementia situation (GDS ≥ 6) signed the written informed consent for participation before any data was recorded. The study protocol was approved by the Ethics Committee of the University Hospital of Vic (2,014,850 PR80). This study was conducted in accordance with the Helsinki Declaration and the local Personal Data Protection Law (LOPD 15/1999).

Consent for publication

Not applicable.

Data Sharing

The anonymized datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

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Author's contributions

JAN, AT, JCM, and XGB were responsible for the conception and design of the study. JAN coordinated and substantially contributed to the data collection. JCM and RO performed the statistical analysis. All authors (JAN, SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) were involved in interpretation of data. JAN wrote the initial draft of the manuscript and all the other authors (SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) critically revised the manuscript. All authors (JAN, SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) have provided approval for the final version of the manuscript submitted for publication and agree to be accountable for all aspects of the work.

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REFERENCES

1 Boyd K, Murray SSA. Recognising and managing key transitions in end of life care. *BMJ* 2010;**341**:c4863. doi:10.1136/bmj.c4863

2 Gomez-Batiste X, Martinez-Munoz M, Blay C, *et al.* Identifying patients with chronic conditions in need of palliative care in the general population: development of the NECPAL tool and preliminary prevalence rates in Catalonia. *BMJ Support Palliat Care* 2013;**3**:300–8. doi:10.1136/bmjspcare-2012-000211

3 Murray SA, Kendall M, Mitchell G, *et al.* Palliative care from diagnosis to death. *BMJ* 2017;**356**:j878. doi:10.1136/bmj.j878

4 Kimbell B, Murray SA, Macpherson S BK. Embracing inherent uncertainty in advanced illness. *BMJ Br Med J* 2016;**354:i3802**.

5 Gómez-Batiste X, Blay C, Broggi MA, *et al.* Ethical Challenges of Early Identification of Advanced Chronic Patients in Need of Palliative Care. *J Palliat Care* 2018;**33**:247–51. doi:10.1177/0825859718788933

6 Amblàs-Novellas J, Espaulella J, Rexach L et al, *et al.* Frailty, severity, progression and shared decision-making: A pragmatic framework for the challenge of clinical complexity at the end of life. *Eur Geriatr Med* 2015;**6**:189–194. doi:10.1016/j.eurger.2015.01.002

7 Cardona-Morrell M, Lewis E, Suman S, *et al.* Recognising older frail patients near the end of life: What next? *Eur J Intern Med* 2017;**45**:84–90. doi:10.1016/j.ejim.2017.09.026

8 Koller K, Rockwood K. Frailty in older adults: Implications for end-of-life care. *Cleve Clin J Med* 2013;**80**:168–74. doi:10.3949/ccjm.80a.12100

9 Stow D, Spiers G, Matthews FE, *et al.* What is the evidence that people with frailty have needs for palliative care at the end of life? A systematic review and narrative synthesis. *Palliat Med* 2019;**33**:399–414. doi:10.1177/0269216319828650

10 Mousa A, Savva GM, Mitnitski A, *et al.* Is frailty a stable predictor of mortality across time? Evidence from the Cognitive Function and Ageing Studies. *Age Ageing* 2018;**47**:721–7. doi:10.1093/ageing/afy077

11 Pialoux T, Goyard J, Hermet R. When frailty should mean palliative care. *J Nurs Educ Pract* 2013;**3**:75–84. doi:10.5430/jnep.v3n7p75

12 Pollack LR, Goldstein NE, Gonzalez WC, *et al.* The Frailty Phenotype and Palliative Care Needs In Older Survivors of Critical Illness Lauren. *J Am Geriatr Soc* 2018;**65**:1168–75. doi:10.1111/jgs.14799.The

13 Lunney JR, Lynn J, Foley DJ, *et al.* Patterns of functional decline at the end of life. *JAMA* 2003;**289**:2387–92. doi:10.1001/jama.289.18.2387

14 Murray S a, Boyd K, Sheikh A. Palliative care in chronic illness. *BMJ* 2005;**330**:611–2. doi:10.1136/bmj.330.7492.611

15 Rodríguez-Mañas L, Féart C, Mann G, *et al.* Searching for an operational definition of frailty: A delphi method based consensus statement. the frailty operative definition-consensus conference project. *Journals Gerontol - Ser A Biol Sci Med Sci* 2013;**68**:62–7. doi:10.1093/gerona/gls119

16 Cesari M, Gambassi G, van Kan GA, *et al.* The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing* 2014;**43**:10–2. doi:10.1093/ageing/aft160

17 Bone AE, Morgan M, Maddocks M, *et al.* Developing a model of short-term integrated palliative and supportive care for frail older people in community settings: perspectives of older people, carers and other key stakeholders. *Age Ageing* 2016;**45**:863–73. doi:10.1093/ageing/afw124

18 Moriarity J, Rutter D, Ross PD, *et al.* End of life care for people with dementia living in care homes. 2012;:4p.

19 Dixon J, King D, Matosevic T, *et al.* Equity in the provision of palliative care in the UK: Review of evidence. 2015;:145.

20 Teggi D. Unexpected death in ill old age: An analysis of disadvantaged dying in the English old population. *Soc Sci Med* 2018;**217**:112–20. doi:10.1016/j.socscimed.2018.09.048

21 Cesari M, Prince M, Thiyagarajan JA, *et al.* Frailty: An Emerging Public Health Priority. *J Am Med Dir Assoc* 2016;**17**:188–92. doi:10.1016/j.jamda.2015.12.016

22 Moorhouse P, Rockwood K, Morley JE, *et al.* Frailty Consensus: A Call to Action.

J Am Med Dir Assoc 2013;**14**:392–7. doi:http://dx.doi.org/10.1016/j.jamda.2013.03.022

23 British Geriatrics Society. End of Life Care in Frailty: Identification and prognostication | British Geriatrics Society. https://www.bgs.org.uk/resources/end-of-life-care-in-frailty-identification-and-prognostication (accessed 29 Nov 2020).

24 Amblàs-Novellas J, Martori JC, Espaulella J, *et al.* Frail-VIG index: a concise frailty evaluation tool for rapid geriatric assessment. *BMC Geriatr* 2018;**18**:29. doi:10.1186/s12877-018-0718-2

25 von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–7. doi:10.1016/S0140-6736(07)61602-X

26 Amblàs-Novellas J, Martori JC, Molist Brunet N, *et al.* Frail-VIG index: Design and evaluation of a new frailty index based on the Comprehensive Geriatric Assessment. *Rev Esp Geriatr Gerontol* 2017;**52**:119–27. doi:10.1016/j.regg.2016.09.003

27 Moreno-Ariño M, Torrente Jiménez I, Cartanyà Gutiérrez A, *et al.* Assessing the strengths and weaknesses of the Clinical Frailty Scale through correlation with a frailty index. *Aging Clin Exp Res* 2020;**32**:2225–32. doi:10.1007/s40520-019-01450-w

28 Madruga-Flores M, Gómez-del Río R, Delgado-Domínguez L, *et al.* Capacidad predictiva de fragilidad basal y fuerza de prensión al ingreso en resultados al alta en una unidad geriátrica de recuperación funcional. *Rev Esp Geriatr Gerontol* Published Online First: 19 January 2021. doi:10.1016/J.REGG.2020.12.002

29 Gómez-Batiste X, Martínez-Muñoz M, Blay C, *et al.* Prevalence and characteristics of patients with advanced chronic conditions in need of palliative care in the general population: A cross-sectional study. *Palliat Med* 2014;**28**:302–11. doi:10.1177/0269216313518266

30 Gómez-Batiste X, Turrillas P, Tebé C, *et al.* NECPAL tool prognostication in advanced chronic illness: A rapid review and expert consensus. *BMJ Support Palliat Care* Published Online First: 2020. doi:10.1136/bmjspcare-2019-002126

31 CENTRAL CATALONIA CHRONICITY RESEARCH GROUP. Utility of NECPAL. https://en.c3rg.com/necpal (accessed 29 Nov 2020).

32 Solans O, Gallego C, Garcia-Cuyas F, *et al.* Shared Medical Record, Personal Health Folder and Health and Social Integrated Care in Catalonia. In: *New Perspectives in Medical Records*. Springer, Cham 2017. 49–64. doi:10.1007/978-3-319-28661-7_4

33 Rockwood K, Mitnitski A. Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty. Clin. Geriatr. Med. 2011;**27**:17–26. doi:10.1016/j.cger.2010.08.008

34 Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. *Mech Age Dev* 2006;**127**:494–6. doi:10.1016/j.mad.2006.01.002

35 Rockwood K, Rockwood MRH, Mitnitski A. Physiological redundancy in older adults in relation to the change with age in the slope of a frailty index. *J Am Geriatr Soc* 2010;**58**:318–23. doi:10.1111/j.1532-5415.2009.02667.x

36 Stow D, Matthews FE, Hanratty B. Frailty trajectories to identify end of life: A longitudinal population-based study. *BMC Med* 2018;**16**:1–7. doi:10.1186/s12916-018-1148-x

37 Evans C, McCarthy M. Prognostic uncertainty in terminal care: can the Karnofsky

index help? *Lancet (London, England)* 1985;**1**:1204–6. doi:10.1016/s0140-6736(85)92876-4

38 Anderson F, Downing GM, Hill J, *et al.* Palliative Performance Scale (PPS): A new tool. *J Palliat Care* 1996;**12**:5–11.

39 van Dijk WD, van den Bemt L, van den Haak-Rongen S, *et al.* Multidimensional prognostic indices for use in COPD patient care. A systematic review. Respir. Res. 2011;**12**:151. doi:10.1186/1465-9921-12-151

40 Walter LC, Brand RJ, Counsell SR, *et al.* Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA* 2001;**285**:2987–94. doi:10.1001/jama.285.23.2987

41 Moine S, Murray SA, Boyd K, *et al.* Palliative care and the endless cycle of serious health-related suffering. Lancet. 2018;**392**:471–2. doi:10.1016/S0140-6736(18)31195-4

42 Aldridge MD, Bradley EH. Epidemiology and patterns of care at the end of life: Rising complexity, shifts in care patterns and sites of death. *Health Aff* 2017;**36**:1175–83. doi:10.1377/hlthaff.2017.0182

43 (NCPC) NC for PC. National Council for Palliative Care (NCPC) Briefing The Government ' s National Commitment For End Of Life Care. 2016.

44 PA C, GE G, DA R, *et al.* Prediction of appropriate timing of palliative care for older adults with non-malignant life-threatening disease: a systematic review. *Age Ageing* 2005;**34**. doi:10.1093/AGEING/AFI054

45 Gill TM, Gahbauer E a, Allore HG, *et al.* Transitions between frailty states among community-living older persons. *Arch Intern Med* 2006;**166**:418–23. doi:10.1001/archinte.166.4.418

46 Liu ZY, Wei YZ, Wei LQ, *et al.* Frailty transitions and types of death in Chinese

older adults: A population-based cohort study. *Clin Interv Aging* 2018;**13**:947–56. doi:10.2147/CIA.S157089

47 The Picker Institute. *Patient - Centered Care 2015 : Scenarios , Vision , Goals & Next Steps*. 2004.

48 Cohen-Mansfield J, Skornick-Bouchbinder M, Brill S. Trajectories of End of Life: A Systematic Review. *Journals Gerontol - Ser B Psychol Sci Soc Sci* 2018;**73**:564–72. doi:10.1093/geronb/gbx093

49 Clegg A, Bates C, Young J, *et al.* Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* 2016;**45**:353–60. doi:10.1093/ageing/afw039

50 Amblàs-Novellas J, Murray SA, Espaulella J, *et al.* 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. *BMJ Open* 2016;**6**:e012340. doi:10.1136/bmjopen-2016-012340

FIGURE LEGENDS

Figure 1. Survival according to the degree of frailty in (A) the total study patients, (B) end-of-life people, and (C) Non End-of-life people.

Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

Figure 3. Survival probability of end-of-life people in the different illness trajectories according to Frail-VIG index value: Frail-VIG index 0.44 (15th percentile) (A), Frail-VIG index 0.56 (median) (B) and Frail-VIG index 0.68 (90th percentile) (C).

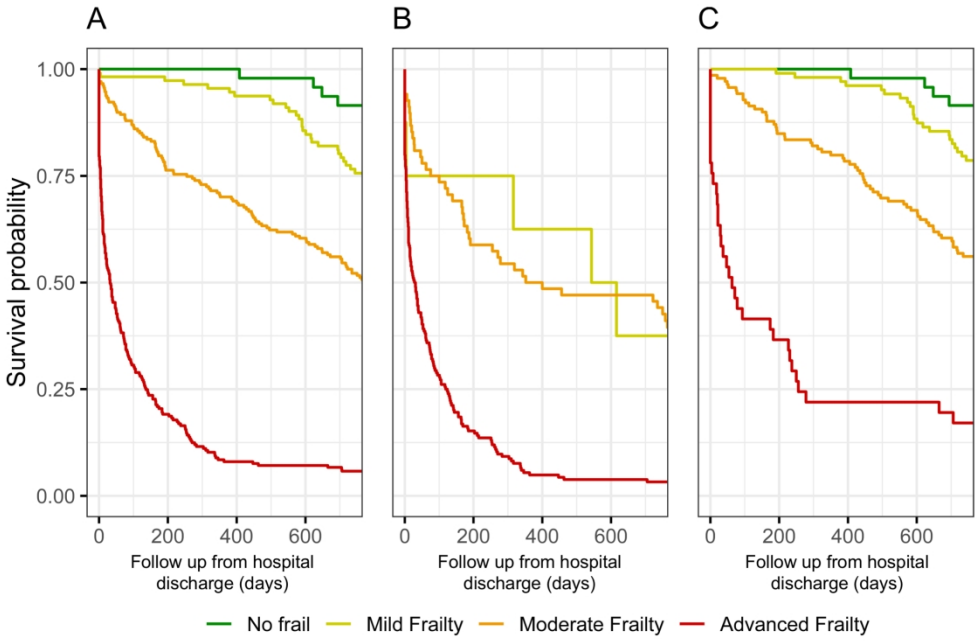

Figure 1. Survival according to the degree of frailty in (A) the total study patients, (B) end-of-life people, and (C) Non End-of-life people.

860x556mm (72 x 72 DPI)

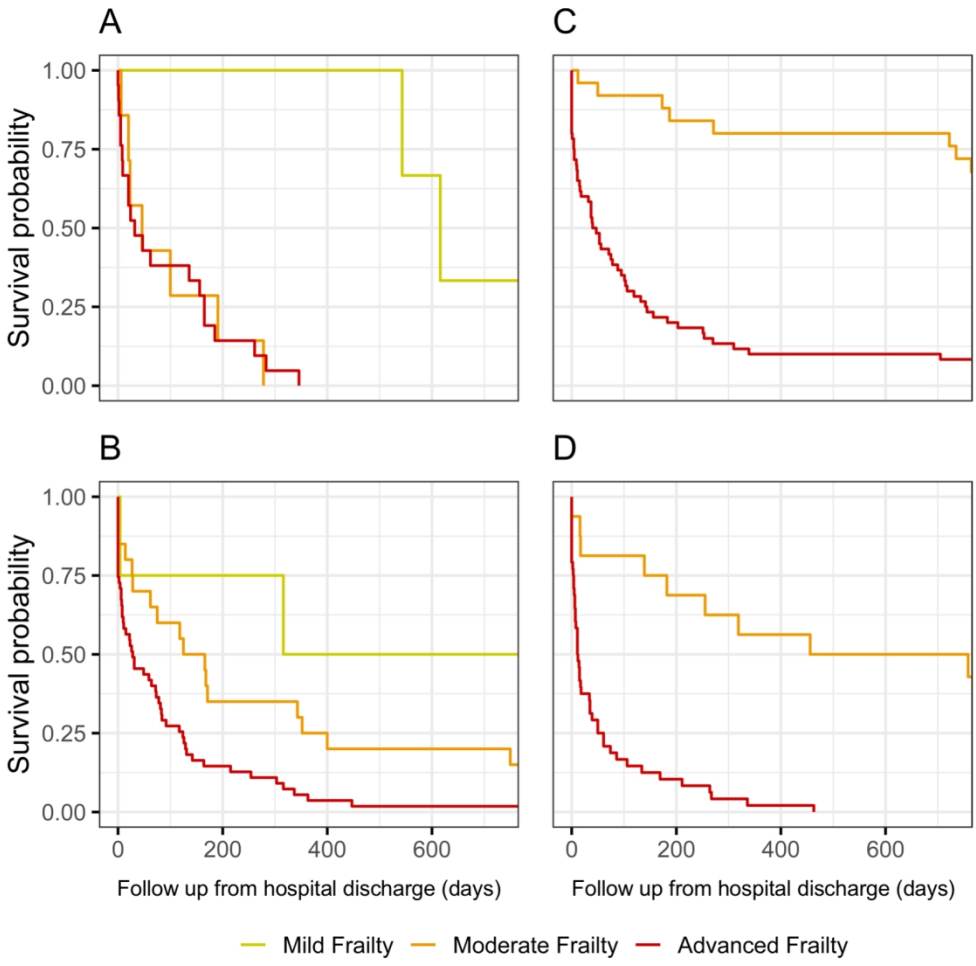

Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

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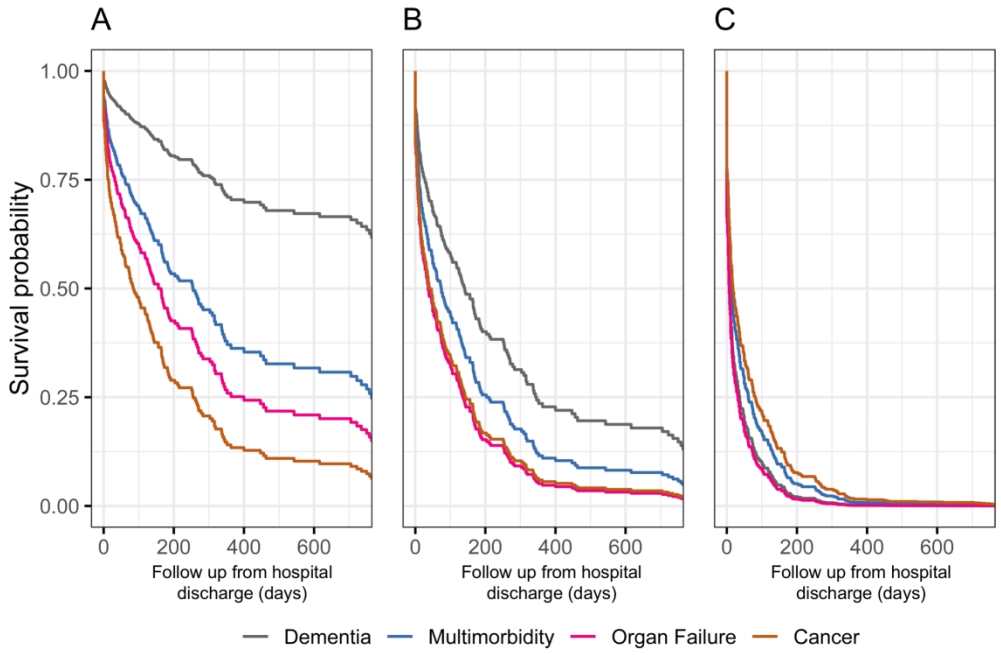

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874x564mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6, 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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	7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
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	9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 11

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-13 7 N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
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	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
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	18

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

BMJ Open

Frailty degree and illness trajectories in older people towards the end-of-life: a prospective observational study

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Secondary Subject Heading:	Geriatric medicine, Palliative care
Keywords:	GERIATRIC MEDICINE, Adult palliative care < PALLIATIVE CARE, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Frailty Degree and Illness Trajectories in Older People towards the End-of-life: a Prospective Observational Study

Authors

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Abstract

Objectives: To assess the degree of frailty in older people with different advanced diseases and its relationship with end-of-life illness trajectories and survival.

Methods: Prospective, observational study, including all patients admitted to the Acute Geriatric Unit of the University Hospital of Vic (Spain) during 12 consecutive months (2014 – 2015), followed for up to two years. Participants were identified as end-of-life people (EOLp) using the NECPAL tool and were classified according to their dominant illness trajectory. The Frail-VIG index, including 22 questions assessing 25 deficits, was used to quantify frailty degree, to calculate the relationship between frailty and mortality (ROC curves), and to assesss the combined effect of frailty degree and illness trajectories on survival (Cox proportional hazards model). Survival curves were plotted using the Kaplan-Meier estimator with participants classified into 4 groups (i.e., no frailty, mild frailty, moderate frailty, and advanced frailty) and were compared using the log-rank test.

Results: Of the 590 persons with a mean (SD) age of 86.4 (5.6) years recruited, 260 (44.1%) were identified as EOLp, distributed into cancer (n=31, 11.9%), organ failure (n=79, 30.4%), dementia (n=86, 33.1%), and multimorbidity (n=64, 24.6%) trajectories. All 260 EOLp had some degree of frailty, mostly advanced frailty (n=184, 70.8%), regardless of the illness trajectory, and 220 (84.6%) died within two years. The area under the ROC curve (CI) after two years of follow-up for EOLp was 0.87 (0.84-0.92) with different patterns of survival decline in the different end-of-life trajectories (p<0.0001). Cox regression analyses showed that each additional deficit of the Frail-VIG index increased the risk of death by 61.5%, 30.1%, 29.6% and 12.9% in people with dementia, organ failure, multimorbidity and cancer, respectively (p<0.01 for all the coefficients).

Conclusions: All older people towards the end-of-life in this study were frail, mostly with advanced frailty. The degree of frailty is related to survival across the different

illness trajectories despite the differing survival patterns among trajectories. Frailty indexes may be useful to assess end-of-life older people, regardless of their trajectory.

Keywords: Frailty, palliative care, mortality, multimorbidity, longitudinal study

Strengths and Limitations of this Study

- To our knowledge, this is the first study that evaluated the degree of frailty using a frailty index in older patients with different advanced illness trajectories.
- This is a real-life study, using tools routinely applied in the Acute Geriatric Unit conducting this study: the NECPAL, to identify people with palliative care needs, and the Frail-VIG index, to measure the degree of frailty and personalization of the interventions.
- In this context, assessing frailty degree may contribute to establish a common language between geriatric and palliative knowledge, with the goal of providing a better care for older people with palliative care needs, specially those in the first end-of-life transition.
- The use of a single computer system collecting the mortality status reported by all health providers prevented loss of patients and missing data, increasing the accuracy of the results.
- The results from this study were obtained in a very old population and the frail VIG index lacks sufficient external validation, potentially limiting their generalizability and raising the need for further studies in younger populations.

INTRODUCTION

The model of care for patients with advanced chronic conditions is currently shifting towards a new paradigm, characterized by early identification of persons with any disease or chronic condition who would benefit from palliative care [1,2]—this corresponds to the first transition in palliative care. Despite the benefits of this early identification,[3]the increasing number of people with palliative care needs, together with their high heterogeneity regarding age, needs, diseases, and chronic illnesses, poses novel challenges for early identification and assessment of these patients.[4,5] Indeed, the progression towards the end of life is conditioned by multiple variables and is strictly individual: not all people age in the same way nor reach the final situation with the same circumstances or needs.[6]

In the context of this new paradigm of "early palliative care", some authors have pointed to frailty as a crucial concept for persons needing palliative care —particularly older people with multimorbidity—, their caregivers, and healthcare professionals, to learn to manage the uncertainty and complexity of these end-of-life situations.[7–9] Given the relationship between mortality and frailty,[10] the concept of frailty has been proposed as a criterion useful in the three key steps ensuring good palliative care,[5,6,11,12] including 1) early identification of persons in end-of-life situation (particularly in cases of advanced frailty); 2) multidimensional assessment and situational diagnosis; and 3) drafting an advanced care plan and sharing decision-making.

Regardless of the proposed uses of frailty as an indicator, palliative care and geriatrics have traditionally used this concept, albeit with different perspectives.[8] In the setting of palliative care, frailty has equated to the third end-of-life trajectory and defined as the gradual decline in physical function, typically associated with dementia.[13,14] In contrast, from the geriatric perspective, frailty is rather a multidimensional clinical entity

defined as a vulnerability state against stressing factors due to limited compensatory mechanisms.[15] Of the multiple instruments developed to assess frailty, frailty indexes (i.e., the ratio between accumulated deficits in a given person and the total possible deficits) may have utility in identifying people with frailty for end-of-life care across all disease groups.[8,16]

A better understanding of how to provide the best palliative care for frail older people has become an international priority[17] and, considering the increased difficulty of identifying dying people in very old age (>85 years),[18–20] the concept of frailty is increasingly acknowledged as a cornerstone in the assessment and care of persons in an end-of-life situation and needing palliative care.[15,21] However, a consensus on how to use the concept of frailty to provide palliative care to end-of-life people (EOLp) remains to be established.[15,22,23] In this study, aimed at improving the care of end-of-life older people, we assessed the degree of frailty in a geriatric cohort with different advanced diseases and its relationship with end-of-life illness trajectories and survival.

METHODS

Study Design and Participants

This was a prospective, observational study, including all patients admitted to the Acute Geriatric unit (AGU) at the University Hospital of Vic (Barcelona, Spain) during 12 consecutive months (January 2014 – January 2015). The University Hospital of Vic is a 200-bed acute care hospital covering a population area of 156,000 inhabitants. Admission criteria to the AGU, which were the criteria for inclusion in this study, were age ≥ 85 years, cognitive decline, and/or end-of-life situation; no exclusion criteria were defined. The methods, including study design, variables, data sources, and study size have been described in a previous study.[24] Of the patients included in this study (i.e., those

admitted to the AGU), those identified as non end-of-life were included in a control group of patients aged ≥ 85 years and/or with cognitive decline. The results of this subanalysis are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[25] All patients and family relatives of patients with advanced dementia situation (GDS ≥ 6) signed the written informed consent for participation before any data was recorded. The study protocol was approved by the Ethics Committee of the University Hospital of Vic (2,014,850 PR80); this study was conducted in accordance with the Helsinki Declaration and the local Personal Data Protection Law (LOPD 15/1999).

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Variables and Data Sources

Frailty was assessed using the Frail-VIG index, a tool consisting in 22 questions to assess 25 deficits commonly associated with age and adverse health outcomes, based on the cumulative deficit model of frailty. Fifteen of the 22 questions refer to chronic conditions, including geriatric conditions and syndromes. The Frail-VIG index is a continuous variable expressed as a score ranging from 0 to 1. To simplify the representation of the survival curves, Frail-VIG index scores were expressed as a categorical variable classified into 4 groups according to the degree of frailty: no frailty (Frail-VIG index score <0.2), mild frailty (Frail-VIG index score 0.2-0.35), moderate frailty (Frail-VIG index score 0.36-0.5), and advanced frailty (Frail-VIG index score

>0.5). In addition to its predicitive value, previous studies have shown the content, construct, criteria, and convergent-divergent construct validity of the Frail-VIG index [24,26–28]. EOLp were identified using the NECPAL tool, a validated tool for the early identification of the need for palliative care among individuals with limited life expectancy.[29–31] EOLp were classified into the 3 archetypal end-of-life trajectories according to the severity and/or progression criteria for their main underlying disease: cancer, organ failure (including chronic pulmonary disease, chronic heart disease, serious chronic liver disease, and serious chronic renal disease), and dementia (including other chronic neurological diseases). People with palliative care needs without a predominant advanced disease were identified as "multimorbidity" group or trajectory, since all had 2 or more underlying chronic conditions.

After inclusion of the last patient in the study (i.e., last admitted patient in the AGU before January 15th, 2015) and before starting data analysis in 2017, patients were followed for up to 24 months (2015 - beginning 2017). Information regarding the patient status after the 24-month follow-up period was obtained from the Shared Medical Record in Catalonia (HC3), a sole electronic database accessible to all healthcare providers in Catalonia that allows healthcare professionals to reliably determine whether a patient is "active" (alive) or deceased (including date of death).[32]

Statistical Analysis

Qualitative variables were presented as frequencies and percentages, whereas quantitative variables were presented as the mean and the standard deviation (SD). Qualitative variables were compared using the Pearson's chi-squared test. In the complete cohort, the concordance between Frail-VIG index score and survival was evaluated using the C-statistics and the Kaplain-Meier estimator was used to plot survival curves for the four frailty degree subgroups, which were compared using the log-rank test. In the group of

people identified as end-of-life, survival curves for each illness trajectory were plotted using the Kaplan-Meier estimator and were compared using the log-rank test. A Cox proportional hazards model with the interaction between Frail-VIG index score and illness trajectories was calculated. Details of the construction of the Cox Proportional hazards model and calculation of the hazard ratios are provided in a Supplementary Material file. The assumption of proportional hazards was checked using the Schoenfeld residuals and a goodness-of-fit test.

The ROC curves were used to assess the ability of the Frail-VIG index to predict survival at one and two years by measuring their area under the receiver-operating curve (AUC) for the different illness trajectories. The significance level for all analyses was set at a two-sided α=0.05. The descriptive statistics analysis of the variables was performed using the SPSS software program (IBM; Chicago, IL; USA), and the survival analysis was performed using the *survival and pROC packages* from the R project (https://www.r-project.org).

RESULTS

Patient Characteristics and End-of-life Status

The study included 590 patients with a mean (SD, range) age of 86.4 (5.6, 48-105) years, of whom 339 (57.5%) were women. Based on the Frail-VIG index scores, 543 (92%) patients showed some degree of frailty, with 111 (18.8%), 207 (35.1%), and 225 (38.1%) patients showing mild, moderate and advanced frailty, respectively. Of the 590 patients included, 53 (8.9%) died during hospitalization, and 330 (55.9%) and 260 (44.1%) were identified as non-EOLp and EOLp, respectively. Of the 260 EOLp, 31 (11.9%), 79 (30.4%), 86 (33.1%), and 64 (24.6%) were classified in cancer, organ failure, dementia, and multimorbidity illness trajectories, respectively.

Relationship between End-of-life Status and Patient Characteristics

EOLp and non-EOLp had similar mean age and sex frequencies, but differed in the distribution among the 4 frailty groups: all EOLp (260) and 283 (85.8%) of the 330 non-EOLp were frail to some extent, with 252 (96.9%) and 180 (54.5%) showing moderate or advanced frailty in the EOLp and non-EOLp group, respectively. Table 1 summarizes the frequencies of EOLp and non-EOLp across the various frailty categories and their main demographic characteristics.

Table 1. Classification of study patients according to the Frail-VIG index scores, demographic characteristics, and end-of-life status (n=590)

	Demographic characteristics		**Frailty Degree, *n (%)***			
	Age (years), *mean (SD)*	Sex (% of women)	Not frail	Mild Frailty	Moderate Frailty	Advanced Frailty
EOLp	86.3 (5.8)	54.6	0 (0)	8 (3.1)	68 (26.1)	184 (70.8)
Non-EOLp	86.5 (5.4)	59.7	47 (14.3)	103 (31.2)	139 (42.1)	41 (12.4)

EOLp: End-of-life people, Non-EOLp: Non End-of-life people; SD, standard deviation

Correspondingly, median Frail-VIG index scores were significantly higher in EOLp compared to non-EOLp: 0.56 and 0.36, respectively ($p<0.001$). In EOLp, the predominant frailty degree was persistently advanced for all end-of-life trajectory categories: cancer, organ failure, dementia, and multimorbidity (range 68-75%) (Table 2). All EOLp in the multimorbidity trajectory (n=64) were classified in the moderate and advanced frailty groups.

Table 2. Classification of end-of-life people according to demographic characteristics, Frail-VIG index scores and end-of-life trajectory (n=260), n (%)

	Demographic characteristics		Frailty degree, n (%)				
	Age (years), *mean (SD)*	Sex (% of women)	Not frail	Mild Frailty	Moderate Frailty	Advanced Frailty	Total
Cancer	85.7 (5.4)	45.2	0 (0)	3 (9.7)	7 (22.6)	21 (67.7)	31 (11.9)
Organ Failure	86.9 (5.3)	46.8	0 (0)	4 (5.1)	20 (25.3)	55 (69.6)	79 (30.4)
Dementia	85.4 (5.3)	65.1	0 (0)	1 (1.1)	25 (29.1)	60 (69.8)	86 (33.1)
Multimorbidity	86.9 (7.3)	54.7	0 (0)	0 (0)	16 (25.0)	48 (75.0)	64 (24.6)
Total	N/A	N/A	0 (0)	8 (3.1)	68 (26.1)	184 (70.8)	260

N/A, not applicable; SD, standard deviation

Relationship between Frailty Degree and Survival

Of the complete cohort (EOLp and non-EOLp), 338 (57.3%) study patients died during the 2-year follow-up period. Mortality was significantly higher in EOLp than in non-EOLp: 220 (84.6%) and 118 (35.7%), respectively ($p<0.001$). The log-rank test comparing the survival curves of each frailty degree revealed significant differences in the overall population ($X^2 = 423$, $p<0.0001$), EOLp ($X^2 = 69.9$, $p<0.0001$), and non-EOLp ($X^2 = 122$, $p<0.0001$) (Figure 1). Correspondingly, the C coefficient for concordance between the survival time and the Frail-VIG score was 0.8, indicating that higher scores of the Frail-VIG index are associated with lower survival.

Relationship between Frailty Degree and Survival in End-of-Life People

The frequencies of death at the end of the 2-year follow-up period for each trajectory in EOLp are presented in Table 3. Survival curves, plotted using the Kaplan-Meier model for each frailty category (i.e., mild, intermediate, and advanced), differed among the different end-of-life trajectories, revealing different patterns of survival decline according to the frailty degree (Figure 2).

Table 3. Status of end-of-life people according to the Frail-VIG index scores and end-of-life trajectory after the 2-year follow-up (n=260), n (%)

	n	Status	Mild Frailty	Moderate Frailty	Advanced Frailty	Total
Cancer	31	Dead	2 (6.5)	7 (22.6)	21 (67.7)	30 (96.8)
		Alive	1 (3.2)	0 (0)	0 (0)	1 (3.2)
Organ Failure	79	Dead	2 (2.5)	16 (20.2)	54 (68.4)	72 (91.1)
		Alive	2 (2.5)	4 (5.1)	1 (1.3)	7 (8.9)
Dementia	86	Dead	1 (1.2)	6 (6.9)	55 (64.0)	62 (72.1)
		Alive	0 (0)	19 (22.1)	5 (5.8)	24 (27.9)
Multimorbidity	64	Dead	0 (0)	8 (12.5)	48 (75.0)	56 (87.5)
		Alive	0 (0)	8 (12.5)	0 (0)	8 (12.5)

A Cox regression model with the interaction between Frail-VIG index and illness trajectories revealed that the effect of the frailty degree on survival was associated with illness trajectories (p<0.01 for all the coefficients), even though the influence of illness trajectory progressively decreased as the frailty degree increased (Figure 3 and Table S1). Sex and age were excluded as covariates due to their lack of statistical significance (Table S2 and S3). The proportional hazard assumption was supported by the Schoenfeld residuals (p>0.1 for both global and each covariate tests). The estimated hazard ratios were 1.61 for people with dementia (95% CI=1.43-1.81), 1.30 for people with organ failure (95% CI=1.18-1.43), 1.30 for people with multimorbidity (95% CI=1.18-1.42), and 1.13 for people with cancer (95% CI=1.02-1.25) (Table S4 and S5). These results show that for each additional deficit of the total of 25 deficits assessed (i.e., a 0.04 increase in the Frail-VIG index) the risk of death increased by 61.5%, 30.1%, 29.6% and 12.9% in people with dementia, organ failure, multimorbidity and cancer, respectively.

The ROC analysis of the Frail-VIG index for the EOLp showed an AUC of 0.87 (95% CI:0.83-0.92) after one year and 0.87 (95% CI:0.84-0.92) after two years of follow-up. Of the 184 EOLp with advanced frailty (Frail-VIG index score > 0.5), 178 (96.7%) had died at two years of follow-up. The AUC differed among each of the four end-of-life trajectories: cancer (1 and 0.93), organ failure (0.86 and 0.90), dementia (0.92 and 0.92) and multimorbidity (0.91 and 0.94), after one and two years of follow-up, respectively. Despite these differences, the AUC remained high irrespective of the illness trajectory. Regarding the sensitivity and specificity of the Frail-VIG index as prognosis factor of mortality, the most sensitive and specific cut-off was 0.5 at both one and two years after follow-up, showing a sensitivity of 0.81 and 0.85 and a specificity of 0.83 and 0.81, respectively.

DISCUSSION

In this prospective, observational study including 590 patients admitted at an Acute Geriatric unit (AGU), we found that all older patients were frail towards the end of life (the prevalence of moderate-to-advanced frailty was 97% among people within an end-of-life trajectory and 55% outside it). Furthermore, advanced frailty was the predominant frailty category (ranged 68 to 75%) for all end-of-life trajectories: cancer, organ failure, dementia, and multimorbidity. Overall, the Frail-VIG index had a high capacity to predict death at one and two years (AUC 0.87), albeit to a different extent for the end-of-life categories cancer, organ failure, dementia and multimorbidity (AUC was always >0.86 for mortality at either one or two years). This finding confirms the hypothesis that the degree of frailty is related to prognosis regardless of the illness trajectory.

The characteristics and outcomes of the cohort assessed in this study, which included all patients admitted to an Acute Geriatric unit (AGU), were similar to those previously reported. All the persons assessed in this study had a Frail-VIG index score <0.8, similar

to previous studies showing that the theoretical maximum score is 0.7. According to these studies, the accumulation of 2/3 of all possible deficits (Frailty index score >0.7) results in death due to the person's inability to overcome more deficits, a phenomenon defined as system failure.[33,34] Likewise, similar to previous studies in other populations, the mortality rate at 1 to 2 years in our cohort was nearly 100% for the EOLp with frailty index score >0.5.[34,35]

Furthermore, we provide evidence showing that the degree of frailty significantly influenced survival irrespective of the advanced illness and end-of-life trajectory. In spite of this general influence, the survival curves according to the frailty degree followed different patterns for the four end-of-life trajectories, enabling the description of different frailty or deficit accumulation end-of-life trajectories according to the main disease, specially in the absence of advanced frailty. As the frailty degree increased, differences between trajectories decreased, resulting in a trend towards a compression of survival curves in advanced frailty situations where mortality is very high irrespective of the main advanced illness and end-of-life trajectory. Thus, in EOLp with cancer, mortality rates were high regardless of the frailty degree (moderate or advanced), leading to the hypothesis, similar to recent studies, that cancer patients have a catastrophic accumulation of deficits.[36] In contrast, EOLp with dementia showed different mortality rates according to their frailty degree and died progressively, likely due to the natural history of the disease, suggesting a slower accumulation of deficits. People with multimorbidity and advanced frailty shows a survival profile similar to people with cancer, while those with moderate frailty have a survival rate more similar to people with dementia. Finally, persons with an organ disease would accumulate deficits in episodes, even though prospective studies with serial frailty indexes would be required to test this hypothesis.

In this regard, similar to recent studies describing different trajectories according to the evolution of the social, spiritual or psychological situation of EOLp,[3] prospective studies following the degree of frailty using electronic frailty indexes have described three different trajectories (i.e., rapidly rising frailty, moderately increasing frailty, and stable frailty).[36] Even though more studies would be required to describe different end-of-life frailty trajectories, the fact that each end-of-life trajectory resulted in different mortality curves supports a dynamic view of EOLp.

The traditional association of frailty to the "third end-of-life trajectory" (i.e., dementia) [13,14] has probably been influenced by the lack of specific prognostic instruments for persons in this trajectory, unlike those in the cancer [37,38] or organ disease [39,40] trajectories. Our results regarding the high prevalence of frailty in all end-of-life trajectories support the validity of the concept that frailty may be present in all trajectories beyond the dementia trajectory. In addition to expanding the concept of frailty, our study underscores the need to consider a further development of the end-of-life trajectories. Of the 260 people who were identified as people in end-of-life situation, 24.6% did not have severity criteria for a single disease, although all of them had at least 2 chronic conditions. The identification of this cluster of people with advanced frailty and multimorbidity can help provide them early palliative care, and the benefits derived from it.[41,42]

Frailty Indices based on a Comprehensive Geriatric Assessment, such as the Frail-VIG index, may help professionals address one of the current challenges in palliative care [18,19,43]: the identification, assessment, and management of older people (i.e., aged >80 years) with palliative care needs [20,44]. First, assessment and quantification of frailty degree, which is suitable to synthesize the results of a multidimensional evaluation, can be useful to validate the identification of people in an end-of-life situation;[12] secondly, due to its ability to discriminate between different degrees of severity, frailty

indexes can be very useful to healthcare professionals for the situational diagnosis of the first and second end-of-life transition,[6,12] and monitorization of EOLp evolution;[45,46] and finally, quantification of frailty would enable palliative care customization [47,48] and engage people, caregivers and healthcare professionals in sharing decision-making and advance care planning.

The results of this study should be interpreted in the context of some limitations, particularly regarding the generalizability of the results. Firstly, the recruitment strategy based on an AGU solely enriched our study sample with older patients, likely precluding the applicability of these study results to younger patients. Secondly, the analysis of EOLp frailty across the various end-of-life trajectory categories importantly reduced the number of patients in each group, thus limiting the statistical power of these analyses. However, despite the reduced number of patients in some groups, our analysis yielded statistically significant results. In spite of its limitations, to our knowledge, this study is the first to evaluate the degree of frailty using a frailty index in very old patients identified as EOLp. Frailty was evaluated in a cohort of geriatric patients, including EOLp and non-EOLp, and the data for this study was collected during routine geriatric assessment, as opposed to previous studies that used electronic health record data to evaluate the degree of frailty.[49] Moreover, the single computer information system of Catalonia (HC3) that collects the medical records and mortality status of all patients reported by all health providers prevented loss of patients up to follow-up.[32] Consequently, the lack of missing data due to the HC3 system, along with the use of standard and validated tools to identify EOLp (NECPAL) and to measure frailty (Frail-VIG index) increased the accuracy of the results obtained from this study. The early identification of people needing palliative care and the more accurate definition of the various end-of-life trajectories opened the door to a novel perspective of palliative care.[50] In this regard,

the use of frailty as an overarching concept in the assessment of all people in an end-of-life situation —at least of those with a multimorbid profile— might contribute to go one step further in this novel approach to palliative care.

CONCLUSIONS

Our results showed that all end-of-life people were frail (mostly with advanced frailty) irrespective of the end-of-life trajectory. Their degree of frailty, measured using the Frail-VIG index, influenced mortality. This indicates a close relationship between frailty, end-of-life status, and mortality for all people who die. Measuring frailty using a frailty index could be useful in routine practice for healthcare professionals to understand the heterogeneous nature of people needing palliative care and tailor their care to the patient's needs. The survival pattern of people with multimorbidity could support the description of a composite illness trajectory for this patient group.

DECLARATIONS

Ethics Approval and Consent to Participate

All patients and family relatives of patients with advanced dementia situation (GDS $\geq$ 6) signed the written informed consent for participation before any data was recorded. The study protocol was approved by the Ethics Committee of the University Hospital of Vic (2,014,850 PR80). This study was conducted in accordance with the Helsinki Declaration and the local Personal Data Protection Law (LOPD 15/1999).

Consent for publication

Not applicable.

Data Sharing

The anonymized datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

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Author's contributions

JAN, AT, JCM, and XGB were responsible for the conception and design of the study. JAN coordinated and substantially contributed to the data collection. JCM and RO performed the statistical analysis. All authors (JAN, SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) were involved in interpretation of data. JAN wrote the initial draft of the manuscript and all the other authors (SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) critically revised the manuscript. All authors (JAN, SAM, AT, JCM, SM, RO, NL, JE, SS and XGB) have provided approval for the final version of the manuscript submitted for publication and agree to be accountable for all aspects of the work.

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REFERENCES

1 Boyd K, Murray SSA. Recognising and managing key transitions in end of life

care. *BMJ* 2010;**341**:c4863. doi:10.1136/bmj.c4863

2 Gomez-Batiste X, Martinez-Munoz M, Blay C, *et al.* Identifying patients with chronic conditions in need of palliative care in the general population: development of the NECPAL tool and preliminary prevalence rates in Catalonia. *BMJ Support Palliat Care* 2013;**3**:300–8. doi:10.1136/bmjspcare-2012-000211

3 Murray SA, Kendall M, Mitchell G, *et al.* Palliative care from diagnosis to death. *BMJ* 2017;**356**:j878. doi:10.1136/bmj.j878

4 Kimbell B, Murray SA, Macpherson S BK. Embracing inherent uncertainty in advanced illness. *BMJ Br Med J* 2016;**354:i3802**.

5 Gómez-Batiste X, Blay C, Broggi MA, *et al.* Ethical Challenges of Early Identification of Advanced Chronic Patients in Need of Palliative Care. *J Palliat Care* 2018;**33**:247–51. doi:10.1177/0825859718788933

6 Amblàs-Novellas J, Espaulella J, Rexach L et al, *et al.* Frailty, severity, progression and shared decision-making: A pragmatic framework for the challenge of clinical complexity at the end of life. *Eur Geriatr Med* 2015;**6**:189–194. doi:10.1016/j.eurger.2015.01.002

7 Cardona-Morrell M, Lewis E, Suman S, *et al.* Recognising older frail patients near the end of life: What next? *Eur J Intern Med* 2017;**45**:84–90. doi:10.1016/j.ejim.2017.09.026

8 Koller K, Rockwood K. Frailty in older adults: Implications for end-of-life care. *Cleve Clin J Med* 2013;**80**:168–74. doi:10.3949/ccjm.80a.12100

9 Stow D, Spiers G, Matthews FE, *et al.* What is the evidence that people with frailty have needs for palliative care at the end of life? A systematic review and narrative synthesis. *Palliat Med* 2019;**33**:399–414. doi:10.1177/0269216319828650

10 Mousa A, Savva GM, Mitnitski A, *et al.* Is frailty a stable predictor of mortality

across time? Evidence from the Cognitive Function and Ageing Studies. *Age Ageing* 2018;**47**:721–7. doi:10.1093/ageing/afy077

11 Pialoux T, Goyard J, Hermet R. When frailty should mean palliative care. *J Nurs Educ Pract* 2013;**3**:75–84. doi:10.5430/jnep.v3n7p75

12 Pollack LR, Goldstein NE, Gonzalez WC, *et al.* The Frailty Phenotype and Palliative Care Needs In Older Survivors of Critical Illness Lauren. *J Am Geriatr Soc* 2018;**65**:1168–75. doi:10.1111/jgs.14799.The

13 Lunney JR, Lynn J, Foley DJ, *et al.* Patterns of functional decline at the end of life. *JAMA* 2003;**289**:2387–92. doi:10.1001/jama.289.18.2387

14 Murray S a, Boyd K, Sheikh A. Palliative care in chronic illness. *BMJ* 2005;**330**:611–2. doi:10.1136/bmj.330.7492.611

15 Rodríguez-Mañas L, Féart C, Mann G, *et al.* Searching for an operational definition of frailty: A delphi method based consensus statement. the frailty operative definition-consensus conference project. *Journals Gerontol - Ser A Biol Sci Med Sci* 2013;**68**:62–7. doi:10.1093/gerona/gls119

16 Cesari M, Gambassi G, van Kan GA, *et al.* The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing* 2014;**43**:10–2. doi:10.1093/ageing/aft160

17 Bone AE, Morgan M, Maddocks M, *et al.* Developing a model of short-term integrated palliative and supportive care for frail older people in community settings: perspectives of older people, carers and other key stakeholders. *Age Ageing* 2016;**45**:863–73. doi:10.1093/ageing/afw124

18 Moriarity J, Rutter D, Ross PD, *et al.* End of life care for people with dementia living in care homes. 2012;:4p.

19 Dixon J, King D, Matosevic T, *et al.* Equity in the provision of palliative care in

the UK: Review of evidence. 2015;:145.

20 Teggi D. Unexpected death in ill old age: An analysis of disadvantaged dying in the English old population. *Soc Sci Med* 2018;**217**:112–20. doi:10.1016/j.socscimed.2018.09.048

21 Cesari M, Prince M, Thiyagarajan JA, *et al.* Frailty: An Emerging Public Health Priority. *J Am Med Dir Assoc* 2016;**17**:188–92. doi:10.1016/j.jamda.2015.12.016

22 Moorhouse P, Rockwood K, Morley JE, *et al.* Frailty Consensus: A Call to Action. *J Am Med Dir Assoc* 2013;**14**:392–7. doi:http://dx.doi.org/10.1016/j.jamda.2013.03.022

23 British Geriatrics Society. End of Life Care in Frailty: Identification and prognostication | British Geriatrics Society. https://www.bgs.org.uk/resources/end-of-life-care-in-frailty-identification-and-prognostication (accessed 29 Nov 2020).

24 Amblàs-Novellas J, Martori JC, Espaulella J, *et al.* Frail-VIG index: a concise frailty evaluation tool for rapid geriatric assessment. *BMC Geriatr* 2018;**18**:29. doi:10.1186/s12877-018-0718-2

25 von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–7. doi:10.1016/S0140-6736(07)61602-X

26 Amblàs-Novellas J, Martori JC, Molist Brunet N, *et al.* Frail-VIG index: Design and evaluation of a new frailty index based on the Comprehensive Geriatric Assessment. *Rev Esp Geriatr Gerontol* 2017;**52**:119–27. doi:10.1016/j.regg.2016.09.003

27 Moreno-Ariño M, Torrente Jiménez I, Cartanyà Gutiérrez A, *et al.* Assessing the

strengths and weaknesses of the Clinical Frailty Scale through correlation with a frailty index. *Aging Clin Exp Res* 2020;**32**:2225–32. doi:10.1007/s40520-019-01450-w

28 Madruga-Flores M, Gómez-del Río R, Delgado-Domínguez L, *et al.* Capacidad predictiva de fragilidad basal y fuerza de prensión al ingreso en resultados al alta en una unidad geriátrica de recuperación funcional. *Rev Esp Geriatr Gerontol* Published Online First: 19 January 2021. doi:10.1016/J.REGG.2020.12.002

29 Gómez-Batiste X, Martínez-Muñoz M, Blay C, *et al.* Prevalence and characteristics of patients with advanced chronic conditions in need of palliative care in the general population: A cross-sectional study. *Palliat Med* 2014;**28**:302–11. doi:10.1177/0269216313518266

30 Gómez-Batiste X, Turrillas P, Tebé C, *et al.* NECPAL tool prognostication in advanced chronic illness: A rapid review and expert consensus. *BMJ Support Palliat Care* Published Online First: 2020. doi:10.1136/bmjspcare-2019-002126

31 CENTRAL CATALONIA CHRONICITY RESEARCH GROUP. Utility of NECPAL. https://en.c3rg.com/necpal (accessed 29 Nov 2020).

32 Solans O, Gallego C, Garcia-Cuyas F, *et al.* Shared Medical Record, Personal Health Folder and Health and Social Integrated Care in Catalonia. In: *New Perspectives in Medical Records*. Springer, Cham 2017. 49–64. doi:10.1007/978-3-319-28661-7_4

33 Rockwood K, Mitnitski A. Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty. Clin. Geriatr. Med. 2011;**27**:17–26. doi:10.1016/j.cger.2010.08.008

34 Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. *Mech Age Dev* 2006;**127**:494–6. doi:10.1016/j.mad.2006.01.002

35 Rockwood K, Rockwood MRH, Mitnitski A. Physiological redundancy in older adults in relation to the change with age in the slope of a frailty index. *J Am Geriatr Soc* 2010;**58**:318–23. doi:10.1111/j.1532-5415.2009.02667.x

36 Stow D, Matthews FE, Hanratty B. Frailty trajectories to identify end of life: A longitudinal population-based study. *BMC Med* 2018;**16**:1–7. doi:10.1186/s12916-018-1148-x

37 Evans C, McCarthy M. Prognostic uncertainty in terminal care: can the Karnofsky index help? *Lancet (London, England)* 1985;**1**:1204–6. doi:10.1016/s0140-6736(85)92876-4

38 Anderson F, Downing GM, Hill J, *et al.* Palliative Performance Scale (PPS): A new tool. *J Palliat Care* 1996;**12**:5–11.

39 van Dijk WD, van den Bemt L, van den Haak-Rongen S, *et al.* Multidimensional prognostic indices for use in COPD patient care. A systematic review. Respir. Res. 2011;**12**:151. doi:10.1186/1465-9921-12-151

40 Walter LC, Brand RJ, Counsell SR, *et al.* Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA* 2001;**285**:2987–94. doi:10.1001/jama.285.23.2987

41 Moine S, Murray SA, Boyd K, *et al.* Palliative care and the endless cycle of serious health-related suffering. Lancet. 2018;**392**:471–2. doi:10.1016/S0140-6736(18)31195-4

42 Aldridge MD, Bradley EH. Epidemiology and patterns of care at the end of life: Rising complexity, shifts in care patterns and sites of death. *Health Aff* 2017;**36**:1175–83. doi:10.1377/hlthaff.2017.0182

43 (NCPC) NC for PC. National Council for Palliative Care (NCPC) Briefing The Government ' s National Commitment For End Of Life Care. 2016.

44 PA C, GE G, DA R, *et al.* Prediction of appropriate timing of palliative care for older adults with non-malignant life-threatening disease: a systematic review. *Age Ageing* 2005;**34**. doi:10.1093/AGEING/AFI054

45 Gill TM, Gahbauer E a, Allore HG, *et al.* Transitions between frailty states among community-living older persons. *Arch Intern Med* 2006;**166**:418–23. doi:10.1001/archinte.166.4.418

46 Liu ZY, Wei YZ, Wei LQ, *et al.* Frailty transitions and types of death in Chinese older adults: A population-based cohort study. *Clin Interv Aging* 2018;**13**:947–56. doi:10.2147/CIA.S157089

47 The Picker Institute. *Patient - Centered Care 2015 : Scenarios , Vision , Goals & Next Steps*. 2004.

48 Cohen-Mansfield J, Skornick-Bouchbinder M, Brill S. Trajectories of End of Life: A Systematic Review. *Journals Gerontol - Ser B Psychol Sci Soc Sci* 2018;**73**:564–72. doi:10.1093/geronb/gbx093

49 Clegg A, Bates C, Young J, *et al.* Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* 2016;**45**:353–60. doi:10.1093/ageing/afw039

50 Amblàs-Novellas J, Murray SA, Espaulella J, *et al.* 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. *BMJ Open* 2016;**6**:e012340. doi:10.1136/bmjopen-2016-012340

FIGURE LEGENDS

Figure 1. Survival according to the degree of frailty in (A) the total study patients, (B) end-of-life people, and (C) Non End-of-life people.

Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

Figure 3. Survival probability of end-of-life people in the different illness trajectories according to Frail-VIG index value: Frail-VIG index 0.44 (15th percentile) (A), Frail-VIG index 0.56 (median) (B) and Frail-VIG index 0.68 (90th percentile) (C).

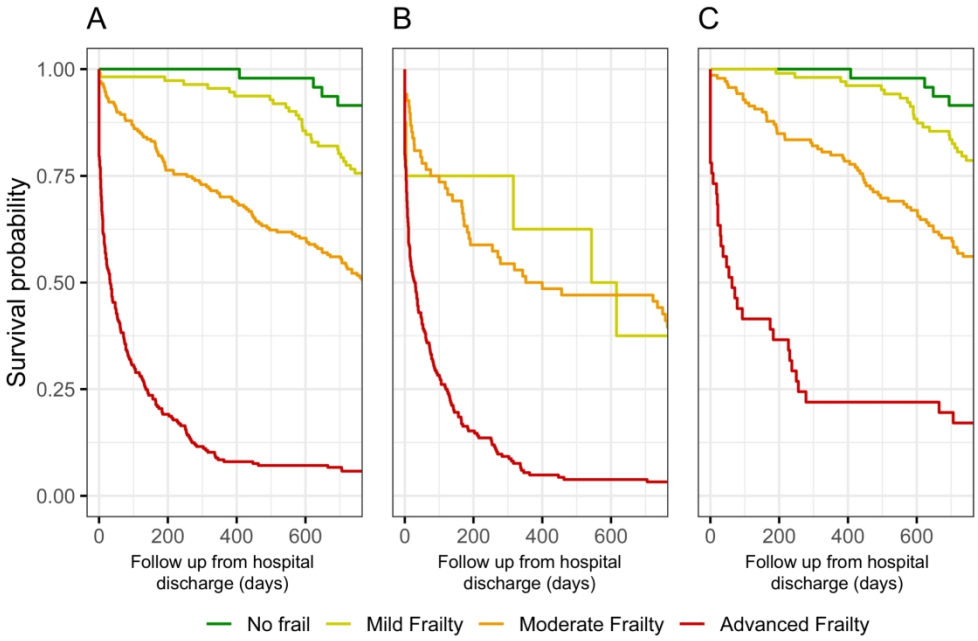

Figure 1. Survival according to the degree of frailty in (A) the total study patients, (B) end-of-life people, and (C) Non End-of-life people.

860x556mm (72 x 72 DPI)

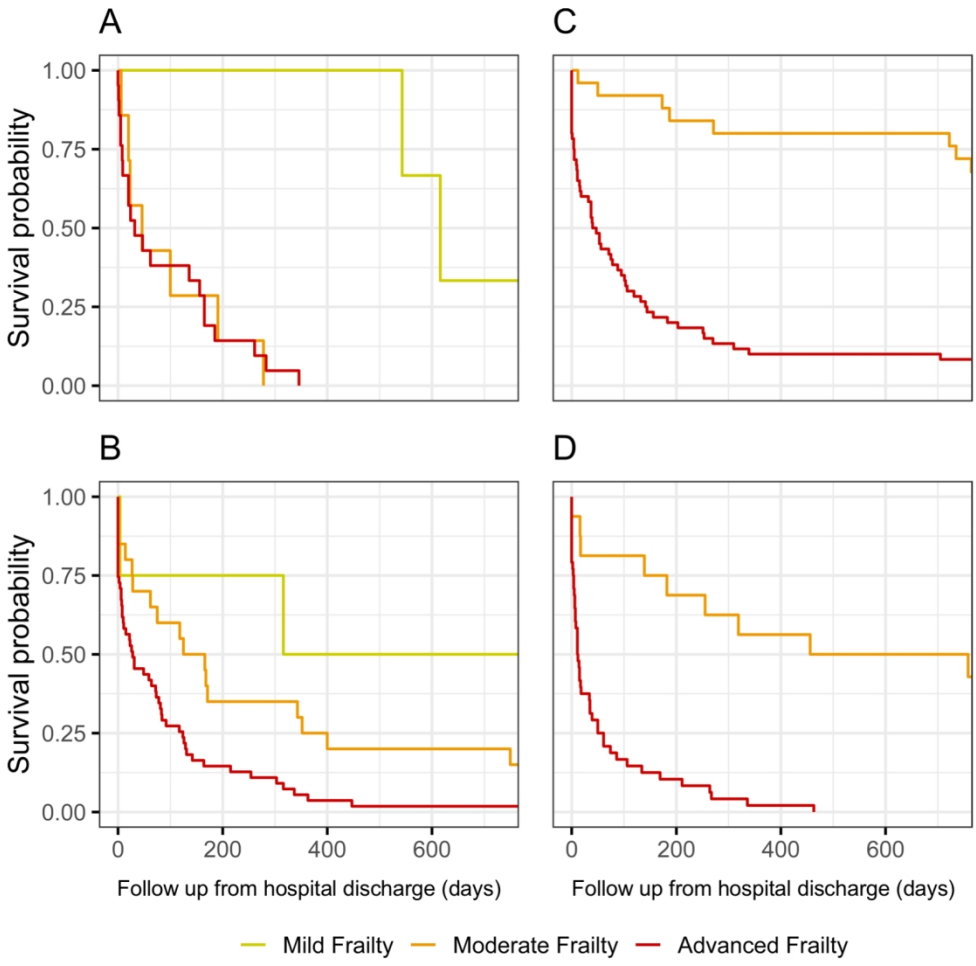

Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

616x593mm (72 x 72 DPI)

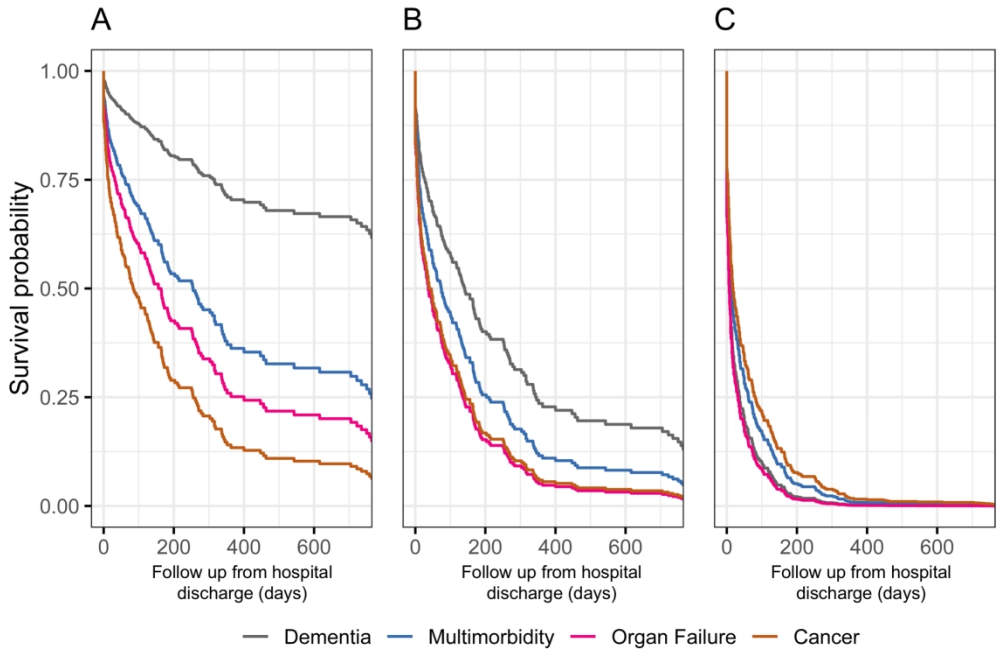

Figure 3. Survival probability of end-of-life poeple in the different illness trajectories according to Frail-VIG index value: Frail-VIG index 0.44 (15th percentile) (A), Frail-VIG index 0.56 (median) (B) and Frail-VIG index 0.68 (90th percentile) (C).

874x564mm (72 x 72 DPI)

Supplementary Information for the Submission by Amblàs-Novellas et al. "Frailty Degree and Illness Trajectories in Older People towards the End-of-life: A Prospective Observational Study".

Supplementary Methods

Construction of the Cox Proportional Hazards Model and Calculation of Hazard Ratios

A Cox Proportional Hazards (PH) model was constructed considering a multiplicative interaction between the Frail-VIG index and the qualitative variable "illness trajectory" (dementia was set as the reference category); see the estimation results in Table S1. When the model was constructed considering sex and age as covariates, sex lacked statistical significance (Table S2) and, similarly, upon removal of sex from the model, age lacked statistical significance (Table S3). Consequently, sex and age were excluded and Frail-VIG index score and Illness trajectories were the only covariates that remained in the final Cox PH model (Table S1).

To calculate hazard ratios for each illness trajectory, each hazard ratio was computed as the exponential of the sum of the coefficient of the Frail-VIG index (11.99) and each interaction coefficient (0, -5.41, -5.51, -8.96), yielding hazard ratios for one unit increase in the Frail-VIG index (Table S4). However, as Frail-VIG index scores are expressed as 0.04 increments for each additional deficit of a total of 25 deficits (1/25=0.04), hazard ratios were subsequently raised to 0.04, to calculate hazard ratios consistent with the units of Frail-VIG index scores (Table S5).

Supplementary Tables

Table S1. Cox Proportional Hazards fit

Variable	Beta	SE	z	P	95% CI
Frail-VIG index score	11.99	1.48	8.09	**<0.001**	(9.08, 14.89)
Illness trajectory					
Dementia (ref)	-	-	-	-	-
Organ Failure	3.75	1.05	3.56	**<0.001**	(1.69, 5.82)
Multimorbidity	3.48	1.08	3.23	**0.001**	(1.37, 5.60)
Cancer	5.69	1.12	5.10	**<0.001**	(3.50, 7.87)
Frail-VIG index by trajectory					
Organ Failure	-5.41	1.82	-2.98	**0.003**	(-8.97, -1.85)
Multimorbidity	-5.51	1.80	-3.07	**0.002**	(-9.02, -1.99)
Cancer	-8.96	1.96	-4.57	**<0.001**	(-12.80, -5.12)

Table S2. Cox Proportional Hazards fit with sex and age

Variable	Beta	SE	z	P	95% CI
Frail-VIG index score	11.91	1.46	8.14	**<0.001**	(9.04, 14.78)
Illness trajectory					
Dementia (ref)	-	-	-	-	-
Organ Failure	3.44	1.05	3.26	**0.001**	(1.37, 5.50)
Multimorbidity	3.13	1.07	2.92	**0.003**	(1.03, 5.23)
Cancer	5.80	1.09	5.32	**<0.001**	(3.66, 7.94)
Sex					
Female (ref)	-	-	-	-	-
Male	0.22	0.14	1.62	0.11	(-0.05, 0.49)
Age	0.03	0.01	2.20	**0.03**	(0.00, 0.05)
Frail-VIG by trajectory					
Organ Failure	-4.96	1.81	-2.74	**0.006**	(-8.52, -1.41)
Multimorbidity	-5.01	1.78	-2.82	**0.005**	(-8.49, -1.53)
Cancer	-9.35	1.92	-4.88	**<0.001**	(-13.11, -5.59)

Table S3. Cox Proportional Hazards fit with age

Variable	Beta	SE	z	P	95% CI
Frail-VIG index score	11.94	1.48	8.09	**<0.001**	(9.05, 14.83)
Illness trajectory					
Dementia (ref)	-	-	-	-	-
Organ Failure	3.57	1.05	3.39	**<0.001**	(1.50, 5.64)
Multimorbidity	3.18	1.08	2.94	**0.003**	(1.06, 5.30)
Cancer	5.77	1.11	5.21	**<0.001**	(3.60, 7.95)
Age	0.02	0.01	1.99	0.05	(0.00, 0.05)
Frail-VIG by trajectory					
Organ Failure	-5.12	1.82	-2.82	**0.005**	(-8.68, -1.56)
Multimorbidity	-5.06	1.79	-2.82	**0.005**	(-8.57, -1.55)
Cancer	-9.17	1.95	-4.71	**<0.001**	(-12.98, -5.35)

Table S4. Hazard ratios for one unit increase in the Frail-VIG index

Variable	Hazard Ratio	Lower	Upper	*P*-value
Dementia	160727.38	8807.45	2933118.39	0.00
Organ Failure	717.52	64.17	8023.37	0.00
Multimorbidity	652.87	62.60	6808.63	0.00
Cancer	20.66	1.47	290.10	0.02

Table S5. Hazard ratios for a 0.04 unit increase in the Frail-VIG index

Variable	Hazard Ratio	Lower	Upper	*P*-value
Dementia	1.62	1.44	1.81	0.00
Organ Failure	1.30	1.18	1.43	0.00
Multimorbidity	1.30	1.18	1.42	0.00
Cancer	1.13	1.02	1.25	0.02

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6, 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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	7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
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	9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 11

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-13 7 N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
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	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
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	18

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.