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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 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.

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3 The survival pattern of people with multimorbidity could support the description of a new
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5 composite illness trajectory.
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8 **Keywords:** Frailty, palliative care, mortality, multimorbidity, longitudinal study
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15 **Strengths and Limitations of this Study**

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

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3 contrast, from the geriatric perspective, frailty is rather a multidimensional clinical entity
4 defined as a vulnerability state against stressing factors due to limited compensatory
5 mechanisms.[15] Of the multiple instruments developed to assess frailty, frailty indexes
6 (i.e., the ratio between accumulated deficits in a given person and the total possible
7 deficits) may have utility in identifying people with frailty for end-of-life care across all
8 disease groups.[8,16]
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12 A better understanding of how to provide the best palliative care for frail older people has
13 become an international priority,[17] and the concept of frailty is increasingly
14 acknowledged as a cornerstone in the assessment and care of persons in an end-of-life
15 situation and needing palliative care.[15,18] However, a consensus on how to use the
16 concept of frailty to provide palliative care to end-of-life people remains to be
17 established.[15,19] In this study, aimed at improving the care of end-of-life people in
18 general, we tested the hypothesis that all end-of-life people are significantly frail
19 irrespective of their underlying diseases and that their frailty is measurable and related to
20 their prognosis.
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39 **METHODS**

40 **Study Design and Participants**

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44 This was a prospective, observational study, including all patients admitted to the Acute
45 Geriatric unit (AGU) at the University Hospital of Vic (Barcelona, Spain) during 12
46 consecutive months (January 2014 – January 2015). The University Hospital of Vic is a
47 200-bed acute care hospital covering a population area of 156,000 inhabitants. Admission
48 criteria to the AGU were age \geq 85 years, cognitive decline, and/or end-of-life situation;
49 no exclusion criteria were defined. The methods, including study design, variables, data
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3 sources, and study size have been described in a previous study conducted in the same
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5 setting.[20] The study results are reported according to the Strengthening the Reporting
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7 of Observational Studies in Epidemiology (STROBE) recommendations.[21] All patients
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9 and family relatives of patients with advanced dementia situation ($GDS \geq 6$) signed the
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11 written informed consent for participation before any data was recorded. The study
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13 protocol was approved by the Ethics Committee of the University Hospital of Vic
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15 (2,014,850 PR80); this study was conducted in accordance with the Helsinki Declaration
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17 and the local Personal Data Protection Law (LOPD 15/1999).
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23 **Patient and Public Involvement**

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26 This research was done without patient involvement. Patients were not invited to
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28 comment on the study design and were not consulted to develop patient relevant outcomes
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30 or interpret the results. Patients were not invited to contribute to the writing or editing of
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32 this document for readability or accuracy.
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37 **Variables and Data Sources**

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41 Frailty was assessed using the Frail-VIG index, a tool consisting in 22 questions to assess
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43 25 deficits commonly associated with age and adverse health outcomes, based on the
44
45 cumulative deficit model of frailty. The Frail-VIG index is a continuous variable ranging
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47 from 0 to 1 and classified into 4 groups: no frailty (Frail-VIG index score <0.2), mild
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49 frailty (Frail-VIG index score 0.2-0.35), moderate frailty (Frail-VIG index score 0.36-
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51 0.5), and advanced frailty (Frail-VIG index score >0.5) [20]. End-of-life people were
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53 identified using the NECPAL tool, a validated tool for the early identification of the need
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55 for palliative care among individuals with limited life expectancy.[22,23] End-of-life
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57 people were classified into the 3 archetypal end-of-life trajectories according to the
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3 severity and/or progression criteria for their main underlying disease: cancer, organ
4 failure (including chronic pulmonary disease, chronic heart disease, serious chronic liver
5 disease, and serious chronic renal disease), and dementia (including other chronic
6 neurological diseases). People with palliative care needs without a predominant advanced
7 disease were identified as "multimorbidity" group or trajectory, since all had 2 or more
8 underlying chronic conditions.
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12 After inclusion of the last patient in the study (i.e., last admitted patient in the AGU before
13 January 15th, 2015) and before starting data analysis in 2017, patients were followed for
14 up to 24 months (2015 - beginning 2017). Information regarding the patient status after
15 the 24-month follow-up period was obtained from the Shared Medical Record in
16 Catalonia (HC3), a sole electronic database accessible to all healthcare providers in
17 Catalonia that allows healthcare professionals to reliably determine whether a patient is
18 "active" (alive) or deceased (including date of death).[24]
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39 **Statistical Analysis**

40 Qualitative variables were presented as frequencies and percentages, whereas quantitative
41 variables were presented as the mean and the standard deviation (SD). Qualitative
42 variables were compared using the Pearson's chi-squared test. The relationship between
43 frailty degree and survival has been evaluated using the C-statistics (to analyze the
44 concordance), the log-rank test (to evaluate the association) and the ROC curves (to
45 measure the prognostic capability of mortality at 24 months). Survival curves were
46 plotted using the Kaplan-Meier estimator, and compared using the log-rank test. The
47 significance level for all analyses was set at a two-sided $\alpha=0.05$. The descriptive statistics
48 analysis of the variables was performed using the SPSS software program (IBM; Chicago,
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3 IL; USA), and the survival analysis was performed using the Survival, pROC, and RMS
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5 packages from the R project (<https://www.r-project.org>).
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8 9 **RESULTS**

10 11 12 13 **Patient Characteristics and End-of-life Status**

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

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40 End-of-life people and non-end-of-life people had similar mean age (86.3 and 86.5 years,
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42 respectively) and sex frequencies (54.6% and 59.7% females, respectively), but differed
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44 in the distribution among the 4 frailty groups: all end-of-life people (260) and 283
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46 (85.8%) of the 330 non-end-of-life people were frail to some extent, with 252 (96.9%)
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48 and 180 (54.5%) showing moderate or advanced frailty in the end-of-life people and non-
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50 end-of-life people group, respectively. Table 1 summarizes the frequencies of end-of-life
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52 and non-end-of-life people across the various frailty categories.
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58 **Table 1.** Classification of study patients according to the Frail-VIG index scores
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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%

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3 CI:0.84-0.92) after two years of follow-up. Of the 184 end-of-life people with advanced
4 frailty (Frail-VIG index score > 0.5), 178 (96.7%) had died at two years of follow-up.
5
6 The AUC differed among each of the faour end-of-life trajectories: cancer (1 and 0.93),
7 organ failure (0.86 and 0.90), dementia (0.92 and 0.92) and multimorbidity (0.91 and
8 0.94), after one and two years of follow-up, respectively. Regarding the sensitivity and
9 specificity of the Frail-VIG index as prognosis factor of mortality, the most sensitive and
10 specific cut-off was 0.5 at both one and two years after follow-up, showing a sensitivity
11 of 0.81 and 0.85 and a specificity of 0.83 and 0.81, respectively.
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22 **DISCUSSION**

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26 In this prospective, observational study including 590 patients admitted at an Acute
27 Geriatric unit (AGU), we found that all older patients were frail towards the end of life
28 (the prevalence of moderate-to-advanced frailty was 97% among people within an end-
29 of-life trajectory and 55% outside it). Furthermore, advanced frailty was the predominant
30 frailty category (ranged 68 to 75%) for all end-of-life trajectories: cancer, organ failure,
31 dementia, and multimorbidity. Overall, the Frail-VIG index had a high capacity to predict
32 death at one and two years (AUC 0.87), albeit to a different extent for the end-of-life
33 categories cancer, organ failure, dementia and multimorbidity (AUC was always >0.86
34 for mortality at either one or two years). This finding confirms the hypothesis that the
35 degree of frailty is related to prognosis regardless of the illness trajectory.
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50 The characteristics and outcomes of the cohort assessed in this study, which included all
51 patients admitted to an Acute Geriatric unit (AGU), were similar to those previously
52 reported. All the persons assessed in this study had a Frail-VIG index score <0.8, similar
53 to previous studies showing that the theoretical maximum score is 0.7. According to these
54 studies, the accumulation of 2/3 of all possible deficits (Frailty index score >0.7) results
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3 in death due to the person's inability to overcome more deficits, a phenomenon defined
4 as system failure.[25,26] Likewise, similar to previous studies in other populations, the
5 mortality rate in our cohort was nearly 100% for the end of life people with frailty index
6 score >0.5.[26,27]
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13 Furthermore, we provide evidence showing that frailty, measured using the Frail-VIG
14 index, significantly influenced survival irrespective of the advanced illness and end-of-
15 life trajectory. In spite of this general influence, the survival curves according to the frailty
16 degree followed different patterns for the four end-of-life trajectories, enabling the
17 description of different frailty or deficit accumulation end-of-life trajectories according
18 to the main disease. Thus, in end-of-life people with cancer, mortality rates were high
19 regardless of the frailty degree (moderate or advanced), leading to the hypothesis, similar
20 to recent studies, that cancer patients have a catastrophic accumulation of deficits.[28] In
21 contrast, end-of-life people with dementia showed different mortality rates according to
22 their frailty degree and died progressively, likely due to the natural history of the disease,
23 suggesting a slower accumulation of deficits. People with multimorbidity and advanced
24 frailty shows a survival profile similar to people with cancer, while those with moderate
25 frailty have a survival rate more similar to people with dementia. Finally, persons with an
26 organ disease would accumulate deficits in episodes, even though prospective studies
27 with serial frailty indexes would be required to test this hypothesis.
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49 In this regard, similar to recent studies describing different trajectories according to the
50 evolution of the social, spiritual or psychological situation of end-of-life people,[3]
51 prospective studies following the degree of frailty using electronic frailty indexes have
52 described three different trajectories (i.e., rapidly rising frailty, moderately increasing
53 frailty, and stable frailty).[28] Even though more studies would be required to describe
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3 different end-of-life frailty trajectories, the fact that each end-of-life trajectory resulted in
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5 different mortality curves supports a dynamic view of end-of-life people.
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9 The traditional association of frailty to the “third end-of-life trajectory” (i.e., dementia)
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11 [13,14] has probably been influenced by the lack of specific prognostic instruments for
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13 persons in this trajectory, unlike those in the cancer [29,30] or organ disease [31,32]
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15 trajectories. Our results regarding the high prevalence of frailty in all end-of-life
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17 trajectories support the validity of the concept that frailty may be present in all trajectories
18
19 beyond the dementia trajectory. In addition to expanding the concept of frailty, our study
20
21 underscores the need to consider a further development of the end-of-life trajectories. Of
22
23 the 260 people who were identified as people in end-of-life situation, 24.6% did not have
24
25 severity criteria for a single disease, although all of them had at least 2 chronic conditions.
26
27 The identification of this cluster of people with advanced frailty and multimorbidity can
28
29 help provide them early palliative care, and the benefits derived from it.[33,34]
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35 Moreover, the fact that the concept of frailty is valid for all end-of-life trajectories grants
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37 practical uses of quantitative frailty assessment in the management and identification of
38
39 end-of-life people.[8] First, assessment and quantification of frailty using a frailty index,
40
41 which is suitable to synthesize the results of a multidimensional evaluation, can be useful
42
43 to validate the identification of people in an end-of-life situation;[12] secondly, due to its
44
45 ability to discriminate between different degrees of severity, frailty indexes can be very
46
47 useful to healthcare professionals for the situational diagnosis of the first and second end-
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49 of-life transition,[6,12] and monitorization of end-of-life people evolution;[35,36] and
50
51 finally, quantification of frailty would enable palliative care customization [37,38] and
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53 engage people, caregivers and healthcare professionals in sharing decision-making and
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55 advance care planning.
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3 The results of this study should be interpreted in the context of some limitations,
4 particularly regarding the generalizability of the results. Firstly, the recruitment strategy
5 based on an AGU solely was likely to enrich our study sample with older patients and
6 consequently, the results of this study may be only applicable to older patients. Secondly,
7 although the study site was a reference hospital covering an area of 156,000 inhabitants,
8 the sociodemographic characteristics of our sample might not match those of the overall
9 population. Finally, the analysis of end-of-life people frailty across the various end-of-
10 life trajectory categories importantly reduced the number of patients in each group, thus
11 limiting the statistical power of these analyses. However, despite the reduced number of
12 patients in some groups, our analysis yielded statistically significant results. In spite of
13 its limitations, to our knowledge, this study is the first to evaluate the degree of frailty
14 using a frailty index in patients identified as end-of-life people. Frailty was evaluated in
15 a cohort of geriatric patients, including end-of-life and non-end-of-life people, and the
16 data for this study was collected during routine geriatric assessment, as opposed to
17 previous studies that used electronic health record data to evaluate the degree of
18 frailty.[39] Moreover, the single computer information system of Catalonia (HC3) that
19 collects the medical records and mortality status of all patients reported by all health
20 providers prevented loss of patients up to follow-up.[24] Consequently, the lack of
21 missing data due to the HC3 system, along with the use of standard and validated tools to
22 identify end-of-life people (NECPAL) and to measure frailty (Frail-VIG index) increased
23 the accuracy of the results obtained from this study. The early identification of people
24 needing palliative care and the more accurate definition of the various end-of-life
25 trajectories opened the door to a novel perspective of palliative care.[40] In this regard,
26 the use of frailty as an overarching concept in the assessment of all people in an end-of-
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3 life situation —at least of those with a multimorbid profile— might contribute to go one
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5 step further in this novel approach to palliative care.
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8 9 **CONCLUSIONS**

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12 Our results showed that all end-of-life people were frail (mostly with advanced frailty)
13
14 irrespective of the end-of-life trajectory. Their degree of frailty, measured using the Frail-
15
16 VIG index, influenced mortality. This indicates a close relationship between frailty, end-
17
18 of-life status, and mortality for all people who die. Measuring frailty using a frailty index
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20 could be useful in routine practice for healthcare professionals to understand the
21
22 heterogeneous nature of people needing palliative care and tailor their care to the patient's
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24 needs. The survival pattern of people with multimorbidity could support the description
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26 of a composite illness trajectory for this patient group.
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32 33 **DECLARATIONS**

34 35 36 **Ethics Approval and Consent to Participate**

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39 All patients and family relatives of patients with advanced dementia situation ($GDS \geq 6$)
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41 signed the written informed consent for participation before any data was recorded. The
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43 study protocol was approved by the Ethics Committee of the University Hospital of Vic
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45 (2,014,850 PR80). This study was conducted in accordance with the Helsinki Declaration
46
47 and the local Personal Data Protection Law (LOPD 15/1999).
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53 54 **Consent for publication**

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57 Not applicable.
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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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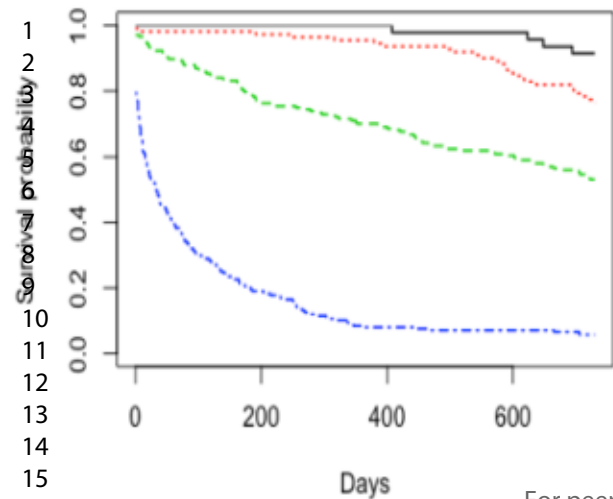
FIGURE LEGENDS

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.

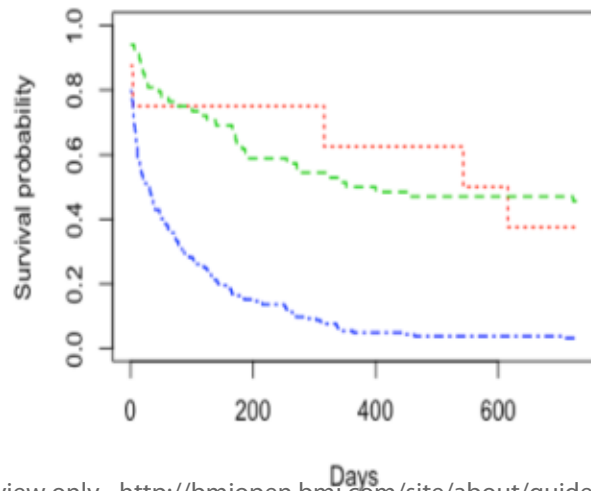
Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

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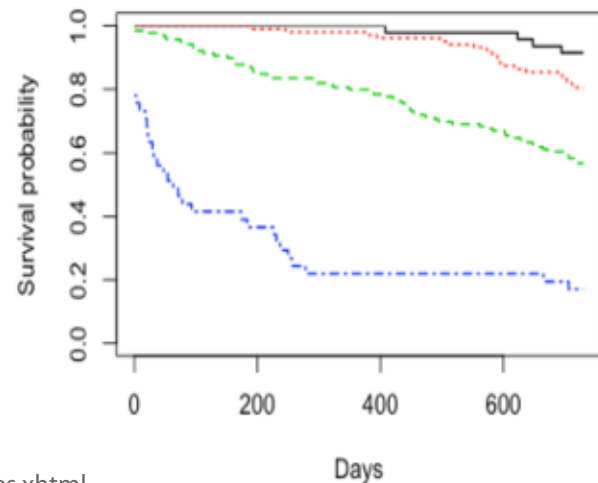
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BMJ Open (B)



(C)

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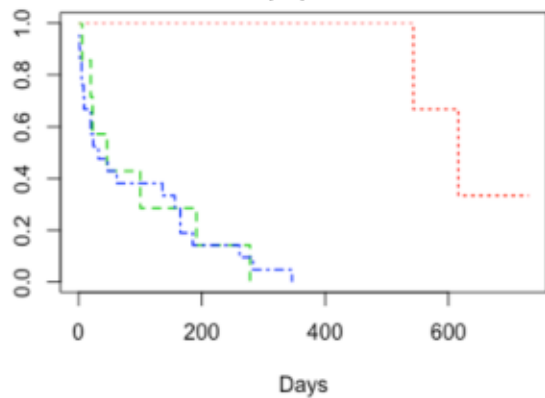
--- Advanced Frailty

--- Moderate Frailty

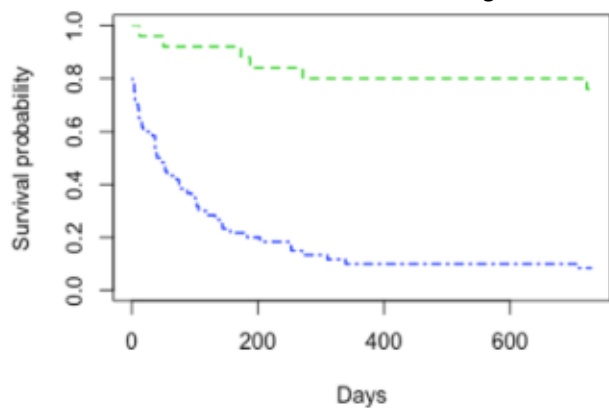
... Mild Frailty

— No frail

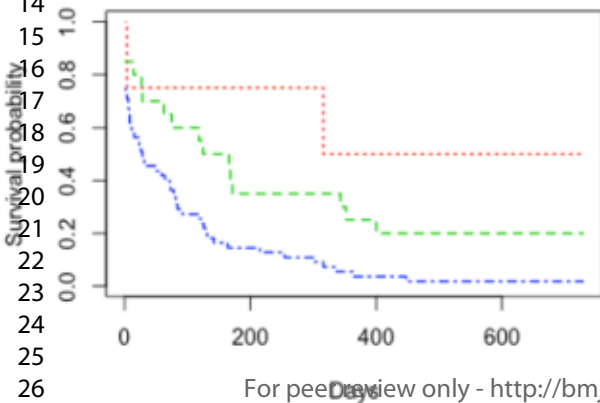
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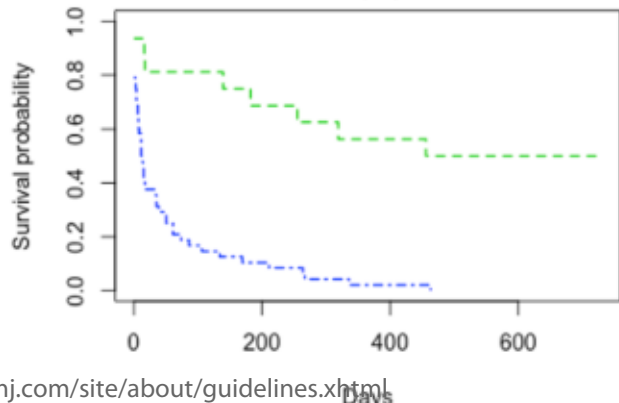
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— Advanced Frailty - - - Moderate Frailty . . . Mild Frailty

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	6, 8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8 8 N/A N/A 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 N/A N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 N/A 11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 11

1	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	9-13
2			(b) Report category boundaries when continuous variables were categorized	7
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
4				
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	13
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
14	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
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
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21	Other information			
22	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
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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>.

BMJ Open

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

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Primary Subject Heading:	Palliative care
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

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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).

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3 **Conclusions:** All older people towards the end-of-life are frail, mostly with advanced
4 frailty. The degree of frailty, the different illness trajectories, and survival show a tight
5 correlation. Frailty indexes may be useful to assess end-of-life older people, regardless of
6 their trajectory.
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13 **Keywords:** Frailty, palliative care, mortality, multimorbidity, longitudinal study
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20 **Strengths and Limitations of this Study**

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

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3 contrast, from the geriatric perspective, frailty is rather a multidimensional clinical entity
4 defined as a vulnerability state against stressing factors due to limited compensatory
5 mechanisms.[15] Of the multiple instruments developed to assess frailty, frailty indexes
6 (i.e., the ratio between accumulated deficits in a given person and the total possible
7 deficits) may have utility in identifying people with frailty for end-of-life care across all
8 disease groups.[8,16]
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12 A better understanding of how to provide the best palliative care for frail older people has
13 become an international priority[17] and, considering the increased difficulty of
14 identifying dying people in very old age (>85 years),[18–20] the concept of frailty is
15 increasingly acknowledged as a cornerstone in the assessment and care of persons in an
16 end-of-life situation and needing palliative care.[15,21] However, a consensus on how to
17 use the concept of frailty to provide palliative care to end-of-life people remains to be
18 established.[15,22,23] In this study, aimed at improving the care of end-of-life older
19 people, we assessed the degree of frailty in a geriatric cohort with different advanced
20 diseases and its relationship with end-of-life illness trajectories and survival.
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40 **METHODS**

41 **Study Design and Participants**

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44 This was a prospective, observational study, including all patients admitted to the Acute
45 Geriatric unit (AGU) at the University Hospital of Vic (Barcelona, Spain) during 12
46 consecutive months (January 2014 – January 2015). The University Hospital of Vic is a
47 200-bed acute care hospital covering a population area of 156,000 inhabitants. Admission
48 criteria to the AGU were age \geq 85 years, cognitive decline, and/or end-of-life situation;
49 no exclusion criteria were defined. The methods, including study design, variables, data
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3 sources, and study size have been described in a previous study.[24] The results of this
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5 subanalysis are reported according to the Strengthening the Reporting of Observational
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7 Studies in Epidemiology (STROBE) recommendations.[25] All patients and family
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9 relatives of patients with advanced dementia situation ($GDS \geq 6$) signed the written
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11 informed consent for participation before any data was recorded. The study protocol was
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13 approved by the Ethics Committee of the University Hospital of Vic (2,014,850 PR80);
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15 this study was conducted in accordance with the Helsinki Declaration and the local
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17 Personal Data Protection Law (LOPD 15/1999).
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23 **Patient and Public Involvement**

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26 This research was done without patient involvement. Patients were not invited to
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28 comment on the study design and were not consulted to develop patient relevant outcomes
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30 or interpret the results. Patients were not invited to contribute to the writing or editing of
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32 this document for readability or accuracy.
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37 **Variables and Data Sources**

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40 Frailty was assessed using the Frail-VIG index, a tool consisting in 22 questions to assess
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42 25 deficits commonly associated with age and adverse health outcomes, based on the
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44 cumulative deficit model of frailty. Fifteen of the 22 questions refer to chronic
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46 conditions, including geriatric conditions and syndromes. The Frail-VIG index is a
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48 continuous variable ranging from 0 to 1 and classified into 4 groups: no frailty (Frail-VIG
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50 index score <0.2), mild frailty (Frail-VIG index score $0.2-0.35$), moderate frailty (Frail-
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52 VIG index score $0.36-0.5$), and advanced frailty (Frail-VIG index score >0.5). In addition
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54 to its predicitive value, previous studies have shown the content, construct, criteria, and
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56 convergent-divergent construct validity of the frail-VIG index [24,26,27]. End-of-life
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3 people were identified using the NECPAL tool, a validated tool for the early identification
4 of the need for palliative care among individuals with limited life expectancy.[28–30]
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6 End-of-life people were classified into the 3 archetypal end-of-life trajectories according
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8 to the severity and/or progression criteria for their main underlying disease: cancer, organ
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10 failure (including chronic pulmonary disease, chronic heart disease, serious chronic liver
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12 disease, and serious chronic renal disease), and dementia (including other chronic
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14 neurological diseases). People with palliative care needs without a predominant advanced
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16 disease were identified as "multimorbidity" group or trajectory, since all had 2 or more
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18 underlying chronic conditions.
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25 After inclusion of the last patient in the study (i.e., last admitted patient in the AGU before
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27 January 15th, 2015) and before starting data analysis in 2017, patients were followed for
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29 up to 24 months (2015 - beginning 2017). Information regarding the patient status after
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31 the 24-month follow-up period was obtained from the Shared Medical Record in
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33 Catalonia (HC3), a sole electronic database accessible to all healthcare providers in
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35 Catalonia that allows healthcare professionals to reliably determine whether a patient is
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37 "active" (alive) or deceased (including date of death).[31]
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42 **Statistical Analysis**

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45 Qualitative variables were presented as frequencies and percentages, whereas quantitative
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47 variables were presented as the mean and the standard deviation (SD). Qualitative
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49 variables were compared using the Pearson's chi-squared test. The concordance between
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51 frailty degree and survival has been evaluated using the C-statistics and the ROC curves
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53 were used to assess the ability of the Frail-VIG index to predict survival at 24 months by
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55 measuring their AUC. Survival curves were plotted using the Kaplan-Meier estimator,
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57 and survival curves for each illness trajectory were compared using the log-rank test. A
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3 Cox proportional hazards model with the interaction between frailty degree and illness
4 trajectories was calculated. The assumption of proportional hazards was checked using
5 the Schoenfeld residuals and a goodness-of-fit test. The significance level for all analyses
6 was set at a two-sided $\alpha=0.05$. The descriptive statistics analysis of the variables was
7 performed using the SPSS software program (IBM; Chicago, IL; USA), and the survival
8 analysis was performed using the *survival* and *pROC* packages from the R project
9 (<https://www.r-project.org>).

20 RESULTS

25 Patient Characteristics and End-of-life Status

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

48 Relationship between End-of-life Status and Patient Characteristics

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51 End-of-life people and non-end-of-life people had similar mean age and sex frequencies,
52 but differed in the distribution among the 4 frailty groups: all end-of-life people (260) and
53 283 (85.8%) of the 330 non-end-of-life people were frail to some extent, with 252
54 (96.9%) and 180 (54.5%) showing moderate or advanced frailty in the end-of-life people
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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 (%)				Total
	Age (years),	Sex (% of women)	Not frail	Mild Frailty	Moderate Frailty	Advanced Frailty	

	<i>mean</i>						
	<i>(SD)</i>						
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 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 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

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3 frailty (Frail-VIG index score > 0.5), 178 (96.7%) had died at two years of follow-up.
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5 The AUC differed among each of the four end-of-life trajectories: cancer (1 and 0.93),
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7 organ failure (0.86 and 0.90), dementia (0.92 and 0.92) and multimorbidity (0.91 and
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9 0.94), after one and two years of follow-up, respectively. Regarding the sensitivity and
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11 specificity of the Frail-VIG index as prognosis factor of mortality, the most sensitive and
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13 specific cut-off was 0.5 at both one and two years after follow-up, showing a sensitivity
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15 of 0.81 and 0.85 and a specificity of 0.83 and 0.81, respectively.
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20 **DISCUSSION**

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24 In this prospective, observational study including 590 patients admitted at an Acute
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26 Geriatric unit (AGU), we found that all older patients were frail towards the end of life
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28 (the prevalence of moderate-to-advanced frailty was 97% among people within an end-
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30 of-life trajectory and 55% outside it). Furthermore, advanced frailty was the predominant
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32 frailty category (ranged 68 to 75%) for all end-of-life trajectories: cancer, organ failure,
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34 dementia, and multimorbidity. Overall, the Frail-VIG index had a high capacity to predict
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36 death at one and two years (AUC 0.87), albeit to a different extent for the end-of-life
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38 categories cancer, organ failure, dementia and multimorbidity (AUC was always >0.86
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40 for mortality at either one or two years). This finding confirms the hypothesis that the
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42 degree of frailty is related to prognosis regardless of the illness trajectory.
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49 The characteristics and outcomes of the cohort assessed in this study, which included all
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51 patients admitted to an Acute Geriatric unit (AGU), were similar to those previously
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53 reported. All the persons assessed in this study had a Frail-VIG index score <0.8, similar
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55 to previous studies showing that the theoretical maximum score is 0.7. According to these
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57 studies, the accumulation of 2/3 of all possible deficits (Frailty index score >0.7) results
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59 in death due to the person's inability to overcome more deficits, a phenomenon defined
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3 as system failure.[32,33] Likewise, similar to previous studies in other populations, the
4 mortality rate at 1 to 2 years in our cohort was nearly 100% for the end of life people with
5 frailty index score >0.5 . [33,34]
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10 Furthermore, we provide evidence showing that the degree of frailty significantly
11 influenced survival irrespective of the advanced illness and end-of-life trajectory. In spite
12 of this general influence, the survival curves according to the frailty degree followed
13 different patterns for the four end-of-life trajectories, enabling the description of different
14 frailty or deficit accumulation end-of-life trajectories according to the main disease,
15 specially in the absence of advanced frailty. As the frailty degree increased, differences
16 between trajectories decreased, resulting in a trend towards a compression of survival
17 curves in advanced frailty situations where mortality is very high irrespective of the main
18 advanced illness and end-of-life trajectory. Thus, in end-of-life people with cancer,
19 mortality rates were high regardless of the frailty degree (moderate or advanced), leading
20 to the hypothesis, similar to recent studies, that cancer patients have a catastrophic
21 accumulation of deficits.[35] In contrast, end-of-life people with dementia showed
22 different mortality rates according to their frailty degree and died progressively, likely
23 due to the natural history of the disease, suggesting a slower accumulation of deficits.
24 People with multimorbidity and advanced frailty shows a survival profile similar to
25 people with cancer, while those with moderate frailty have a survival rate more similar to
26 people with dementia. Finally, persons with an organ disease would accumulate deficits
27 in episodes, even though prospective studies with serial frailty indexes would be required
28 to test this hypothesis.
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55 In this regard, similar to recent studies describing different trajectories according to the
56 evolution of the social, spiritual or psychological situation of end-of-life people,[3]
57 prospective studies following the degree of frailty using electronic frailty indexes have
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3 described three different trajectories (i.e., rapidly rising frailty, moderately increasing
4 frailty, and stable frailty).[35] Even though more studies would be required to describe
5 different end-of-life frailty trajectories, the fact that each end-of-life trajectory resulted in
6 different mortality curves supports a dynamic view of end-of-life people.
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13 The traditional association of frailty to the “third end-of-life trajectory” (i.e., dementia)
14 [13,14] has probably been influenced by the lack of specific prognostic instruments for
15 persons in this trajectory, unlike those in the cancer [36,37] or organ disease [38,39]
16 trajectories. Our results regarding the high prevalence of frailty in all end-of-life
17 trajectories support the validity of the concept that frailty may be present in all trajectories
18 beyond the dementia trajectory. In addition to expanding the concept of frailty, our study
19 underscores the need to consider a further development of the end-of-life trajectories. Of
20 the 260 people who were identified as people in end-of-life situation, 24.6% did not have
21 severity criteria for a single disease, although all of them had at least 2 chronic conditions.
22 The identification of this cluster of people with advanced frailty and multimorbidity can
23 help provide them early palliative care, and the benefits derived from it.[40,41]
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40 Frailty Indices based on a Comprehensive Geriatric Assessment, such as the Frail-VIG
41 index, may help professionals address one of the current challenges in palliative care
42 [18,19,42]: the identification, assessment, and management of older people (i.e., aged
43 >80 years) with palliative care needs [20,43]. First, assessment and quantification of
44 frailty degree, which is suitable to synthesize the results of a multidimensional evaluation,
45 can be useful to validate the identification of people in an end-of-life situation;[12]
46 secondly, due to its ability to discriminate between different degrees of severity, frailty
47 indexes can be very useful to healthcare professionals for the situational diagnosis of the
48 first and second end-of-life transition,[6,12] and monitorization of end-of-life people
49 evolution;[44,45] and finally, quantification of frailty would enable palliative care
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3 customization [46,47] and engage people, caregivers and healthcare professionals in
4 sharing decision-making and advance care planning.
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8 The results of this study should be interpreted in the context of some limitations,
9 particularly regarding the generalizability of the results. Firstly, the recruitment strategy
10 based on an AGU solely was likely to enrich our study sample with older patients, likely
11 precluding the applicability of these study results to younger patients. Secondly, the
12 analysis of end-of-life people frailty across the various end-of-life trajectory categories
13 importantly reduced the number of patients in each group, thus limiting the statistical
14 power of these analyses. However, despite the reduced number of patients in some
15 groups, our analysis yielded statistically significant results. In spite of its limitations, to
16 our knowledge, this study is the first to evaluate the degree of frailty using a frailty index
17 in very old patients identified as end-of-life people. Frailty was evaluated in a cohort of
18 geriatric patients, including end-of-life and non-end-of-life people, and the data for this
19 study was collected during routine geriatric assessment, as opposed to previous studies
20 that used electronic health record data to evaluate the degree of frailty.[48] Moreover, the
21 single computer information system of Catalonia (HC3) that collects the medical records
22 and mortality status of all patients reported by all health providers prevented loss of
23 patients up to follow-up.[31] Consequently, the lack of missing data due to the HC3
24 system, along with the use of standard and validated tools to identify end-of-life people
25 (NECPAL) and to measure frailty (Frail-VIG index) increased the accuracy of the results
26 obtained from this study. The early identification of people needing palliative care and
27 the more accurate definition of the various end-of-life trajectories opened the door to a
28 novel perspective of palliative care.[49] In this regard, the use of frailty as an overarching
29 concept in the assessment of all people in an end-of-life situation —at least of those with
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3 a multimorbid profile— might contribute to go one step further in this novel approach to
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5 palliative care.
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8 9 **CONCLUSIONS**

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12 Our results showed that all end-of-life people were frail (mostly with advanced frailty)
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14 irrespective of the end-of-life trajectory. Their degree of frailty, measured using the Frail-
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16 VIG index, influenced mortality. This indicates a close relationship between frailty, end-
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18 of-life status, and mortality for all people who die. Measuring frailty using a frailty index
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20 could be useful in routine practice for healthcare professionals to understand the
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22 heterogeneous nature of people needing palliative care and tailor their care to the patient's
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24 needs. The survival pattern of people with multimorbidity could support the description
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26 of a composite illness trajectory for this patient group.
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35 36 **DECLARATIONS**

37 38 39 **Ethics Approval and Consent to Participate**

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42 All patients and family relatives of patients with advanced dementia situation ($GDS \geq 6$)
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44 signed the written informed consent for participation before any data was recorded. The
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46 study protocol was approved by the Ethics Committee of the University Hospital of Vic
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48 (2,014,850 PR80). This study was conducted in accordance with the Helsinki Declaration
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50 and the local Personal Data Protection Law (LOPD 15/1999).
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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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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).

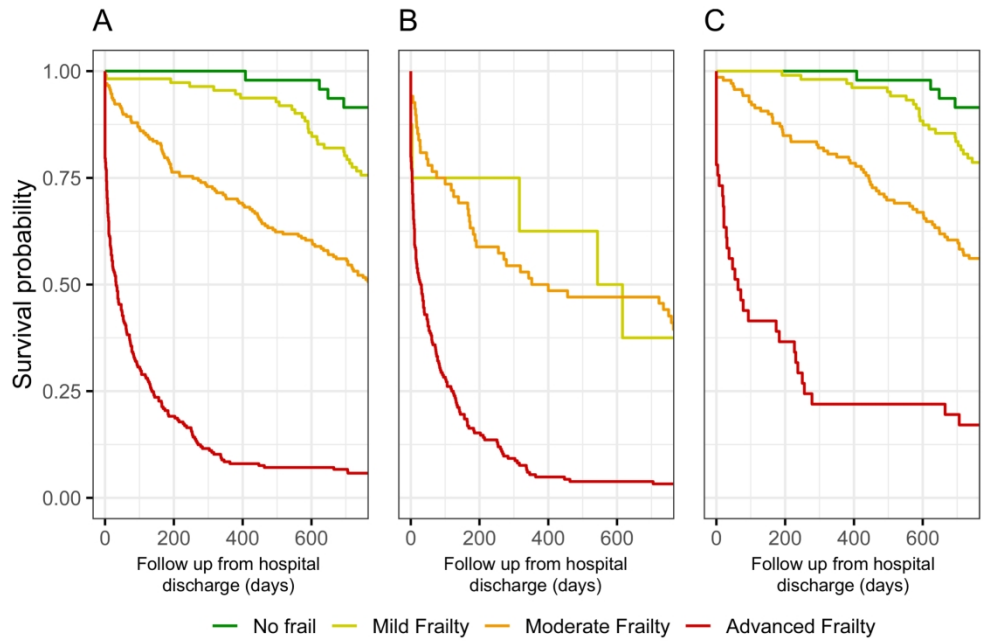


Figure 1. Survival according to the degree of frailty in (A) the total study patients, (B) end-of-life people, and (C) Non End-of-life people.

860x556mm (72 x 72 DPI)

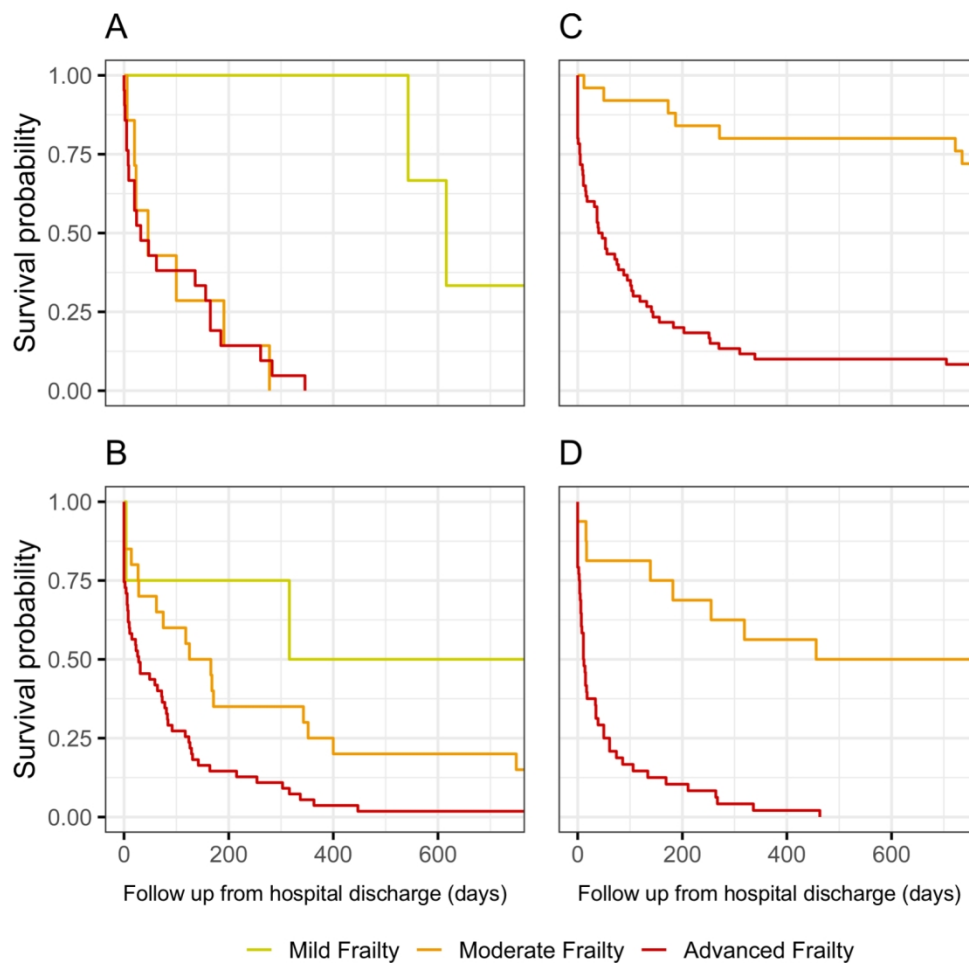


Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

616x593mm (72 x 72 DPI)

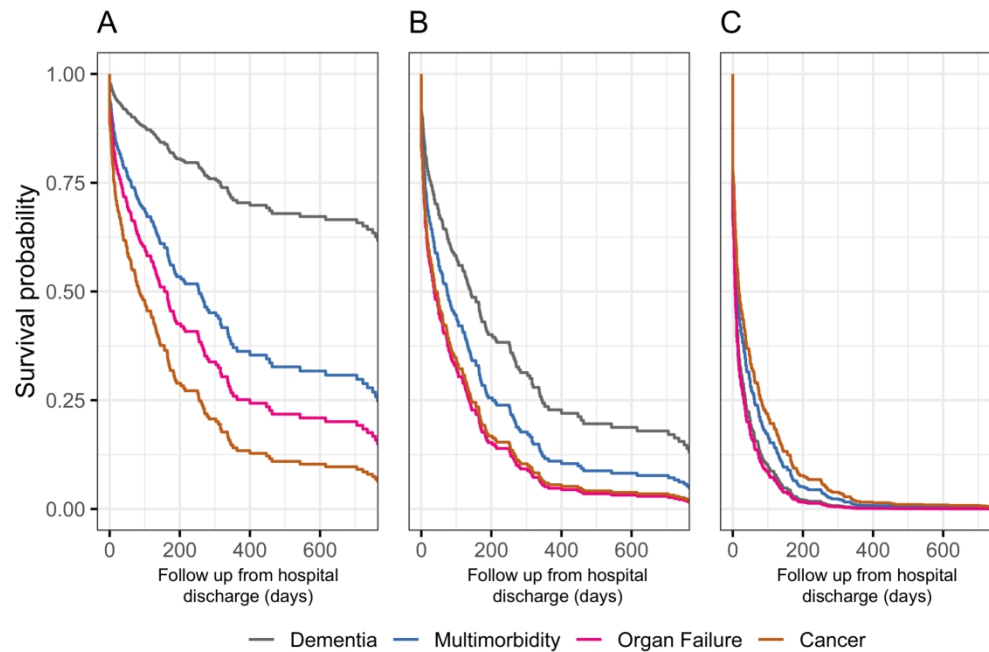


Figure 3. Survival probability of end-of-life people in the different illness trajectories according to Frail-VIG index value: Frail-VIG index 0.44 (15th percentile) (A), Frail-VIG index 0.56 (median) (B) and Frail-VIG index 0.68 (90th percentile) (C).

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	6, 8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8 8 N/A N/A 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 N/A N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 N/A 11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 11

1	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	9-13
2			(b) Report category boundaries when continuous variables were categorized	7
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
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11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	13
14	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
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
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18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
20				
21	Other information			
22				
23	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
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26 *Give information separately for exposed and unexposed groups.

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29 **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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BMJ Open

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

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Primary Subject Heading:	Palliative care
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

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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).

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3 **Conclusions:** All older people towards the end-of-life in this study were frail, mostly
4 with advanced frailty. The degree of frailty is related to survival across the different
5 illness trajectories despite the differing survival patterns among trajectories. Frailty
6 indexes may be useful to assess end-of-life older people, regardless of their trajectory.
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14 **Keywords:** Frailty, palliative care, mortality, multimorbidity, longitudinal study
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18 **Strengths and Limitations of this Study**

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

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

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

33 34 35 36 **METHODS**

37 38 39 40 41 **Study Design and Participants**

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43 This was a prospective, observational study, including all patients admitted to the Acute
44 Geriatric unit (AGU) at the University Hospital of Vic (Barcelona, Spain) during 12
45 consecutive months (January 2014 – January 2015). The University Hospital of Vic is a
46 200-bed acute care hospital covering a population area of 156,000 inhabitants. Admission
47 criteria to the AGU, which were the criteria for inclusion in this study, were age \geq 85
48 years, cognitive decline, and/or end-of-life situation; no exclusion criteria were defined.
49 The methods, including study design, variables, data sources, and study size have been
50 described in a previous study.[24] Of the patients included in this study (i.e., those
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3 admitted to the AGU), those identified as non end-of-life were included in a control group
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5 of patients aged ≥ 85 years and/or with cognitive decline. The results of this subanalysis
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7 are reported according to the Strengthening the Reporting of Observational Studies in
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9 Epidemiology (STROBE) recommendations.[25] All patients and family relatives of
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11 patients with advanced dementia situation ($GDS \geq 6$) signed the written informed consent
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13 for participation before any data was recorded. The study protocol was approved by the
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15 Ethics Committee of the University Hospital of Vic (2,014,850 PR80); this study was
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17 conducted in accordance with the Helsinki Declaration and the local Personal Data
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19 Protection Law (LOPD 15/1999).
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25 **Patient and Public Involvement**

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27 This research was done without patient involvement. Patients were not invited to
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29 comment on the study design and were not consulted to develop patient relevant outcomes
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31 or interpret the results. Patients were not invited to contribute to the writing or editing of
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33 this document for readability or accuracy.
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39 **Variables and Data Sources**

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41 Frailty was assessed using the Frail-VIG index, a tool consisting in 22 questions to assess
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43 25 deficits commonly associated with age and adverse health outcomes, based on the
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45 cumulative deficit model of frailty. Fifteen of the 22 questions refer to chronic
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47 conditions, including geriatric conditions and syndromes. The Frail-VIG index is a
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49 continuous variable ranging from 0 to 1 and classified into 4 groups: no frailty (Frail-VIG
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51 index score <0.2), mild frailty (Frail-VIG index score $0.2-0.35$), moderate frailty (Frail-
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53 VIG index score $0.36-0.5$), and advanced frailty (Frail-VIG index score >0.5). In addition
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55 to its predictive value, previous studies have shown the content, construct, criteria, and
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57 convergent-divergent construct validity of the Frail-VIG index [24,26–28]. EOLp were
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3 identified using the NECPAL tool, a validated tool for the early identification of the need
4 for palliative care among individuals with limited life expectancy.[29–31] EOLp were
5 classified into the 3 archetypal end-of-life trajectories according to the severity and/or
6 progression criteria for their main underlying disease: cancer, organ failure (including
7 chronic pulmonary disease, chronic heart disease, serious chronic liver disease, and
8 serious chronic renal disease), and dementia (including other chronic neurological
9 diseases). People with palliative care needs without a predominant advanced disease were
10 identified as "multimorbidity" group or trajectory, since all had 2 or more underlying
11 chronic conditions.
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23 After inclusion of the last patient in the study (i.e., last admitted patient in the AGU before
24 January 15th, 2015) and before starting data analysis in 2017, patients were followed for
25 up to 24 months (2015 - beginning 2017). Information regarding the patient status after
26 the 24-month follow-up period was obtained from the Shared Medical Record in
27 Catalonia (HC3), a sole electronic database accessible to all healthcare providers in
28 Catalonia that allows healthcare professionals to reliably determine whether a patient is
29 "active" (alive) or deceased (including date of death).[32]
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41 **Statistical Analysis**

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43 Qualitative variables were presented as frequencies and percentages, whereas quantitative
44 variables were presented as the mean and the standard deviation (SD). Qualitative
45 variables were compared using the Pearson's chi-squared test. In the complete cohort, the
46 concordance between frailty degree and survival was evaluated using the C-statistics and
47 the Kaplan-Meier estimator was used to plot survival curves, which were compared using
48 the log-rank test. In the group of people identified as end-of-life, survival curves for each
49 illness trajectory were plotted using the Kaplan-Meier estimator and were compared using
50 the log-rank test, and a Cox proportional hazards model with the interaction between
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3 frailty degree and illness trajectories was calculated. The assumption of proportional
4 hazards was checked using the Schoenfeld residuals and a goodness-of-fit test. The ROC
5 curves were used to assess the ability of the Frail-VIG index to predict survival at one
6 and two years by measuring their area under the receiver-operating curve (AUC) for the
7 different illness trajectories. The significance level for all analyses was set at a two-sided
8 $\alpha=0.05$. The descriptive statistics analysis of the variables was performed using the SPSS
9 software program (IBM; Chicago, IL; USA), and the survival analysis was performed
10 using the *survival* and *pROC* packages from the R project (<https://www.r-project.org>).
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22 RESULTS

23 Patient Characteristics and End-of-life Status

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27 The study included 590 patients with a mean (SD, range) age of 86.4 (5.6, 48-105) years,
28 of whom 339 (57.5%) were women. Based on the Frail-VIG index scores, 543 (92%)
29 patients showed some degree of frailty, with 111 (18.8%), 207 (35.1%), and 225 (38.1%)
30 patients showing mild, moderate and advanced frailty, respectively. Of the 590 patients
31 included, 53 (8.9%) died during hospitalization, and 330 (55.9%) and 260 (44.1%) were
32 identified as non-EOLp) and EOLp, respectively. Of the 260 EOLp, 31 (11.9%), 79
33 (30.4%), 86 (33.1%), and 64 (24.6%) were classified in cancer, organ failure, dementia,
34 and multimorbidity illness trajectories, respectively.
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50 Relationship between End-of-life Status and Patient Characteristics

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52 EOLp and non-EOLp had similar mean age and sex frequencies, but differed in the
53 distribution among the 4 frailty groups: all EOLp (260) and 283 (85.8%) of the 330 non-
54 EOLp were frail to some extent, with 252 (96.9%) and 180 (54.5%) showing moderate
55 or advanced frailty in the EOLp and non-EOLp group, respectively. Table 1 summarizes
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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 (%)				Total
	Age (years), mean (SD)	Sex (% of women)	Not frail	Mild Frailty	Moderate Frailty	Advanced Frailty	
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.

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3 Despite these differences, the AUC remained high irrespective of the illness trajectory.
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5 Regarding the sensitivity and specificity of the Frail-VIG index as prognosis factor of
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7 mortality, the most sensitive and specific cut-off was 0.5 at both one and two years after
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9 follow-up, showing a sensitivity of 0.81 and 0.85 and a specificity of 0.83 and 0.81,
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11 respectively.
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14 15 **DISCUSSION**

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18 In this prospective, observational study including 590 patients admitted at an Acute
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20 Geriatric unit (AGU), we found that all older patients were frail towards the end of life
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22 (the prevalence of moderate-to-advanced frailty was 97% among people within an end-
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24 of-life trajectory and 55% outside it). Furthermore, advanced frailty was the predominant
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26 frailty category (ranged 68 to 75%) for all end-of-life trajectories: cancer, organ failure,
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28 dementia, and multimorbidity. Overall, the Frail-VIG index had a high capacity to predict
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30 death at one and two years (AUC 0.87), albeit to a different extent for the end-of-life
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32 categories cancer, organ failure, dementia and multimorbidity (AUC was always >0.86
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34 for mortality at either one or two years). This finding confirms the hypothesis that the
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36 degree of frailty is related to prognosis regardless of the illness trajectory.
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41 The characteristics and outcomes of the cohort assessed in this study, which included all
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43 patients admitted to an Acute Geriatric unit (AGU), were similar to those previously
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45 reported. All the persons assessed in this study had a Frail-VIG index score <0.8, similar
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47 to previous studies showing that the theoretical maximum score is 0.7. According to these
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49 studies, the accumulation of 2/3 of all possible deficits (Frailty index score >0.7) results
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51 in death due to the person's inability to overcome more deficits, a phenomenon defined
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53 as system failure.[33,34] Likewise, similar to previous studies in other populations, the
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55 mortality rate at 1 to 2 years in our cohort was nearly 100% for the EOLp with frailty
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57 index score >0.5.[34,35]
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3 Furthermore, we provide evidence showing that the degree of frailty significantly
4 influenced survival irrespective of the advanced illness and end-of-life trajectory. In spite
5 of this general influence, the survival curves according to the frailty degree followed
6 different patterns for the four end-of-life trajectories, enabling the description of different
7 frailty or deficit accumulation end-of-life trajectories according to the main disease,
8 specially in the absence of advanced frailty. As the frailty degree increased, differences
9 between trajectories decreased, resulting in a trend towards a compression of survival
10 curves in advanced frailty situations where mortality is very high irrespective of the main
11 advanced illness and end-of-life trajectory. Thus, in EOLp with cancer, mortality rates
12 were high regardless of the frailty degree (moderate or advanced), leading to the
13 hypothesis, similar to recent studies, that cancer patients have a catastrophic accumulation
14 of deficits.[36] In contrast, EOLp with dementia showed different mortality rates
15 according to their frailty degree and died progressively, likely due to the natural history
16 of the disease, suggesting a slower accumulation of deficits. People with multimorbidity
17 and advanced frailty shows a survival profile similar to people with cancer, while those
18 with moderate frailty have a survival rate more similar to people with dementia. Finally,
19 persons with an organ disease would accumulate deficits in episodes, even though
20 prospective studies with serial frailty indexes would be required to test this hypothesis.

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45 In this regard, similar to recent studies describing different trajectories according to the
46 evolution of the social, spiritual or psychological situation of EOLp,[3] prospective
47 studies following the degree of frailty using electronic frailty indexes have described three
48 different trajectories (i.e., rapidly rising frailty, moderately increasing frailty, and stable
49 frailty).[36] Even though more studies would be required to describe different end-of-life
50 frailty trajectories, the fact that each end-of-life trajectory resulted in different mortality
51 curves supports a dynamic view of EOLp.
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3 The traditional association of frailty to the “third end-of-life trajectory” (i.e., dementia)
4 [13,14] has probably been influenced by the lack of specific prognostic instruments for
5 persons in this trajectory, unlike those in the cancer [37,38] or organ disease [39,40]
6 trajectories. Our results regarding the high prevalence of frailty in all end-of-life
7 trajectories support the validity of the concept that frailty may be present in all trajectories
8 beyond the dementia trajectory. In addition to expanding the concept of frailty, our study
9 underscores the need to consider a further development of the end-of-life trajectories. Of
10 the 260 people who were identified as people in end-of-life situation, 24.6% did not have
11 severity criteria for a single disease, although all of them had at least 2 chronic conditions.
12 The identification of this cluster of people with advanced frailty and multimorbidity can
13 help provide them early palliative care, and the benefits derived from it.[41,42]

14 Frailty Indices based on a Comprehensive Geriatric Assessment, such as the Frail-VIG
15 index, may help professionals address one of the current challenges in palliative care
16 [18,19,43]: the identification, assessment, and management of older people (i.e., aged
17 >80 years) with palliative care needs [20,44]. First, assessment and quantification of
18 frailty degree, which is suitable to synthesize the results of a multidimensional evaluation,
19 can be useful to validate the identification of people in an end-of-life situation;[12]
20 secondly, due to its ability to discriminate between different degrees of severity, frailty
21 indexes can be very useful to healthcare professionals for the situational diagnosis of the
22 first and second end-of-life transition,[6,12] and monitorization of EOLp
23 evolution;[45,46] and finally, quantification of frailty would enable palliative care
24 customization [47,48] and engage people, caregivers and healthcare professionals in
25 sharing decision-making and advance care planning.

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

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

21 **Ethics Approval and Consent to Participate**

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23 All patients and family relatives of patients with advanced dementia situation ($GDS \geq 6$)
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25 signed the written informed consent for participation before any data was recorded. The
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27 study protocol was approved by the Ethics Committee of the University Hospital of Vic
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29 (2,014,850 PR80). This study was conducted in accordance with the Helsinki Declaration
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31 and the local Personal Data Protection Law (LOPD 15/1999).
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38 **Consent for publication**

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40 Not applicable.
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44 **Data Sharing**

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46 The anonymized datasets analyzed during the current study are available from the
47
48 corresponding author on reasonable request.
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52 **Competing interests**

53
54 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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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).

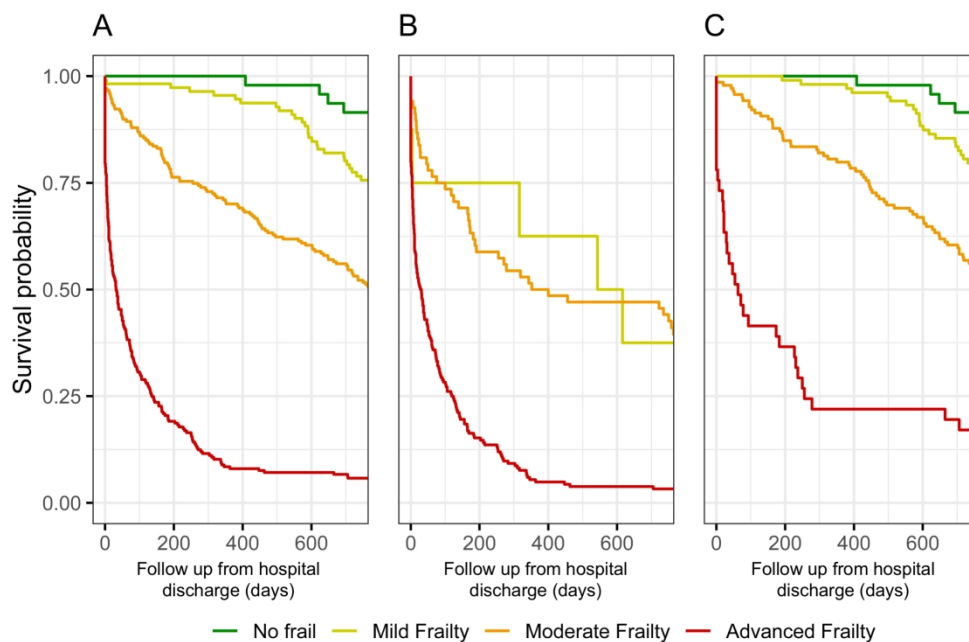


Figure 1. Survival according to the degree of frailty in (A) the total study patients, (B) end-of-life people, and (C) Non End-of-life people.

860x556mm (72 x 72 DPI)

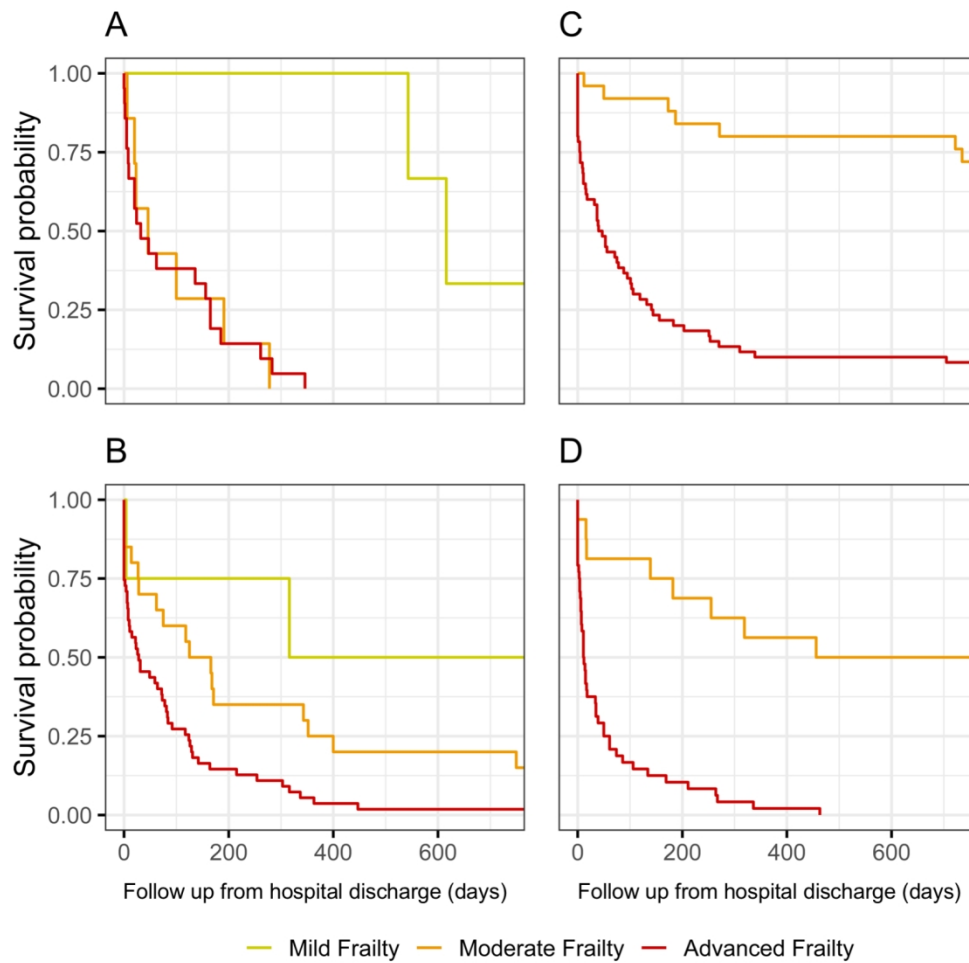


Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

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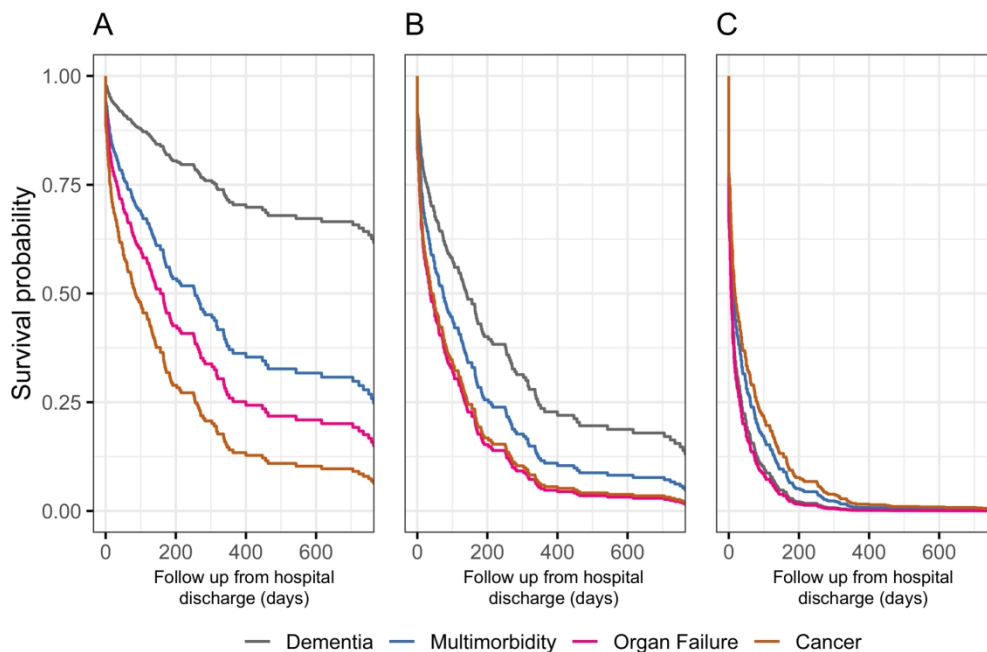


Figure 3. Survival probability of end-of-life people in the different illness trajectories according to Frail-VIG index value: Frail-VIG index 0.44 (15th percentile) (A), Frail-VIG index 0.56 (median) (B) and Frail-VIG index 0.68 (90th percentile) (C).

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	6, 8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8 8 N/A N/A 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 N/A N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 N/A 11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 11

1	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	9-13
2			(b) Report category boundaries when continuous variables were categorized	7
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
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11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	13
14	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
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
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18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
20				
21	Other information			
22				
23	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
24				

*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
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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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For peer review only

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 assess 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

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3 illness trajectories despite the differing survival patterns among trajectories. Frailty
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5 indexes may be useful to assess end-of-life older people, regardless of their trajectory.
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10 **Keywords:** Frailty, palliative care, mortality, multimorbidity, longitudinal study
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14 **Strengths and Limitations of this Study**

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

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

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

35 36 **METHODS**

37 38 39 40 **Study Design and Participants**

41 This was a prospective, observational study, including all patients admitted to the Acute
42 Geriatric unit (AGU) at the University Hospital of Vic (Barcelona, Spain) during 12
43 consecutive months (January 2014 – January 2015). The University Hospital of Vic is a
44 200-bed acute care hospital covering a population area of 156,000 inhabitants. Admission
45 criteria to the AGU, which were the criteria for inclusion in this study, were age \geq 85
46 years, cognitive decline, and/or end-of-life situation; no exclusion criteria were defined.
47 The methods, including study design, variables, data sources, and study size have been
48 described in a previous study.[24] Of the patients included in this study (i.e., those
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3 admitted to the AGU), those identified as non end-of-life were included in a control group
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5 of patients aged ≥ 85 years and/or with cognitive decline. The results of this subanalysis
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7 are reported according to the Strengthening the Reporting of Observational Studies in
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9 Epidemiology (STROBE) recommendations.[25] All patients and family relatives of
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11 patients with advanced dementia situation (GDS ≥ 6) signed the written informed consent
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13 for participation before any data was recorded. The study protocol was approved by the
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15 Ethics Committee of the University Hospital of Vic (2,014,850 PR80); this study was
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17 conducted in accordance with the Helsinki Declaration and the local Personal Data
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19 Protection Law (LOPD 15/1999).
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25 **Patient and Public Involvement**

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27 This research was done without patient involvement. Patients were not invited to
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29 comment on the study design and were not consulted to develop patient relevant outcomes
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31 or interpret the results. Patients were not invited to contribute to the writing or editing of
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33 this document for readability or accuracy.
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39 **Variables and Data Sources**

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41 Frailty was assessed using the Frail-VIG index, a tool consisting in 22 questions to assess
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43 25 deficits commonly associated with age and adverse health outcomes, based on the
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45 cumulative deficit model of frailty. Fifteen of the 22 questions refer to chronic
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47 conditions, including geriatric conditions and syndromes. The Frail-VIG index is a
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49 continuous variable expressed as a score ranging from 0 to 1. To simplify the
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51 representation of the survival curves, Frail-VIG index scores were expressed as a
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53 categorical variable classified into 4 groups according to the degree of frailty: no frailty
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55 (Frail-VIG index score <0.2), mild frailty (Frail-VIG index score 0.2-0.35), moderate
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57 frailty (Frail-VIG index score 0.36-0.5), and advanced frailty (Frail-VIG index score
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3 >0.5). In addition to its predictive value, previous studies have shown the content,
4 construct, criteria, and convergent-divergent construct validity of the Frail-VIG index
5 [24,26–28]. EOLp were identified using the NECPAL tool, a validated tool for the early
6 identification of the need for palliative care among individuals with limited life
7 expectancy.[29–31] EOLp were classified into the 3 archetypal end-of-life trajectories
8 according to the severity and/or progression criteria for their main underlying disease:
9 cancer, organ failure (including chronic pulmonary disease, chronic heart disease, serious
10 chronic liver disease, and serious chronic renal disease), and dementia (including other
11 chronic neurological diseases). People with palliative care needs without a predominant
12 advanced disease were identified as "multimorbidity" group or trajectory, since all had 2
13 or more underlying chronic conditions.

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

22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 **Statistical Analysis**

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48 Qualitative variables were presented as frequencies and percentages, whereas quantitative
49 variables were presented as the mean and the standard deviation (SD). Qualitative
50 variables were compared using the Pearson's chi-squared test. In the complete cohort, the
51 concordance between Frail-VIG index score and survival was evaluated using the C-
52 statistics and the Kaplan-Meier estimator was used to plot survival curves for the four
53 frailty degree subgroups, which were compared using the log-rank test. In the group of
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3 people identified as end-of-life, survival curves for each illness trajectory were plotted
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5 using the Kaplan-Meier estimator and were compared using the log-rank test. A Cox
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7 proportional hazards model with the interaction between Frail-VIG index score and
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9 illness trajectories was calculated. Details of the construction of the Cox Proportional
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11 hazards model and calculation of the hazard ratios are provided in a Supplementary
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13 Material file. The assumption of proportional hazards was checked using the Schoenfeld
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15 residuals and a goodness-of-fit test.
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19 The ROC curves were used to assess the ability of the Frail-VIG index to predict survival
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21 at one and two years by measuring their area under the receiver-operating curve (AUC)
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23 for the different illness trajectories. The significance level for all analyses was set at a
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25 two-sided $\alpha=0.05$. The descriptive statistics analysis of the variables was performed using
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27 the SPSS software program (IBM; Chicago, IL; USA), and the survival analysis was
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29 performed using the *survival* and *pROC* packages from the R project ([https://www.r-](https://www.r-project.org)
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31 [project.org](https://www.r-project.org)).
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36 RESULTS

41 Patient Characteristics and End-of-life Status

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43 The study included 590 patients with a mean (SD, range) age of 86.4 (5.6, 48-105) years,
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45 of whom 339 (57.5%) were women. Based on the Frail-VIG index scores, 543 (92%)
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47 patients showed some degree of frailty, with 111 (18.8%), 207 (35.1%), and 225 (38.1%)
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49 patients showing mild, moderate and advanced frailty, respectively. Of the 590 patients
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51 included, 53 (8.9%) died during hospitalization, and 330 (55.9%) and 260 (44.1%) were
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53 identified as non-EOLp and EOLp, respectively. Of the 260 EOLp, 31 (11.9%), 79
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55 (30.4%), 86 (33.1%), and 64 (24.6%) were classified in cancer, organ failure, dementia,
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57 and multimorbidity illness trajectories, respectively.
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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, <i>n</i> (%)			
	Age (years), <i>mean (SD)</i>	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.

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

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32 In this prospective, observational study including 590 patients admitted at an Acute
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34 Geriatric unit (AGU), we found that all older patients were frail towards the end of life
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36 (the prevalence of moderate-to-advanced frailty was 97% among people within an end-
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38 of-life trajectory and 55% outside it). Furthermore, advanced frailty was the predominant
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40 frailty category (ranged 68 to 75%) for all end-of-life trajectories: cancer, organ failure,
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42 dementia, and multimorbidity. Overall, the Frail-VIG index had a high capacity to predict
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44 death at one and two years (AUC 0.87), albeit to a different extent for the end-of-life
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46 categories cancer, organ failure, dementia and multimorbidity (AUC was always >0.86
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48 for mortality at either one or two years). This finding confirms the hypothesis that the
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50 degree of frailty is related to prognosis regardless of the illness trajectory.
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55 The characteristics and outcomes of the cohort assessed in this study, which included all
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57 patients admitted to an Acute Geriatric unit (AGU), were similar to those previously
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59 reported. All the persons assessed in this study had a Frail-VIG index score <0.8, similar
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3 to previous studies showing that the theoretical maximum score is 0.7. According to these
4 studies, the accumulation of 2/3 of all possible deficits (Frailty index score >0.7) results
5 in death due to the person's inability to overcome more deficits, a phenomenon defined
6 as system failure.[33,34] Likewise, similar to previous studies in other populations, the
7 mortality rate at 1 to 2 years in our cohort was nearly 100% for the EOLp with frailty
8 index score >0.5.[34,35]
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11 Furthermore, we provide evidence showing that the degree of frailty significantly
12 influenced survival irrespective of the advanced illness and end-of-life trajectory. In spite
13 of this general influence, the survival curves according to the frailty degree followed
14 different patterns for the four end-of-life trajectories, enabling the description of different
15 frailty or deficit accumulation end-of-life trajectories according to the main disease,
16 specially in the absence of advanced frailty. As the frailty degree increased, differences
17 between trajectories decreased, resulting in a trend towards a compression of survival
18 curves in advanced frailty situations where mortality is very high irrespective of the main
19 advanced illness and end-of-life trajectory. Thus, in EOLp with cancer, mortality rates
20 were high regardless of the frailty degree (moderate or advanced), leading to the
21 hypothesis, similar to recent studies, that cancer patients have a catastrophic accumulation
22 of deficits.[36] In contrast, EOLp with dementia showed different mortality rates
23 according to their frailty degree and died progressively, likely due to the natural history
24 of the disease, suggesting a slower accumulation of deficits. People with multimorbidity
25 and advanced frailty shows a survival profile similar to people with cancer, while those
26 with moderate frailty have a survival rate more similar to people with dementia. Finally,
27 persons with an organ disease would accumulate deficits in episodes, even though
28 prospective studies with serial frailty indexes would be required to test this hypothesis.
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3 In this regard, similar to recent studies describing different trajectories according to the
4 evolution of the social, spiritual or psychological situation of EOLp,[3] prospective
5 studies following the degree of frailty using electronic frailty indexes have described three
6 different trajectories (i.e., rapidly rising frailty, moderately increasing frailty, and stable
7 frailty).[36] Even though more studies would be required to describe different end-of-life
8 frailty trajectories, the fact that each end-of-life trajectory resulted in different mortality
9 curves supports a dynamic view of EOLp.

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

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25 Frailty Indices based on a Comprehensive Geriatric Assessment, such as the Frail-VIG
26 index, may help professionals address one of the current challenges in palliative care
27 [18,19,43]: the identification, assessment, and management of older people (i.e., aged
28 >80 years) with palliative care needs [20,44]. First, assessment and quantification of
29 frailty degree, which is suitable to synthesize the results of a multidimensional evaluation,
30 can be useful to validate the identification of people in an end-of-life situation;[12]
31 secondly, due to its ability to discriminate between different degrees of severity, frailty
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3 indexes can be very useful to healthcare professionals for the situational diagnosis of the
4 first and second end-of-life transition,[6,12] and monitorization of EOLp
5 evolution;[45,46] and finally, quantification of frailty would enable palliative care
6 customization [47,48] and engage people, caregivers and healthcare professionals in
7 sharing decision-making and advance care planning.
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10 The results of this study should be interpreted in the context of some limitations,
11 particularly regarding the generalizability of the results. Firstly, the recruitment strategy
12 based on an AGU solely enriched our study sample with older patients, likely precluding
13 the applicability of these study results to younger patients. Secondly, the analysis of
14 EOLp frailty across the various end-of-life trajectory categories importantly reduced the
15 number of patients in each group, thus limiting the statistical power of these analyses.
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17 However, despite the reduced number of patients in some groups, our analysis yielded
18 statistically significant results. In spite of its limitations, to our knowledge, this study is
19 the first to evaluate the degree of frailty using a frailty index in very old patients identified
20 as EOLp. Frailty was evaluated in a cohort of geriatric patients, including EOLp and non-
21 EOLp, and the data for this study was collected during routine geriatric assessment, as
22 opposed to previous studies that used electronic health record data to evaluate the degree
23 of frailty.[49] Moreover, the single computer information system of Catalonia (HC3) that
24 collects the medical records and mortality status of all patients reported by all health
25 providers prevented loss of patients up to follow-up.[32] Consequently, the lack of
26 missing data due to the HC3 system, along with the use of standard and validated tools to
27 identify EOLp (NECPAL) and to measure frailty (Frail-VIG index) increased the
28 accuracy of the results obtained from this study. The early identification of people
29 needing palliative care and the more accurate definition of the various end-of-life
30 trajectories opened the door to a novel perspective of palliative care.[50] In this regard,
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3 the use of frailty as an overarching concept in the assessment of all people in an end-of-
4 life situation —at least of those with a multimorbid profile— might contribute to go one
5 step further in this novel approach to palliative care.
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10 11 **CONCLUSIONS**

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14 Our results showed that all end-of-life people were frail (mostly with advanced frailty)
15 irrespective of the end-of-life trajectory. Their degree of frailty, measured using the Frail-
16 VIG index, influenced mortality. This indicates a close relationship between frailty, end-
17 of-life status, and mortality for all people who die. Measuring frailty using a frailty index
18 could be useful in routine practice for healthcare professionals to understand the
19 heterogeneous nature of people needing palliative care and tailor their care to the patient's
20 needs. The survival pattern of people with multimorbidity could support the description
21 of a composite illness trajectory for this patient group.
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36 37 **DECLARATIONS**

38 39 40 **Ethics Approval and Consent to Participate**

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42 All patients and family relatives of patients with advanced dementia situation ($GDS \geq 6$)
43 signed the written informed consent for participation before any data was recorded. The
44 study protocol was approved by the Ethics Committee of the University Hospital of Vic
45 (2,014,850 PR80). This study was conducted in accordance with the Helsinki Declaration
46 and the local Personal Data Protection Law (LOPD 15/1999).
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56 57 **Consent for publication**

58 Not applicable.
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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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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).

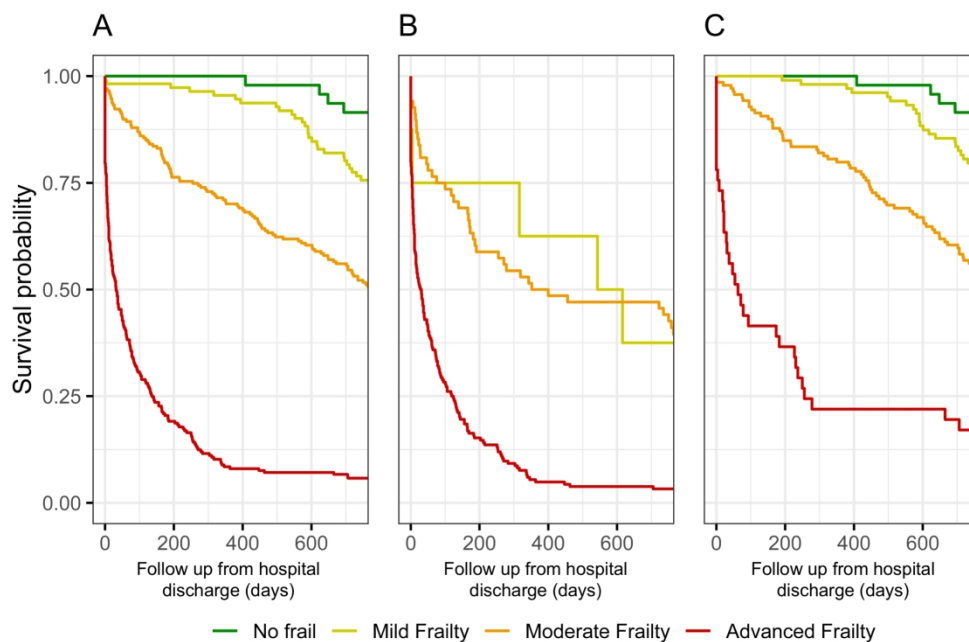


Figure 1. Survival according to the degree of frailty in (A) the total study patients, (B) end-of-life people, and (C) Non End-of-life people.

860x556mm (72 x 72 DPI)

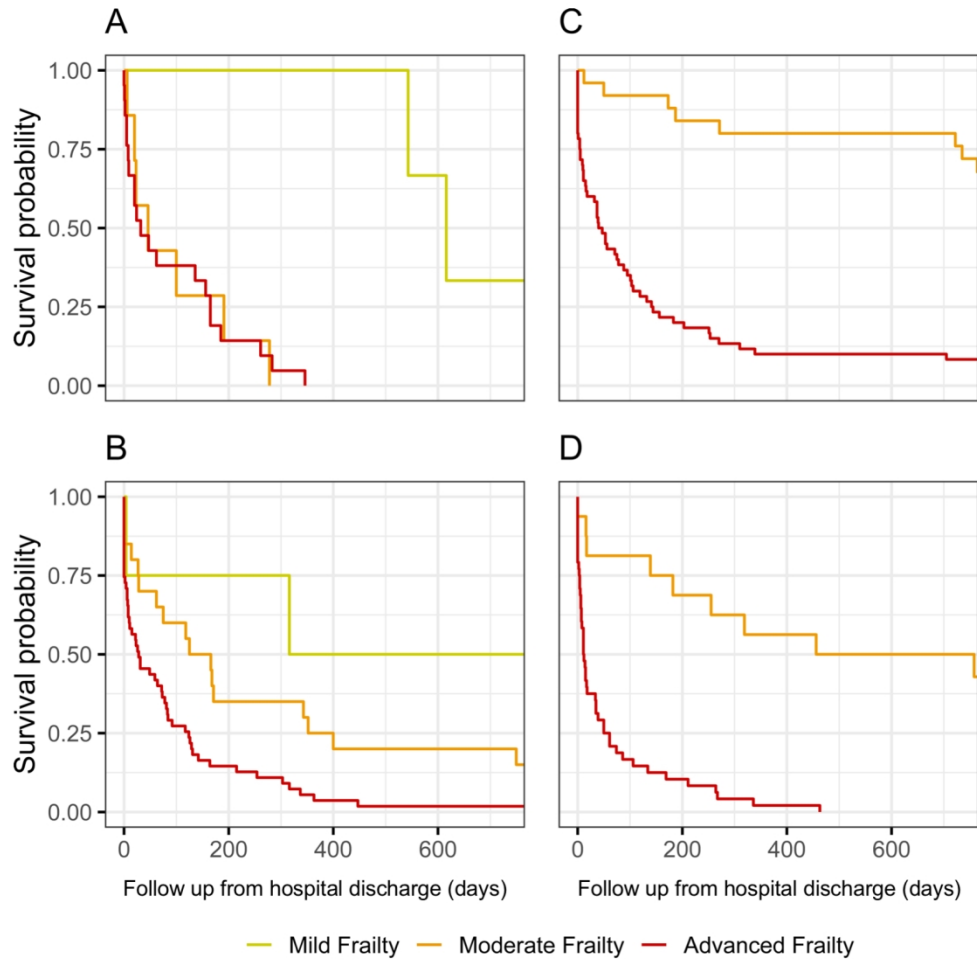


Figure 2. Survival according to the degree of frailty and end-of-life trajectory: (A) cancer, (B) organ failure, (C) dementia, and (D) Multimorbidity.

616x593mm (72 x 72 DPI)

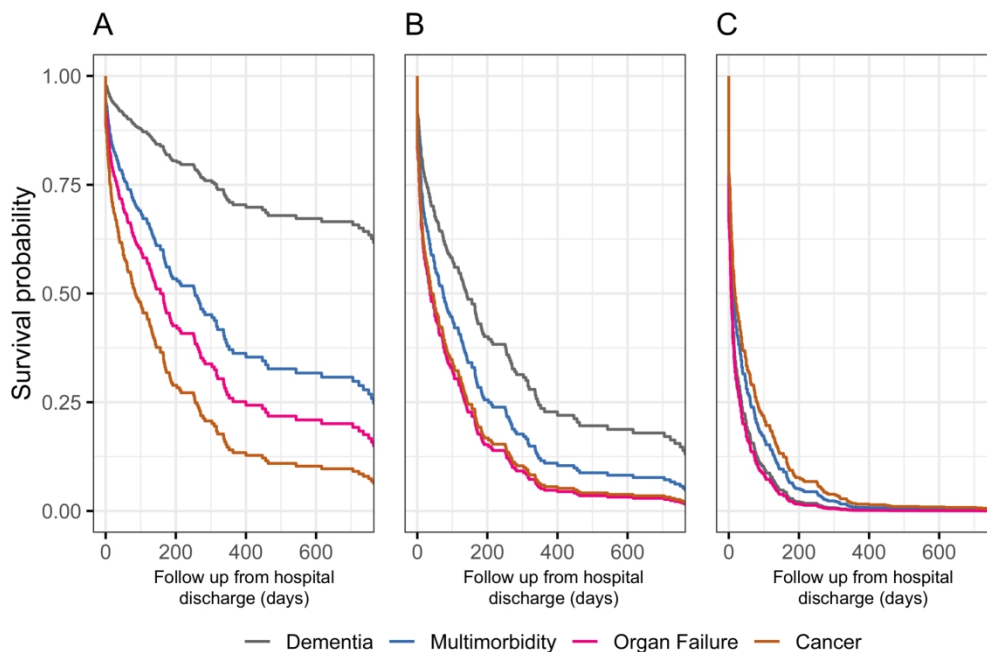


Figure 3. Survival probability of end-of-life people in the different illness trajectories according to Frail-VIG index value: Frail-VIG index 0.44 (15th percentile) (A), Frail-VIG index 0.56 (median) (B) and Frail-VIG index 0.68 (90th percentile) (C).

874x564mm (72 x 72 DPI)

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3 **Supplementary Information for the Submission by Amblàs-Novellas et**
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6 **al. “Frailty Degree and Illness Trajectories in Older People towards the**
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For peer review only

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	6, 8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8 8 N/A N/A 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 N/A N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 N/A 11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 11

1	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	9-13
2			(b) Report category boundaries when continuous variables were categorized	7
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
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5				
6	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
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8				
9				
10				
11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	13
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
14	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
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
16				
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21	Other information			
22	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
23				
24				
25				

*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>.