PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Frailty degree and illness trajectories in older people towards the end-of-life: a prospective observational study
AUTHORS	Amblàs-Novellas, Jordi; Murray, Scott; Oller, Ramon; Torné, Anna; Martori, Joan Carles; Moine, Sébastien; Latorre, Nadina; Espaulella, Joan; Santaeugènia, Sebastià; Gómez-Batiste, Xavier

VERSION 1 – REVIEW

REVIEWER	Teggi, Diana University of Bath, Social and Policy Sciences
REVIEW RETURNED	01-Aug-2020

GENERAL COMMENTS	Thank you for submitting this very interesting and well-researched manuscript on a very important topic for the care of the dying in old age: frailty. Suggestion that frailty indexes can help identify dying in old age, even in the absence of a main malignant condition, is particularly welcomed. However, this result could have been drawn out more, especially in relation to the continued difficulty in identifying dying in very old age (see Coventry et al., 2005; Teggi, 2018), which concurs to the underprovision of specialist palliative care to adults aged 85+ in England (see Dixon et al., 2015; Moriarity et al., 2012; National Council for Palliative Care, 2015). Abstract: 1. Methods: It is not explained how the manuscript asses the relationship of frailty to end-of-life illness trajectories. For the sake of claritfy, it would be useful to mention survival analysis here. 2. Results: It would be more effective to describe the patterns of survival decline according to frailty degree - especially in the case of multimorbidity - rather than simply hinting at them. The results reported in the abstract are very descriptve, but they do not clarify what the principal finding of the study is. Body: 1. The study's stated aim is to improve "the care of end-of-life people in general" (p.8), however the sample is of patients aged 85 or above. Rather than introducing bias towards older patients (p. 6), the study's focus on older

	people is a strength if acknowledged within the context of population ageing, increasing deaths from chronic conditions, and, most importantly, difficulties in identifying dying in very old age (80/85+). Moreovoer, as the authors recognise, the results might not apply to younger adults. To both avoid bias and increase the value of the paper given, the study's stated aim could be recalibrated in the direction of older people. 2. The authors state that the hospital's catchement area might have skewed the sociodemographic characteristics of the sample, but they do not state in what direction (p.6). On the other hand, limitations concerning the representativeness of the sample as stated on p.18 are welcomed. 3. Given the wide readership of the journal, it seems appropriate to explain in lay terms the fundamentals of survival analysis as well as to spend more words about the c-statistics, long-rank test and ROC curves (i.e. why they were used and to evaluate precisely what). 4. Typo on page 15 (*four).

REVIEWER	Stow, Daniel Newcastle University, Population and Health Sciences Institute
REVIEW RETURNED	30-Sep-2020

GENERAL COMMENTS	GENERAL Thank you for inviting me to review this article. This article builds on previous work by the same authors published in BMC medicine in 2018 presenting survival curves stratified by four categories of frailty severity. As far as I can see the present article uses the same cohort of individuals, and a similar analysis strategy. Here the novelty lies in an analysis that is further stratified on four disease trajectories (cancer, organ failure, dementia and multimorbidity). The authors find that frailty is high amongst people who have been judged as 'end of life' using the NECPAL tool, and that higher levels of frailty reduce survival time across all diagnostic categories (with the possible exception of cancer, where the curves for moderate and advanced frailty are indistinguishable). Examining frailty at the end of life and its impact on survival across different disease trajectories is interesting and has the potential to inform approaches to shared decision making at the end of life. However, I am concerned about the robustness of the main. Kaplan Meier is quite a descriptive tool, and isn't really useful for testing hypotheses across multiple groups, as the authors do here. The reliance on stratification for comparison can lead to problems where there are a large number of variables of interest, and should be interpreted very cautiously when cell sizes are small (as is the case

	here). I am also unclear as to the steps taken to correct for multiple comparisons. I would recommend using Cox regression as a robust method for testing the association between frailty, primary diagnosis, and survival, whilst also adjusting for age and sex (e.g. survival time predicted by diagnosis + a frailty/diagnosis interaction, also adjusted for age and sex). As the authors focus on cut points towards the paper, these could be used as a binary classifier (or simply 'advanced frailty), which might address the very small cell sizes in some of the stratified groups I also think that the aims and message of the paper are made less clear by the comparison to the 330 people with cognitive decline – it might be simpler to omit this group and focus on the end of life message: mortality prognostication / survival comparison between people defined as end of life vs people with cognitive decline doesn't seem a useful one or relate to the aims of the study. SPECIFIC COMMENTS Abstract P5 line 13 Methods – The study design is very well described, but it would be helpful to see the methods for analysis here too (Kaplan meier survival curves?) P5 line 44 Results – "significant relationship between frailty degree and survival": can you be more precise here? Reduced survival? Median survival time between groups? P5 line 48 Results – "Differences in frailty degree between four illness trajectories and survival" it isn't clear what is meant here. Is there a reference illness trajectory, and which of the comparators had higher or lower frailty degrees? I'm not sure it's helpful to say 'there were differences', especially given the conclusion drawn in the next paragraph. I'm not sure that Kaplan Meier is the most appropriate method to use for comparison here P5 line 57 - Conclusion – I think this could be clarified: how could frailty indices be useful for assessing end of life older people? Are the authors suggesting they could be used for prognosis (this is mentioned in the aims at the end of the introduction)? P6 line 3 Conclusion – "Pattern of survival"…. Without further detail in the methods/results, it's hard to see how this conclusion has been arrived at – also see comments re: Kaplan Meir curves for comparison – what is a 'pattern of survival'? STRENGTHS AND LIMITATIONS P6 Line 52 – This may be a matter of editorial taste, but here only one limitation is highlighted. The authors mention

	more at the end of the discussion. But for example there was no external validation for frail-VIG, and the score was validated against mortality as an outcome in a group of people already identified as being 'end of life' via the NECPAL tool. INTRODUCTION P8 line 29 – consensus concept frailty to provide palliative care – My reading of the two references provided here is they seek consensus around a general definition of frailty, without specific focus on palliative care. Recently published BGS guidelines on frailty and end of life care may be something to consider referencing here as specific approaches and definitions are used there. P8 line 30 – I think it would be helpful to readers if these aims could be clarified slightly – the wording in the abstract/objectives is clearer. METHOD P8 line 56 - NECPAL was used to define end of life – readers of BMJ open would benefit from a simple description (could be supplemental material) of this tool P9 line 5 – "in the same setting" – as far as I can see (and this is not a criticism or a limitation) the article under present review is a sub analysis of the data collected for study reference [20] RESULTS P11 line 13 – A table 1 of patient characteristics by age sex and disease trajectory would be easier to interpret than having the information in paragraphs and would give readers an idea of potential sociodemographic variation across disease trajectories (were people in the cancer group younger than people in the multimorbidity group? For example) P11 line 24 – based on inclusion criteria, all patients should either be cognitive decline n=330?, or end of life n=260. The rest of the paper really only addresses the n=260 with end of life. It might be clearer if the authors could clarify that this is a sub analysis. 590 people were recruited to the main study, but this study considers the 260 who were end of life. I'm not sure that the extra information in the results/tables relating frailty to the 330 people with cognitive decline is helpful or relevant to the question the author's address. I can see that they are included in figure one, but is a comparison of survival between people at end of life and people with cognitive decline a useful one? P11 line 35 – Do any of the items in the VIG index also overlap with the how multimorbidity was defined?

	P 14 line 53 – given that other studies have found frailty indices to be relatively poor prognostic indicators for individuals it is encouraging to see these high AUC values. However, given the setting (people identified as end of life via NECPAL) these values are not entirely surprising. PLOTS Plots p27 and p28 – for clarity on the x-axis, is this time after entry to study (days)?

VERSION 1 – AUTHOR RESPONSE

Response to reviewer #1, Dr. Diana Teggi

The authors would like to thank the receipt of Dr Teggi's comments, which will certainly improve the quality of the manuscript. Please, find a point-by-point response to the reviewer's comments below.

Comment 1. However, this result (referring to the usefulness of frailty indexes to identify dying in old age, even in the absence of a malignant condition) could have been drawn out more, especially in relation to the continued difficulty in identifying dying in very old age (see Coventry et al., 2005; Teggi, 2018), which concurs to the underprovision of specialist palliative care to adults aged 85+ in England (see Dixon et al., 2015; Moriarity et al., 2012; National Council for Palliative Care, 2015)

> **Response:** As requested by the reviewer, we have mentioned the difficulty of identifying very old dying people and included additional references in the introduction (references #18, 19, 20) and discussion sections (references #18, 19, 20, 42, 43) of the revised manuscript (pages 6 and 15).

Comment 2. (Abstract) Methods: It is not explained how the manuscript assesses the relationship of frailty to end-of-life illness trajectories. For the sake of clarity, it would be useful to mention survival analysis here.

> **Response:** We agree with the reviewer that a complete description of the statistical methods used in this study was missing from the abstract. In addition to the methods used to plot and compare survival curves, we have included a sentence describing the statistics used to evaluate the relationship between frailty degree and survival in the abstract of the revised version of the manuscript (page 3).

Comment 3. (Abstract) Results: It would be more effective to describe the patterns of survival decline according to frailty degree - especially in the case of multimorbidity - rather than simply hinting at them. The results reported in the abstract are very descriptive, but they do not clarify what the principal finding of the study is

> **Response:** We agree that, in the abstract section, the results were insufficiently described. The main finding of the study (i.e., all people identified as end-of-life people were frail regardless of the illness trajectory) was not sufficiently emphasized and the relationship between frailty degree and survival (overall and in the different illness trajectories) was not described. To address this the revised manuscript now includes new data using the Cox regression model, and we have removed the results

from the Kaplan-Meier model and have described those from the Cox model in the results section of the abstract of the revised version of the manuscript (page 3).

Comment 4. The study's stated aim is to improve "the care of end-of-life people in general" (p.8), however the sample is of patients aged 85 or above. Rather than introducing bias towards older patients (p. 6), the study's focus on older people is a strength if acknowledged within the context of population ageing, increasing deaths from chronic conditions, and, most importantly, difficulties in identifying dying in very old age (80/85+). Moreover, as the authors recognise, the results might not apply to younger adults. To both avoid bias and increase the value of the paper given, the study's stated aim could be recalibrated in the direction of older people.

Response: We agree with the reviewer that the very old age of the study population should be interpreted as a strength rather than a limitation of this study. To emphasize the added value of results obtained in older people, we have removed the population age as a bias and have specified the aim of the study as focussing on **older** people in the Strengths and Limitations and Introduction sections of the revised version of the manuscript (pages 4 and 6). Additionally, we have added a sentence in the discussion section of the revised version of the manuscript (page 15) regarding the applicability and usefulness of our study results in the context of the current challenge of identifying very old people needing palliative care.

Comment 5. The authors state that the hospital's catchement area might have skewed the sociodemographic characteristics of the sample, but they do not state in what direction (p.6). On the other hand, limitations concerning the representativeness of the sample as stated on p.18 are welcomed.

Response: We agree with the reviewer that the study limitations were very general and insufficiently explained. We have reworded the study limitations and removed the sociodemographic characteristics of the study sample (i.e., rural area and older population) as a limitation, and added that potential lack of applicability to younger populations in the Strengths and Limitations and discussion sections of the revised version of the manuscript (pages 5 and 16).

Comment 6. Given the wide readership of the journal, it seems appropriate to explain in lay terms the fundamentals of survival analysis as well as to spend more words about the c-statistics, long-rank test and ROC curves (i.e. why they were used and to evaluate precisely what).

Response: We agree that the description of the statistical methods used in the manuscript was excessively technical and probably not suitable for the wide readership of the journal. In addition to the description of the Cox regression analysis of survival, we have clarified the statistical methods use in the methods section of the revised version of the manuscript (page 8-9).

Comment 7. Typo on page 15 (*four).

Response: This typo has been corrected.

Response to reviewer #2. Dr. Daniel Stow.

The authors would like to thank t Dr. Stow for these comments, which will certainly improve the quality of the manuscript. Please, find a point-by-point response to these comments below.

Comment 1. Kaplan Meier is quite a descriptive tool, and isn't really useful for testing hypotheses across multiple groups, as the authors do here. The reliance on stratification for comparison can lead to problems where there are a large number of variables of interest, and should be interpreted very cautiously when cell sizes are small (as is the case here). I am also unclear as to the steps taken to correct for multiple comparisons. I would recommend using Cox regression as a robust method for testing the association between frailty, primary diagnosis, and survival, whilst also adjusting for age and sex (e.g. survival time predicted by diagnosis + a frailty/diagnosis interaction, also adjusted for age and sex).

> **Response:** As requested by the reviewer and, considering that data met the hypothesis of proportional hazards, we have used the Cox regression to test the association between frailty, illness trajectory, and survival. The results from these analyses have been included in a new Figure (Figure 3) and additional text in the abstract (page 3), methods (page 9), results (page 11-12), and discussion (page 14) sections of the revised version of the manuscript.

Comment 2. As the authors focus on cut points towards the paper, these could be used as a binary classifier (or simply 'advanced frailty), which might address the very small cell sizes in some of the stratified groups.

> **Response:** We thank the reviewer for this insightful observation. The use of a continuous measure of frailty (frail VIG index) enables the classification of people in non-binary categories. While the classic view of palliative care tended to classify end-of-life people according to binary categories, in the context of current palliative care approaches, which are more progressive and synchronic, we believe that the use of a continuous variable enabling non-binary classifications provides increased versatility. Furthermore, despite the reduced number of patients in some groups, their statistical power was sufficient to yield statistically significant results.

Comment 3. I also think that the aims and message of the paper are made less clear by the comparison to the 330 people with cognitive decline – it might be simpler to omit this group and focus on the end of life message: mortality prognostication / survival comparison between people defined as end of life vs people with cognitive decline doesn't seem a useful one or relate to the aims of the study.

> **Response:** We thank the reviewer for his insightful comment. The 330 people included in this study were non-end-of-life people and were used as a control group. Despite the similar demographic characteristics (i.e., age and sex) of the 260 end-of-life and 330 non-end-of-life people (included in revised Table 1) their frailty profiles differed, enabling us to identify an association between higher frailty scores and end-of-life status.

Comment 4. Abstract P5 line 13 Methods – The study design is very well described, but it would be helpful to see the methods for analysis here too (Kaplan meier survival curves?)

> **Response:** We agree with the reviewer that the methods section of the abstract lacked a description of the statistical methods used. We have now included a description of the statistical methods used in this study in the abstract of the revised version of the manuscript (page 3).

Comment 5. Abstract P5 line 44 Results – "significant relationship between frailty degree and survival": can you be more precise here? Reduced survival? Median survival time between groups?

> **Response:** We agree with the reviewer that the results included in the abstract section were poorly described and a precise description of the relationship between frailty degree and survival was

missing. We have included a clause indicating that higher scores of the Frail-VIG index are associated with lower survival in the abstract section of the revised version of the manuscript (page 3).

Comment 6. Abstract P5 line 48 Results – "Differences in frailty degree between four illness trajectories and survival" it isn't clear what is meant here. Is there a reference illness trajectory, and which of the comparators had higher or lower frailty degrees? I'm not sure it's helpful to say 'there were differences', especially given the conclusion drawn in the next paragraph. I'm not sure that Kaplan Meier is the most appropriate method to use for comparison here.

Response: We agree with the reviewer that results may not have been precisely explained and may seem contradictory. However, we had initially discarded a description of the results regarding survival profiles of the different illness trajectories due to the space constraints of the abstract section. In this regard, even though our results show that end-of life people are frail regardless of their illness trajectories, the survival profiles of people with different frailty degrees were differed in the different illness trajectories; considering none of the illness trajectories as a reference, they were compared among them. Furthermore, we have considered the reviewer's suggestion of using Cox regression models to analyse survival according to illness trajectory and frailty degree. To clarify the results of the survival analysis, we have focussed the results in the abstract section of the revised version of the manuscript in those from the Cox regression model (page 3).

Comment 7. P5 line 57 - Conclusion – I think this could be clarified: how could frailty indices be useful for assessing end of life older people? Are the authors suggesting they could be used for prognosis (this is mentioned in the aims at the end of the introduction)?

Response: We agree with the reviewer that the writing of the conclusions was unspecific and, to provide more details, have modified the conclusions in the abstract section of the revised version of the manuscript (page 4).

Comment 8. P6 line 3 Conclusion – "Pattern of survival"…. Without further detail in the methods/results, it's hard to see how this conclusion has been arrived at – also see comments re: Kaplan Meir curves for comparison – what is a 'pattern of survival'?

Response: We agree with the reviewer that, due to the space constraints, the results included in the abstract were excessively summarized. We have added novel information to explain de results regarding survival using the Cox regression model in the results (page 3) and conclusions (page 4) of the abstract section of the revised version of the manuscript.

Comment 9. This may be a matter of editorial taste, but here only one limitation is highlighted. The authors mention more at the end of the discussion. But for example there was no external validation for frail-VIG, and the score was validated against mortality as an outcome in a group of people already identified as being 'end of life' via the NECPAL tool.

Response: We agree with the reviewer that no limitations regarding the Frail-VIG index were included in the manuscript. Regarding the external validation for the Frail-VIG, its ability to predict morality was evaluated in the original study describing the Frail-VIG index, in both the end-of-life cohort, identified using the NECPAL tool, and in the complete study sample (Amblàs-Novellas, 2018). In addition to its predictive value, this study evaluated content validity and construct validity

(discriminatory capacity). Other studies have demonstrated the convergent-divergent construct validity (Amblàs-Novellas, 2017) and the criteria validity of the Frail-VIG (Moreno-Ariño, 2020). Given the previously reported validation of the Frail-VIG index, in this study, the validation of the Frail-VIG was not considered a limitation. We have added the information and references regarding the validation of the frail-VIG index in the methods section of the revised version of the manuscript (page 7).

Comment 9. P8 line 29 – consensus concept frailty to provide palliative care – My reading of the two references provided here is they seek consensus around a general definition of frailty, without specific focus on palliative care. Recently published BGS guidelines on frailty and end of life care may be something to consider referencing here as specific approaches and definitions are used there.

Response: We thank the reviewer for this insightful comment, as these guidelines were not published at the time this manuscript was in preparation. We agree with the reviewer that these guidelines are worth considering and have added them as a reference in the introduction section of the revised version of the manuscript (page 6, reference #23).

Comment 10. P8 line 30 – I think it would be helpful to readers if these aims could be clarified slightly – the wording in the abstract/objectives is clearer.

Response: We agree with the reviewer that the aims, stated as a hypothesis, were not appropriately worded in the introduction section. In the revised version of the manuscript, we have modified the wording of the aims and used the clearer wording of the abstract (page 6).

Comment 11. P8 line 56 - NECPAL was used to define end of life – readers of BMJ open would benefit from a simple description (could be supplemental material) of this tool

Response: We agree with the reviewer that information regarding the NECPAL tool would be useful for BMJ open readers. Our research group provides a description and detailed information on the different dimensions evaluated by the NECPAL tool on its website https://en.c3rg.com/necpal, which we have included as a reference (#30) in the methods section of the revised version of the manuscript (page 8).

Comment 12. P9 line 5 – "in the same setting" – as far as I can see (and this is not a criticism or a limitation) the article under present review is a sub analysis of the data collected for study reference [20]

Response: We agree with the reviewer that the fact that this was a sub analysis of the results obtained in the original study was not clearly stated and, given that the use of "in the same setting" might be misleading, we have deleted this clause from the revised version of the manuscript and have stated that this is a sub analysis (page 7).

Comment 13. P11 line 13 – A table 1 of patient characteristics by age sex and disease trajectory would be easier to interpret than having the information in paragraphs and would give readers an idea of potential sociodemographic variation across disease trajectories (were people in the cancer group younger than people in the multimorbidity group? For example)

Response: Even though patients' demographic characteristics according to disease trajectories had been included in our previous publication (Amblàs-Novellas et al. 2006), we agree with the reviewer

that including these data in this manuscript would facilitate its interpretation. We have included the age and sex of study patients according to their end-of-life situation (EOLp and NonEOLp) and end-of-life trajectories (cancer, organ failure, dementia, and multimorbidity) in Tables 1 and 2 of the revised manuscript, respectively, and have removed any redundant data from the text.

Comment 14. P11 line 24 – based on inclusion criteria, all patients should either be cognitive decline n=330?, or end of life n=260. The rest of the paper really only addresses the n=260 with end of life. It might be clearer if the authors could clarify that this is a sub analysis. 590 people were recruited to the main study, but this study considers the 260 who were end of life. I'm not sure that the extra information in the results/tables relating frailty to the 330 people with cognitive decline is helpful or relevant to the question the author's address. I can see that they are included in figure one, but is a comparison of survival between people at end of life and people with cognitive decline a useful one?

Response: We agree with the reviewer's that these comparisons may not be relevant. However, of the 590 people considered in this study, 260 were end-of-life and 330 were non-end-of-life people (and not people with cognitive decline), and were used as a control group. Even though the two groups had similar demographic characteristics (i.e., age and sex), their classification according to their frailty degree, and their median frailty-VIG scores were significantly different. We believe that comparisons between end-of-life and non-end-of-life are useful, enabling us to identify an association between higher frailty scores and end-of-life status.

Comment 15. P11 line 35 – Do any of the items in the VIG index also overlap with the how multimorbidity was defined?

Response: We thank the reviewer for this comment. Of the 22 items (i.e., questions) included in the calculation of the Frail-VIG index, 15 refer to chronic conditions, including geriatric diseases and syndromes. All the patients who were classified in the multimorbidity illness trajectory had two or more of these chronic conditions, as defined by the WHO (https://apps.who.int/iris/bitstream/handle/10665/252275/9789241511650-eng.pdf;jsessionid=BF929E1330346103428668CB1C571284?sequence=1). We have added a sentence to clarify this issue in the methods section of the revised version of the manuscript (page 7), besides the definition of multimorbidity, which was already included in the first version (page 8).

Comment 16. P 14 line 53 – given that other studies have found frailty indices to be relatively poor prognostic indicators for individuals it is encouraging to see these high AUC values. However, given the setting (people identified as end of life via NECPAL) these values are not entirely surprising.

Response: We agree with the reviewer's that the value of frailty index as a prognostic indicator in a population identified as end-of-life people may be partly expected. Nevertheless, in the complete cohort (n=590) including end-of-life and non-end-of-life people, the frail VIG index was able to discriminate mortality in people with no frailty and moderate frailty, compared to people with advanced frailty.

Comment 17. Plots p27 and p28 – for clarity on the x-axis, is this time after entry to study (days)?

Response: We agree with the reviewer that the X-axis was not appropriately labelled and have changed the labelling in Figures 1, 2 and 3 of the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Teggi, Diana University of Bath, Social and Policy Sciences
REVIEW RETURNED	02-Jan-2021

GENERAL COMMENTS	Thank you for revising and resubmitting this seminal paper on a topical issue. The relevance and contested status of the concept of frailty for the timely identification of older people as end-of-life is very well-framed in the introduction. This provides a strong and clear rationale for the study. The abstract and results are presented in a clear and concise manner. The results are evaluated in light of the challenges to EOLC posed by an increasingly older population at the time of death (85+), hence providing a significant contribution to the geriatric and palliative care literature. Spotted typos: - page 40, line 22: *(January 2014 - January 2015 - page 45, line 42: *ass

REVIEWER	Stow, Daniel Newcastle University, Population and Health Sciences Institute
REVIEW RETURNED	22-Jan-2021

GENERAL COMMENTS	Thank you to the authors for considering previous comments and responding to each in turn. I still think lack of clarity in the methods section makes interpreting the findings of this study difficult. I have copied in my responses to responses below. MINOR POINTS P4 – line 3. "All older people towards the end of life are frail" In this study / in this setting surely/ all older participants were frail (the first line of the conclusion – it's a selected population recruited at point of entry to an acute geriatric ward) P4 – line 8 "To assess end of life people" <- can you be a little clearer about this recommendation: assess in what way? Is the frailty index telling you something about symptoms, or survival time> P11 – typo ass -> as P18 – line 13 "likely to enrich" <- I think this has been touched on before, but given the setting I think it more than likely

	Comment 1. Kaplan Meier is quite a descriptive tool, and isn't really useful for testing hypotheses across multiple groups, as the authors do here. The reliance on stratification for comparison can lead to problems where there are a large number of variables of interest, and should be interpreted very cautiously when cell sizes are small (as is the case here). I am also unclear as to the steps taken to correct for multiple comparisons. I would recommend using Cox regression as a robust method for testing the association between frailty, primary diagnosis, and survival, whilst also adjusting for age and sex (e.g. survival time predicted by diagnosis + a frailty/diagnosis interaction, also adjusted for age and sex). Response: As requested by the reviewer and, considering that data met the hypothesis of proportional hazards, we have used the Cox regression to test the association between frailty, illness trajectory, and survival. The results from these analyses have been included in a new Figure (Figure 3) and additional text in the abstract (page 3), methods (page 9), results (page 11-12), and discussion (page 14) sections of the revised version of the manuscript. • I'm glad to see the authors checked the assumptions of proportionality. Rather than just reporting a p value in the abstract, the range of HRs would give readers a better idea of the magnitude of the relationship. Can you be clearer in the methods about who was in the model (was this just the end of life group, or did you include the non end of life people too?) and can you clarify how you treated the frailty variable in the model (frailty indices usually between 0 and 1, interpretation of hazard ratios would be per 1 unit increase, which doesn't match what is written in the results section – 0.004 increase = 61% increase in HR?) Comment 2. As the authors focus on cut points towards the paper, these could be used as a binary classifier (or simply 'advanced frailty), which might address the very small cell sizes in some of the stratified groups. Response: We thank the reviewer for this insightful observation. The use of a continuous measure of frailty (frail VIG index) enables the classification of people in non-binary categories. While the classic view of palliative care tended to classify end-of-life people according to binary categories, in the context of current palliative care approaches, which are more progressive and synchronic, we believe that

	the use of a continuous variable enabling non-binary classifications provides increased versatility. Furthermore, despite the reduced number of patients in some groups, their statistical power was sufficient to yield statistically significant results. • The justification of the non-binary approach is now clearer in your revised methods and results Comment 3. I also think that the aims and message of the paper are made less clear by the comparison to the 330 people with cognitive decline – it might be simpler to omit this group and focus on the end of life message: mortality prognostication / survival comparison between people defined as end of life vs people with cognitive decline doesn't seem a useful one or relate to the aims of the study. Response: We thank the reviewer for his insightful comment. The 330 people included in this study were non-end-of-life people and were used as a control group. Despite the similar demographic characteristics (i.e., age and sex) of the 260 end-of-life and 330 non-end-of-life people (included in revised Table 1) their frailty profiles differed, enabling us to identify an association between higher frailty scores and end-of-life status. • Can you be clearer in the study design/methods that this group is being used as a control? Comment 4. Abstract P5 line 13 Methods – The study design is very well described, but it would be helpful to see the methods for analysis here too (Kaplan meier survival curves?) Response: We agree with the reviewer that the methods section of the abstract lacked a description of the statistical methods used. We have now included a description of the statistical methods used in this study in the abstract of the revised version of the manuscript (page 3). • Methods are now slightly clearer, but I'm still not clear on how the models were constructed. There are also results appearing in the 'prognostic utility' section that aren't described (1 year mortality, stratification by disease) Comment 5. Abstract P5 line 44 Results – "significant relationship between frailty degree and survival": can you be more precise here? Reduced survival? Median survival time between groups? Response: We agree with the reviewer that the results included in the abstract section were poorly described and a precise description of the relationship between frailty

	degree and survival was missing. We have included a clause indicating that higher scores of the Frail-VIG index are associated with lower survival in the abstract section of the revised version of the manuscript (page 3). • Clearer but please describe the effect/ range of effects, not just a p value Comment 6. Abstract P5 line 48 Results – "Differences in frailty degree between four illness trajectories and survival" it isn't clear what is meant here. Is there a reference illness trajectory, and which of the comparators had higher or lower frailty degrees? I'm not sure it's helpful to say 'there were differences', especially given the conclusion drawn in the next paragraph. I'm not sure that Kaplan Meier is the most appropriate method to use for comparison here. Response: We agree with the reviewer that results may not have been precisely explained and may seem contradictory. However, we had initially discarded a description of the results regarding survival profiles of the different illness trajectories due to the space constraints of the abstract section. In this regard, even though our results show that end-of life people are frail regardless of their illness trajectories, the survival profiles of people with different frailty degrees were differed in the different illness trajectories; considering none of the illness trajectories as a reference, they were compared among them. Furthermore, we have considered the reviewer's suggestion of using Cox regression models to analyse survival according to illness trajectory and frailty degree. To clarify the results of the survival analysis, we have focussed the results in the abstract section of the revised version of the manuscript in those from the Cox regression model (page 3). • Now slightly clearer. I think more clarity needed about the move to AUROC though. This wasn't an aim of the study – test of diagnostic accuracy = STARD. Comment 7. P5 line 57 - Conclusion – I think this could be clarified: how could frailty indices be useful for assessing end of life older people? Are the authors suggesting they could be used for prognosis (this is mentioned in the aims at the end of the introduction)? Response: We agree with the reviewer that the writing of the conclusions was unspecific and, to provide more details, have modified the conclusions in the abstract section of the revised version of the manuscript (page 4). • I think this is slightly clearer but see comment re: "All

	older people towards the end of life ARE frail?" Frailty is related to survival duration across the disease categories (less clear for cancer?) Comment 8. P6 line 3 Conclusion – "Pattern of survival"…. Without further detail in the methods/results, it's hard to see how this conclusion has been arrived at – also see comments re: Kaplan Meir curves for comparison – what is a 'pattern of survival'? Response: We agree with the reviewer that, due to the space constraints, the results included in the abstract were excessively summarized. We have added novel information to explain de results regarding survival using the Cox regression model in the results (page 3) and conclusions (page 4) of the abstract section of the revised version of the manuscript. • Abstract conclusion now clearer but see above re wording (all older people towards end of life ARE frail vs were frail/in this study Comment 9. This may be a matter of editorial taste, but here only one limitation is highlighted. The authors mention more at the end of the discussion. But for example there was no external validation for frail-VIG, and the score was validated against mortality as an outcome in a group of people already identified as being 'end of life' via the NECPAL tool. Response: We agree with the reviewer that no limitations regarding the Frail-VIG index were included in the manuscript. Regarding the external validation for the Frail-VIG, its ability to predict morality was evaluated in the original study describing the Frail-VIG index, in both the end-of-life cohort, identified using the NECPAL tool, and in the complete study sample (Amblàs-Novellas, 2018). In addition to its predictive value, this study evaluated content validity and construct validity (discriminatory capacity). Other studies have demonstrated the convergent-divergent construct validity (Amblàs-Novellas, 2017) and the criteria validity of the Frail-VIG (Moreno-Ariño, 2020). Given the previously reported validation of the Frail-VIG index, in this study, the validation of the Frail-VIG was not considered a limitation. We have added the information and references regarding the validation of the frail-VIG index in the methods section of the revised version of the manuscript (page 7). • Looking at these references – Amblas novellas 2018 and 2017 seem to be looking at the same 590 people (i.e not external validation)

	Comment 9. P8 line 29 – consensus concept frailty to provide palliative care – My reading of the two references provided here is they seek consensus around a general definition of frailty, without specific focus on palliative care. Recently published BGS guidelines on frailty and end of life care may be something to consider referencing here as specific approaches and definitions are used there. Response: We thank the reviewer for this insightful comment, as these guidelines were not published at the time this manuscript was in preparation. We agree with the reviewer that these guidelines are worth considering and have added them as a reference in the introduction section of the revised version of the manuscript (page 6, reference #23). • Thank you for adding this in Comment 10. P8 line 30 – I think it would be helpful to readers if these aims could be clarified slightly – the wording in the abstract/objectives is clearer. Response: We agree with the reviewer that the aims, stated as a hypothesis, were not appropriately worded in the introduction section. In the revised version of the manuscript, we have modified the wording of the aims and used the clearer wording of the abstract (page 6). • I think these aims are clearer now thank you Comment 11. P8 line 56 - NECPAL was used to define end of life – readers of BMJ open would benefit from a simple description (could be supplemental material) of this tool Response: We agree with the reviewer that information regarding the NECPAL tool would be useful for BMJ open readers. Our research group provides a description and detailed information on the different dimensions evaluated by the NECPAL tool on its website https://en.c3rg.com/necpal, which we have included as a reference (#30) in the methods section of the revised version of the manuscript (page 8). • Thank you for adding the reference and updating the description Comment 12. P9 line 5 – "in the same setting" – as far as I can see (and this is not a criticism or a limitation) the article under present review is a sub analysis of the data collected for study reference [20] Response: We agree with the reviewer that the fact that this was a sub analysis of the

	results obtained in the original study was not clearly stated and, given that the use of "in the same setting" might be misleading, we have deleted this clause from the revised version of the manuscript and have stated that this is a sub analysis (page 7). • Thank you for clarifying this Comment 13. P11 line 13 – A table 1 of patient characteristics by age sex and disease trajectory would be easier to interpret than having the information in paragraphs and would give readers an idea of potential sociodemographic variation across disease trajectories (were people in the cancer group younger than people in the multimorbidity group? For example) Response: Even though patients' demographic characteristics according to disease trajectories had been included in our previous publication (Amblàs-Novellas et al. 2006), we agree with the reviewer that including these data in this manuscript would facilitate its interpretation. We have included the age and sex of study patients according to their end-of-life situation (EOLp and NonEOLp) and end-of-life trajectories (cancer, organ failure, dementia, and multimorbidity) in Tables 1 and 2 of the revised manuscript, respectively, and have removed any redundant data from the text. • Much clearer – thank you Comment 14. P11 line 24 – based on inclusion criteria, all patients should either be cognitive decline n=330?, or end of life n=260. The rest of the paper really only addresses the n=260 with end of life. It might be clearer if the authors could clarify that this is a sub analysis. 590 people were recruited to the main study, but this study considers the 260 who were end of life. I'm not sure that the extra information in the results/tables relating frailty to the 330 people with cognitive decline is helpful or relevant to the question the author's address. I can see that they are included in figure one, but is a comparison of survival between people at end of life and people with cognitive decline a useful one? Response: We agree with the reviewer's that these comparisons may not be relevant. However, of the 590 people considered in this study, 260 were end-of-life and 330 were non-end-of-life people (and not people with cognitive decline), and were used as a control group. Even though the two groups had similar demographic characteristics (i.e., age and sex), their classification according to their frailty degree, and their median

	frailty-VIG scores were significantly different. We believe that comparisons between end-of-life and non-end-of-life are useful, enabling us to identify an association between higher frailty scores and end-of-life status. • Can you clarify that the control group situation "Admission criteria to the AGU were age ≥ 85 years, cognitive decline, and/or end-of-life situation; no exclusion criteria were defined. Comment 15. P11 line 35 – Do any of the items in the VIG index also overlap with the how multimorbidity was defined? Response: We thank the reviewer for this comment. Of the 22 items (i.e., questions) included in the calculation of the Frail-VIG index, 15 refer to chronic conditions, including geriatric diseases and syndromes. All the patients who were classified in the multimorbidity illness trajectory had two or more of these chronic conditions, as defined by the WHO (https://apps.who.int/iris/bitstream/handle/10665/252275/9789241511650-eng.pdf;jsessionid=BF929E1330346103428668CB1C571284?sequence=1). We have added a sentence to clarify this issue in the methods section of the revised version of the manuscript (page 7), besides the definition of multimorbidity, which was already included in the first version (page 8). • Thank you Comment 16. P 14 line 53 – given that other studies have found frailty indices to be relatively poor prognostic indicators for individuals it is encouraging to see these high AUC values. However, given the setting (people identified as end of life via NECPAL) these values are not entirely surprising. Response: We agree with the reviewer's that the value of frailty index as a prognostic indicator in a population identified as end-of-life people may be partly expected. Nevertheless, in the complete cohort (n=590) including end-of-life and non-end-of-life people, the frail VIG index was able to discriminate mortality in people with no frailty and moderate frailty, compared to people with advanced frailty. • I can see that you looked at the FI in the mixed group of EOL/nonEOL people, and agree this comment is relevant to that. However, I still don't see the utility/relevance of the final paragraph of the results section "Prognosis Value of the Frail-VIG Index"

	The study doesn't state it aims to be a prognostic study or a diagnostic test study (STROBE used for reporting here, rather than STARD ?). In this paragraph you're looking only at the end of life people "The prognostic value of the Frail-VIG index for the end-of-life people" (and introducing a 1 year time point not mentioned in the methods) this feels like a slightly fatalistic way to view of frailty because this group are defined as being 'end of life' (frailty will predict death in those already predicted to die?) Comment 17. Plots p27 and p28 – for clarity on the x-axis, is this time after entry to study (days)? Response: We agree with the reviewer that the X-axis was not appropriately labelled and have changed the labelling in Figures 1, 2 and 3 of the revised manuscript. • Thank you

VERSION 2 – AUTHOR RESPONSE

Response to reviewer #1, Dr. Diana Teggi

The typos spotted by the reviewer have been all corrected.

Response to reviewer #2. Dr. Daniel Stow.

The authors would like to thank Dr. Stow for these comments, which will certainly improve the quality of the manuscript. Please, find a point-by-point response to these comments below.

Minor points:

- P4 – line 3. "All older people towards the end of life are frail" In this study / in this setting surely/ all older participants were frail (the first line of the conclusion – it's a selected population recruited at point of entry to an acute geriatric ward).

Response: To align this conclusion with the analysis of a very old population performed in this study and considering additional comments 7 and 8, we have rephrased the conclusion into "All older people towards the end-of-life in this study were frail…"

- P4 – line 8 "To assess end of life people" <- can you be a little clearer about this recommendation: assess in what way? Is the frailty index telling you something about symptoms, or survival time>

Response: To be more specific, we have rephrased this conclusion into "to identify end-of-life older people needing palliative care."

- P11 – typo ass -> as

Response: This typo has been corrected.

- P18 – line 13 “likely to enrich” <- I think this has been touched on before, but given the setting I think it more than likely

Response: We agree that adding likely to this sentence was inappropriate and have removed it from the revised version of them manuscript.

Comment 1. Kaplan Meier is quite a descriptive tool, and isn’t really useful for testing hypotheses across multiple groups, as the authors do here. The reliance on stratification for comparison can lead to problems where there are a large number of variables of interest, and should be interpreted very cautiously when cell sizes are small (as is the case here). I am also unclear as to the steps taken to correct for multiple comparisons. I would recommend using Cox regression as a robust method for testing the association between frailty, primary diagnosis, and survival, whilst also adjusting for age and sex (e.g. survival time predicted by diagnosis + a frailty/diagnosis interaction, also adjusted for age and sex).

Response: As requested by the reviewer and, considering that data met the hypothesis of proportional hazards, we have used the Cox regression to test the association between frailty, illness trajectory, and survival. The results from these analyses have been included in a new Figure (Figure 3) and additional text in the abstract (page 3), methods (page 9), results (page 11-12), and discussion (page 14) sections of the revised version of the manuscript.

Additional Comments:

1. I’m glad to see the authors checked the assumptions of proportionality. Rather than just reporting a p value in the abstract, the range of HRs would give readers a better idea of the magnitude of the relationship

Response: We agree with the reviewer that the results were not sufficiently detailed in the abstract and, in its revised version, we have included the results regarding the association between increased frailty and risk of death in the different illness trajectories (page 3-4).

2. Can you be clearer in the methods about who was in the model (was this just the end of life group, or did you include the non end of life people too?).

Response: We agree with the reviewer that the populations included in the model were not specified. To clarify the study groups (i.e., total cohort and non-end-of-life people) used for each of the analyses, we have reorganized the statistical analysis paragraph in the methods section of the revised version of the manuscript (page 9). Given the limited word count of the abstract section and its current extension, we have not included this information in the revised abstract. However, we are willing to reconsider this decision at the reviewer’s request. Additionally, to make the distinction between the results obtained in the complete cohort and those obtained in people identified as end-of-life, we have added and an additional subheading (“Relationship between Frailty Degree and Survival in End-of-Life People”) in the results section of the revised version of the manuscript (page 12).

3. Can you clarify how you treated the frailty variable in the model (frailty indices usually between 0 and 1, interpretation of hazard ratios would be per 1 unit increase, which doesn't match what is written in the results section – 0.004 increase = 61% increase in HR?)

Response: We agree with the reviewer that the definition of the frailty variable was not well described in the model and needed clarification. The risk of death was calculated according to the accumulated deficits, whereby each deficit out of the 25 assessed added 0.04 points (1/25) and, therefore, the calculation of hazard ratios would be per 0.04 increase (1 deficit=0.04). Consequently, the manuscript's figures do not correspond to the hazard ratios of the Frail-VIG index, they are the hazard ratios of the Frail-VIG/0.04. We believe that this unit transformation provides a better interpretation of the effect of the Frail-VIG index on the hazard risk. To clarify this issue, we explain this unit transformation in the results section of the revised version of the manuscript (page 12).

Comment 3. I also think that the aims and message of the paper are made less clear by the comparison to the 330 people with cognitive decline – it might be simpler to omit this group and focus on the end of life message: mortality prognostication / survival comparison between people defined as end of life vs people with cognitive decline doesn't seem a useful one or relate to the aims of the study.

Response: We thank the reviewer for his insightful comment. The 330 people included in this study were non-end-of-life people and were used as a control group. Despite the similar demographic characteristics (i.e., age and sex) of the 260 end-of-life and 330 non-end-of-life people (included in revised Table 1) their frailty profiles differed, enabling us to identify an association between higher frailty scores and end-of-life status.

Additional Comment: Can you be clearer in the study design/methods that this group is being used as a control?

Response: We agree with the reviewer that this was still unclear in the manuscript and have added a sentence explaining the use of non-end-of-life people as controls in the first paragraph of the methods section of the revised manuscript (page 7).

Comment 4. Abstract P5 line 13 Methods – The study design is very well described, but it would be helpful to see the methods for analysis here too (Kaplan meier survival curves?)

Response: We agree with the reviewer that the methods section of the abstract lacked a description of the statistical methods used. We have now included a description of the statistical methods used in this study in the abstract of the revised version of the manuscript (page 3).

Additional Comments:

1. Methods are now slightly clearer, but I'm still not clear on how the models were constructed.

Response: We agree with the reviewer that the description of the Cox proportional hazards model in the methods section of the abstract may seem insufficient. However, the model was directly built with the interactions between frailty degree and illness trajectories, and we consider that any further explanation of the model would be excessively technical in the context of an abstract.

2. There are also results appearing in the 'prognostic utility' section that aren't described (1 year mortality, stratification by disease)

Response: We agree with the reviewer that the manuscript was missing part of the methods used to obtain some of the presented results. We have added an additional clause to explain the methods used to assess the prognosis value of the Frail-VIG index in the abstract and methods sections of the revised version of the manuscript (page 3 and 9).

Comment 5. Abstract P5 line 44 Results – "significant relationship between frailty degree and survival": can you be more precise here? Reduced survival? Median survival time between groups?

Response: We agree with the reviewer that the results included in the abstract section were poorly described and a precise description of the relationship between frailty degree and survival was missing. We have included a clause indicating that higher scores of the Frail-VIG index are associated with lower survival in the abstract section of the revised version of the manuscript (page 3).

Additional Comment: Clearer but please describe the effect/ range of effects, not just a p value

Response: In the abstract section of the revised version of the manuscript, we have specified the effects of increased frailty in the risk of death (page 3- 4).

Comment 6. Abstract P5 line 48 Results – "Differences in frailty degree between four illness trajectories and survival" it isn't clear what is meant here. Is there a reference illness trajectory, and which of the comparators had higher or lower frailty degrees? I'm not sure it's helpful to say 'there were differences', especially given the conclusion drawn in the next paragraph. I'm not sure that Kaplan Meier is the most appropriate method to use for comparison here.

Response: We agree with the reviewer that results may not have been precisely explained and may seem contradictory. However, we had initially discarded a description of the results regarding survival profiles of the different illness trajectories due to the space constraints of the abstract section. In this regard, even though our results show that end-of life people are frail regardless of their illness trajectories, the survival profiles of people with different frailty degrees differed in the different illness trajectories; considering none of the illness trajectories as a reference, they were compared among them. Furthermore, we have considered the reviewer's suggestion of using Cox regression models to analyse survival according to illness trajectory and frailty degree. To clarify the results of the survival analysis, we have focussed the results in the abstract section of the revised version of the manuscript in those from the Cox regression model (page 3).

Additional Comment: Now slightly clearer. I think more clarity needed about the move to AUROC though. This wasn't an aim of the study – test of diagnostic accuracy = STARD.

Response: We agree with the review that assessing the performance of the Frail-VIG as an indicator of prognosis was not the aim of this study. To avoid confusions, we have removed the heading "Prognosis value of the Frail-VIG" and have rephrased the description of the results. These results are included, in the revised version of the manuscript, in the previous paragraph "Relationship between Frailty Degree and Survival in End-of-Life People" (page 13).

Comment 7. P5 line 57 - Conclusion – I think this could be clarified: how could frailty indices be useful for assessing end of life older people? Are the authors suggesting they could be used for prognosis (this is mentioned in the aims at the end of the introduction)?

Response: We agree with the reviewer that the writing of the conclusions was unspecific and, to provide more details, have modified the conclusions in the abstract section of the revised version of the manuscript (page 4).

Additional Comment: I think this is slightly clearer but see comment re: "All older people towards the end of life ARE frail?" Frailty is related to survival duration across the disease categories (less clear for cancer?)

Response: To clarify the conclusions of this study in the abstract section, we have reworded the second sentence (page 4).

Comment 8. P6 line 3 Conclusion – "Pattern of survival"…. Without further detail in the methods/results, it's hard to see how this conclusion has been arrived at – also see comments re: Kaplan Meir curves for comparison – what is a 'pattern of survival'?

Response: We agree with the reviewer that, due to the space constraints, the results included in the abstract were excessively summarized. We have added novel information to explain de results regarding survival using the Cox regression model in the results (page 3) and conclusions (page 4) of the abstract section of the revised version of the manuscript.

Additional comment: Abstract conclusion now clearer but see above re wording (all older people towards end of life ARE frail vs were frail/in this study

Response: We agree with the reviewer that the writing of the conclusions was unclear and have substantially rephrased them in the revised version of the manuscript (page 4).

Comment 9. This may be a matter of editorial taste, but here only one limitation is highlighted. The authors mention more at the end of the discussion. But for example there was no external validation for Frail-VIG, and the score was validated against mortality as an outcome in a group of people already identified as being 'end of life' via the NECPAL tool.

Response: We agree with the reviewer that no limitations regarding the Frail-VIG index were included in the manuscript. Regarding the external validation for the Frail-VIG, its ability to predict morality was evaluated in the original study describing the Frail-VIG index, in both the end-of-life cohort, identified using the NECPAL tool, and in the complete study sample (Amblàs-Novellas, 2018). In addition to its predictive value, this study evaluated content validity and construct validity (discriminatory capacity). Other studies have demonstrated the convergent-divergent construct validity (Amblàs-Novellas, 2017) and the criteria validity of the Frail-VIG (Moreno-Ariño, 2020). Given the previously reported validation of the Frail-VIG index, in this study, the validation of the Frail-VIG was not considered a limitation. We have added the information and references regarding the validation of the Frail-VIG index in the methods section of the revised version of the manuscript (page 7).

Additional Comment: Looking at these references – Amblas novellas 2018 and 2017 seem to be looking at the same 590 people (i.e not external validation)

Response: The reviewer is right in pointing out that these two references included the same population and we apologize for not providing the correct references. We have added two additional references that use and validate the Frail-VIG index in two different patient populations in the revised version of the manuscript (Moreno-Ariño, 2020 and Madruga-Flores, 2021, references 27 and 28, page 8), and have mentioned "insufficient external validation" as a limitation of this study in the strengths and limitations section (page 5).

Comment 14. P11 line 24 – based on inclusion criteria, all patients should either be cognitive decline n=330?, or end of life n=260. The rest of the paper really only addresses the n=260 with end of life. It might be clearer if the authors could clarify that this is a sub analysis. 590 people were recruited to the main study, but this study considers the 260 who were end of life. I'm not sure that the extra information in the results/tables relating frailty to the 330 people with cognitive decline is helpful or relevant to the question the author's address. I can see that they are included in figure one, but is a comparison of survival between people at end of life and people with cognitive decline a useful one?

Response: We agree with the reviewer's that these comparisons may not be relevant. However, of the 590 people considered in this study, 260 were end-of-life and 330 were non-end-of-life people (and not people with cognitive decline), and were used as a control group. Even though the two groups had similar demographic characteristics (i.e., age and sex), their classification according to their frailty degree, and their median frailty-VIG scores were significantly different. We believe that comparisons between end-of-life and non-end-of-life are useful, enabling us to identify an association between higher frailty scores and end-of-life status.

Additional Comment: Can you clarify that the control group situation "Admission criteria to the AGU were age ≥ 85 years, cognitive decline, and/or end-of-life situation; no exclusion criteria were defined.

Response: We agree with the reviewer that the study groups were not defined and have included two additional explanatory sentences in the methods section of the revised version of the manuscript (page 7).

Comment 16. P 14 line 53 – given that other studies have found frailty indices to be relatively poor prognostic indicators for individuals it is encouraging to see these high AUC values. However, given the setting (people identified as end of life via NECPAL) these values are not entirely surprising.

Response: We agree with the reviewer's that the value of frailty index as a prognostic indicator in a population identified as end-of-life people may be partly expected. Nevertheless, in the complete cohort (n=590) including end-of-life and non-end-of-life people, the Frail-VIG index was able to discriminate mortality in people with no frailty and moderate frailty, compared to people with advanced frailty.

Additional comment: I can see that you looked at the FI in the mixed group of EOL/nonEOL people, and agree this comment is relevant to that. However, I still don't see the utility/relevance of the final paragraph of the results section "Prognosis Value of the Frail-VIG Index". The study doesn't state it aims to be a prognostic study or a diagnostic test study (STROBE used for reporting here, rather than STARD ?). In this paragraph you're looking only at the end of life people "The prognostic value of the Frail-VIG index for the end-of-life people" (and introducing a 1 year time point not mentioned in

the methods) this feels like a slightly fatalistic way to view of frailty because this group are defined as being 'end of life' (frailty will predict death in those already predicted to die?)

Response: We agree with the reviewer that the aim of this study is not prognosis. The title of paragraph "Prognosis Value of the Frail-VIG index" referred to the performance of the Frail-VIG index in the different trajectories rather than the prognosis value of the frailty degree. The results included in this paragraph aimed to confirm the expected/anticipated association of frailty, measured using the Frail-VIG, and survival in this study's end-of-life group. We believe that the results included in this paragraph showing frailty (mostly advanced frailty) and its association with survival may be useful for healthcare professionals to confirm the end-of-life situation. Furthermore, this paragraph shows that the AUC is high regardless of the illness trajectory, further confirming that that frailty, and specially advanced frailty, is common in all very old people in an end-of-life situation. Nevertheless, we agree with the reviewer that the title of this subheading was misleading and, in the revised version of the manuscript, have removed this subheading and fused this paragraph with the previous one (page 13).

VERSION 3 – REVIEW

REVIEWER	Stow, Daniel Newcastle University, Population and Health Sciences Institute
REVIEW RETURNED	04-Mar-2021

GENERAL COMMENTS	COMMENTS TO AUTHORS Thank you to the authors for their considered and comprehensive responses to my previous comments. I still think the methods are still a little unclear: • Methods - Can you confirm what covariates you included in the models (age and sex should be included) – a supplemental table with the coefficients for the main effects and interaction would clarify this. • Methods - Can you make it clear in this section if you used the Frail VIG index (0-1), "frailty degree" (as currently stated – and which might imply the description on page 4 of a 4-level variable ranging from 0=no frailty to 3=advanced frailty?), or the number of deficits (0-25)? • In your results section it looks like you used the raw deficit score (0-25) in the models and not the frail VIG (0-1), or frailty degree (0-3) – is this correct (and if so can you justify the assumption of a linear effect here?) RELEVANT TEXT FROM THE PAPER METHODS And a cox proportional hazards model with the interaction between frailty degree and illness trajectories was calculated

	RESULTS 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). Theseresults 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 AUTHOR RESPONSE TO MY COMMENT We agree with the reviewer that the definition of the frailty variable was not well described in the model and needed clarification. The risk of death was calculated according to the accumulated deficits, whereby each deficit out of the 25 assessed added 0.04 points (1/25) and, therefore, the calculation of hazard ratios would be per 0.04 increase (1 deficit=0.04). Consequently, the manuscript's figures do not correspond to the hazard ratios of the Frail-VIG index, they are the hazard ratios of the Frail-VIG/0.04. We believe that this unit transformation provides a better interpretation of the effect of the Frail-VIG index on the hazard risk. To clarify this issue, we explain this unit transformation in the results section of the revised version of the manuscript (page 12).

VERSION 3 – AUTHOR RESPONSE

Comment 1. Can you confirm what covariates you included in the models (age and sex should be included) – a supplemental table with the coefficients for the main effects and interaction would clarify this.

Response: The Cox proportional hazards models built for this study included Frail-VIG index scores and the four illness trajectories. Sex and age evaluated together and age evaluated alone lacked statistical significance and, for this reason, these covariates were excluded from the model. To completely explain the construction of the model, we have included additional tables with the coefficients for the main effects and interactions of the covariates included and excluded in the Cox proportional hazards model (i.e., sex + age and age) (Tables S1, S2 and S3) in a new supplementary

material file and have included additional sentences in the methods and results sections of the revised version of the manuscript (page 9 and 12).

Comment 2. Can you make it clear in this section if you used the Frail VIG index (0-1), "frailty degree" (as currently stated – and which might imply the description on page 4 of a 4-level variable ranging from 0=no frailty to 3=advanced frailty?), or the number of deficits (0-25)?

Response: We thank the reviewer for this comment as the explanation regarding the different uses of the Frail-VIG index were certainly unclear. The Frail-VIG index may be expressed as a continuous variable (Frail-VIG index score) using the Frail-VIG index (0-1), in which each additional deficit of a total of 25 deficits assessed is 0.04 (1/25), and as a categorical variable classified in four frailty degrees (no frailty, mild frailty, moderate frailty, and advanced frailty). For the statistical analysis requiring continuous variables, including the AUC/ROC curves, C-statistics, and Cox regression, we used the Frail-VIG index expressed as a continuous variable (with each additional deficit = 0.04). For the Kaplan-Meier estimator and long-rank test, we have used the Frail-VIG expressed as a categorical variable. The different applications of the Frail-VIG index have been clarified in the methods section of the revised version of the manuscript (pages 7-9).

Comment 3. In your results section it looks like you used the raw deficit score (0-25) in the models and not the frail VIG (0-1), or frailty degree (0-3) – is this correct (and if so can you justify the assumption of a linear effect here?)

Response: In the Cox proportional hazards model, we used the Frail-VIG index score expressed as a continuous variable ranging 0-1, calculated as the number of accumulated deficits divided by the total of possible deficits (25). To calculate the hazard ratios, 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 (see Table S1). To compute the hazard ratios for a 0.04 unit increase in the Frail-VIG index, the hazard ratios for one unit increase in the Frail-VIG index were transformed. The computation of the hazard ratios for oneunit increase and for a 0.04-unit increase in the Frail-VIG index have been included in additional text (Supplementary Methods) and tables (Table S4 and S5) in the new Supplementary Material file of the revised version of the manuscript.

VERSION 4 – REVIEW

REVIEWER	Stow, Daniel Newcastle University, Population and Health Sciences Institute
REVIEW RETURNED	23-Mar-2021

GENERAL COMMENTS	A very interesting and useful paper - thank you to the authors for addressing my comments : the supplemental tables and revisions to the methods/results are much clearer.