Author's response to reviews

Title: Prevalence of frailty and its associated factors in older hospitalised patients in Vietnam

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Author’s response to reviews:
RESPONSE TO REVIEWERS COMMENTS ON MANUSCRIPT ID BGTC-D-17-00168

We would like to thank the reviewers for the time spent reviewing our manuscript and for their useful comments, and to thank the editors for the opportunity to respond.

We have specifically responded to the issues raised as detailed below, and would be happy to address any further issues if required.

Reviewer reports:

Monica Perracini, PT, PhD (Reviewer 1): Overall, this study related to frailty in hospitalized older adults in Vietnam is interesting and well written. Its main strength is that it was conducted in a developing country, since there is a scarcity of studies with this population. Although, the results are not surprising or new, it's critically important for police makers worldwide to be aware about frailty as a public health concern.

Major problems

1. Page 4 1st Paragraph - please provide relevant information about the relation between hospitalization and frailty. There is relevant literature concerning frailty transitions and
hospitalization. The discussion about the impact of hospitalizations upon frail and non-frail patients should be addressed. The fact that frailty is related with hospitalization is well known.

Response: Thank you for your comment. We have added the following sentences in the Introduction section:

“There is increasing evidence that frailty is a significant predictor of hospitalisation and adverse outcomes after discharge in older people, such as readmission, increased risks of disability and mortality. According to a systematic review and meta-analysis in 2016, frailty was significantly associated with higher hospitalisation risks (pooled Odds Ratio 1.90, 95% CI 1.74-2.07, p<0.00001) (Kojima et al 2016).” (Please see Introduction, lines 9-13)

2. Page 4 2nd Paragraph - you can expand your argumentation about the necessity of conducting studies on frailty in developing countries with the fact that the long-term burden of chronic diseases is significant in the population living in this area.

Response: We have added this sentence in the first paragraph of Discussion:

“This evidence suggests a need for studies on frailty in developing countries as the long-term burden of chronic diseases is significant in the population living in these parts of the world” (Please see Discussion, lines 10-12)

3. Page 4 last Paragraph - Is the National Geriatric Hospital different in any way of other hospitals in Vietnam? I do think that this can be left out from the objective.

Response: Thank you for your suggestion. We have removed the last sentence of the last paragraph of Discussion

4. Page 5, 1st Paragraph line 1 - This is a cross-sectional study.

Response: This study was designed as a prospective cohort study. For this manuscript, we just present the cross-sectional analysis, the follow up data will be analysed and presented in a separate manuscript. We have added an explanation in Methods:

“This paper just reported the cross-sectional baseline data, the follow up data will be analysed and presented in a separate manuscript.” (Please see Methods, lines 17-19)

5. Page 5 line 17 - Authors did not report how they addressed the independent variables. Was it done by a questionnaire? Who answered the questions? Patients themselves or proxies?

Response: Data collection was obtained from interviews with participants/ their caregivers and also from medical records (including socio-demographics, detailed medical history, co-
morbidities, clinical assessments and prescribed medications and non-prescription medications). We have added more explanation as follows:

“Data was collected from medical records and included socio-demographics, detailed medical history, co-morbidities, clinical assessments and prescribed medications and non-prescription medications. All participants were interviewed for the Reported Edmonton Frail Scale (details are presented in Frailty definition), and for their nutritional status based on one question “How would you describe your diet”. For participants with severe cognitive impairments (7/461 participants), interviews were conducted with their caregivers” (Please see Methods, lines 11-16).

6. Authors should provide information and references to what they considered poor nutritional status, BMI classification.


7. Page 5, line 39 Provide the reference for the cut-off points reported for grip strength.


“Weakness: Grip strength in the dominant hand was measured with a dynamometer (Jamar TM Hidraulic Hand Dynamometer 5030J1 made in USA), adjusted for gender and body mass index (BMI) according to the lowest quintile. This method is consistent with the method in the original study conducted by Fried et al in 2001.”

8. Page 6, 1st Paragraph line 1 - include 0.8 m/s as the appropriate information since 5 seconds is not currently used.

Response: Although the criterion of 0.8m/s has been intensively applied recently, the criterion of time to walk 4 metres more than 5 seconds has also been commonly used in research, especially in France. In Asia-Pacific region, this criterion was also used in the Frailty Intervention Trial (Cameron, I. D., N. Fairhall, et al. (2013). "A multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial." BMC Med 11: 65.). Actually, the time to walk 4 metres more than 5 seconds is equivalent to a walking speed <0.8m/s.

9. Page 6 line 4 - Physical activity is defined as any body movement with muscle contraction energy expenditure. Authors used planned exercise as the criteria. Please provide a reference for this or explain why you decided to address it in this way. Fried's phenotype clearly refers the low
physical activity as an indirect measure of energy expenditure. There was a probably overestimation of the prevalence of this criterion. If so, refers it as a study limitation. Probably this is one of the main reasons why you observed a high prevalence of the low physical activity component of the Fried phenotype. The reported physical performance component of the REFS also addresses quite vigorous-intensity activities. This may be better discussed.

Response: Thank you for your suggestion. In fact, other studies have also adapted measures for Fried phenotype criteria in different populations. Fried et al. have shown that surrogates for individual frailty phenotype criteria are possible. (Eckel SP, Bandeen-Roche K, Chaves PH, Fried LP, Louis TA. Surrogate screening models for the low physical activity criterion of frailty. Aging clinical and experimental research. 2011 Jun;23(3):209–16). We have referred this as a study limitation as follows:

“Another limitation of our study is that we defined low physical activity based on participants’ report that “I rarely or never do any physical activities” (Please see the last paragraph of Discussion)

10. Page 6 line 51 - Please clearly specify if at the logistic regression analysis you compared frail older people with non-frail and pre-frail. Report how you addressed dummy variables and multicollinearity.

Response: In this study, we just divided participants into two groups: frail and non-frail (the non-frail included the robust and the pre-frail)

11. Page 6 line 56 - Describe how many patients came from each different ward.

Response: We have added this sentence: “The proportion of participants from each ward were 33.6% (cardiology), 23.2% (neurology), 18.7% (general medicine), 14.1% (endocrinology), and 10.4% (private general medicine ward)”. (Please see Results, lines 2-4)

12. Page 8 line 12 - Authors should be cautious when saying the protein supplementation can reverse frailty. The reference provided states clearly that there is no clear evidence till date for supporting the use of protein supplementation alone to reverse frailty or even show improvement on muscle mass and muscle function.

Response: We have rephrased this sentence and add more references: “Several observational studies suggested that protein supplementation may help decelerate frailty and the Asia-Pacific Clinical Practice Guidelines for the Management of Frailty also conditionally recommended caloric and protein supplementation in frail older people with weight loss”. (Please see Discussion, lines 19-22)
13. Page 8 line 24 - The association between frailty and cardiovascular disease is not new. So the important issue here is the fact that these patients usually are not assessed in terms of frailty and there is a window of opportunity to prevent secondary consequences related to frailty in this population, such as falls and other geriatric syndromes. This should be better discussed.

Response: We have added these sentences in the third paragraph of Discussion:

“Our current medical practices are disease-based and older patients with cardiovascular diseases are usually not assessed in terms of frailty. Frailty assessment could provide a window of opportunity to prevent adverse outcomes related to frailty in this population, such as falls and other geriatric syndromes.”

14. Minor problems: Make a revision on tables format. A p value of 0.00 should be reported as < 0.001. Provide p values with 2 or 3 decimal cases, but you have to have standardization for that.

Response: We have revised the tables as suggested.

Oleg Zaslavsky (Reviewer 2):

The purpose of this study was to examine frailty in older and hospitalized older adults in Vietnam. The unique cohort and two methods to evaluate frailty is a likely strength of this manuscript. However, I have some concerns about the way data was collected, analyzed and presented here.

1. Methods: Need clear explanation of sample size considerations (how many approached and screened out and reasons for not being included), recruitment flow (flowchart would be ideal):

Response: The recruiting team were postgraduate students. We acknowledged that our team lacked experience and we did not record the exact number of patients approached and the reasons for not being included, hence we cannot introduce a flow chart. Based on the hospital database, the total number of admissions to the targeted wards during the study period (from 4/2015 to 10/2015) was 1559. The recruiting team did not recruit participants during weekends, holidays and during the time that they were busy with other tasks such as examinations at schools and the duties at their workplaces. However, during the recruiting time, they made their best efforts to recruit consecutive patients.

We have added this as a limitation of the study (Please see the last part of Discussion)

2. Missing data (what about those who did not have all frailty criteria collected/ missing data on risk factors)
Response: The recruiting team tried to collect all frailty components, therefore all participants had complete data for frailty criteria. For other factors, the missing data were random, therefore only the available data were analysed (i.e. the missing data were ignored by SPSS).

3. Data collection procedures (cognitive screening? proxies in those with cognitive deficits?)

Response: We did not perform cognitive screening. For those with severe cognitive impairments based on diagnosis in medical records (7/461), we collected data from their caregivers and from the medical records. Please see more details in response to comments 5-6 of Reviewer 1.

4. Definition of the main variables (data collection tools? Self report vs ICD codes)

Response: Please refer to responses to comments 5-6 of Reviewer 1.

5. Frailty criteria (translation and cultural adaptation)

Response: As all the components and measurements of the Fried’s criteria and the Reported Edmonton Frail Scale are not culture-specific, we just made a translation into Vietnamese language. Details on the application of Fried’s methods to assess the cut-off for grip strength using the lowest quartile of our population are provided in response to point 7 raised by Reviewer 1.

6. In addition, it would be beneficial for the readers to understand why these specific frailty tools were selected. The authors mentioned that there are more than 20 different approaches to evaluate frailty but the reasons for selecting Fried's and Edmonton scales were not explained.

Response: These two scales are frequently used in research in the region. According to the Asia-Pacific Clinical Practice Guidelines for the Management of Frailty, Fried’s frailty criteria is strongly recommended for identifying frailty in clinical settings. The reason for choosing the Reported Edmonton Frail Scale was also stated in the manuscript as below. In addition, the REFS includes cognition as one of its component, which can help us get some insights when compared with a physical frailty scale such as the Fried frailty phenotype.

“All participants were also assessed with the REFS. This scale has been validated for use in acute inpatients in previous studies [18-23]. Compared to Fried’s frailty phenotype, the REFS is based on a questionnaire on how the patient functioned prior to the illness that brought them into hospital, is not heavily influenced by the acute illness, easy to apply for older inpatients and less time-consuming. The scale involves nine frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance).” (Please see Methods section, Frailty definition)
7. The authors also mentioned that frailty is used for risk stratification, but outcomes were not collected here. Although, prevalence of frailty in hospitalized patients is important for epidemiological purposes, it would strengthen the manuscript to also collect outcome data such as length of stay, complication rate, mortality, etc.

Response: We will present the outcome data in a separate manuscript. We currently do not have these data analysed.

8. Page 4, Line 58: Study population. The authors did not explain of sample size calculation in this study. Notably, the workflow or flow chart of participant recruitment would be helpful to have a better picture about the overall flow and frequency of missing data.

Response: Sample size was calculated according to this formula: \( N = \frac{Z^2(1-\alpha/2) \times P \times (1-P)}{d^2} \), (P: prevalence of frailty in literature). Based on previous studies, the prevalence of frailty in hospitalized patients ranged from 30% to 60% (Nobrega et al., 2013; Khandelwal et al., 2012; Perera et al., 2009; Purser et al., 2006). With a 99% confidence interval (Z= 2.33) and a desired absolute precision of 1% (d=0.01), the estimated sample size is around 500 participants.

A flowchart is not available as explained in response to comment 1.

9. Page 5, Line 10-11: The exclusion criteria. The authors explained that they excluded "blind" and "deaf" older person. How were these defined? Self report?

Response: “Blind” and “deaf” were defined based on reports from the participants or their caregivers, then confirmed with clinical examinations from the recruiting doctors and also from the medical records.

10. Although cognitive deficits are common in this population, it is unclear whether or not cognitive screening was administered. This is important information because some frailty criteria are self reported and it might be challenging to get valid and reliable information from a patient with severe cognitive impairment. If the authors included reports from proxies, it should also be explicitly stated.

Response: As response to comment 3, we did not perform cognitive screening. For those with severe cognitive impairments (7/461), we collected information from their caregivers and from the medical records. Please refer to response to comments 5-6 of Reviewer 1 for more information. According to our observation so far, the prevalence of dementia in hospitalised patients at our hospital is pretty low.

11. Page 5, Line 16: Why oral rather than written consent was collected. Practicality or some other consideration were involved? Need more explanation of why oral consent is appropriate in this study especially in vulnerable and hospitalized older adults. The cognitive assessment is
critical for informed consent form both legal and ethical standpoint. Moreover, as previously mentioned both RESF and Fried’ frailty phenotypes have self-report items; how did the authors retrieve data from persons with cognitive impairment is unclear.

Response: Oral consent is a common practice in Vietnam. In our culture, people (especially older people) usually hesitate, worry and feel uncomfortable when they have to sign in written forms. For those with severe cognitive impairments, we collected data from their caregivers and from the medical records.

12. Page 5, Line 25: Frailty instruments. Need clear explanation on whether or not frailty tools were translated and culturally adapted to local setting.

Response: As in response to comment 5, all the components and measurements of the Fried’s criteria and the Reported Edmonton Frail Scale are not culture-specific, we just made a translation into Vietnamese language.

13. No information was given on what "some adaption" Fried's frailty phenotype means.

Response: We have added more details in this sentence” “The Fried frailty phenotype included five criteria proposed by Fried with some adaptation in the slowness and low physical activity components” (Please see Methods, lines 17-18).

13. Page 6, Line 37: Need more explanation of the scientific reasoning and the definition for each potential risk factor. Also, please describe how were those data (medical record, ICD-10, or other resources) collected.

Response: As frailty is a complex multifactorial biological syndrome that is characterised by a cumulative dysregulation of physiological processes and occurs as a result of impacts from multiple physical, social and environmental factors, we tried to include all of the mentioned variables as potential risk factors (age, gender, nutritional status, underweight, comorbidities such as cardiovascular diseases, hypertension, type 2 diabetes, chronic pulmonary diseases, renal impairment, cancer, osteoarthritis, anaemia and socio-economic factors). Please refer to response to comments 5-6 of Reviewer 1 for more information.

14. Results: #Page 7, Line 5-6: The term " poor reported nutritional status" is not well defined. More information and explanation is needed.

Response: We have added more explanation (Please see Methods section, lines 13-16)

“All participants were interviewed for the Reported Edmonton Frail Scale (details are presented in Frailty definition), and for their nutritional status based on one question “How would you
describe your diet”. For participants with severe cognitive impairments (7/461 participants), interviewed were conducted with their caregivers.”

15. Discussion #Page 8, Line 5: Again need more explanation about the definition of poor nutrition status; why it is relate only to protein intake? Moreover, this study did not explore protein consumption pattern of the participants. Thus, discussion part needs more information about that.

Response: We have addressed this question as in response to comment 14. The main aim of this study was to explore the prevalence of frailty and its associated factors. We hope that this finding can provide us preliminary evidence to design future studies that specially aim at nutrition in older people.

16. Page 8, Line 24-30: The authors stated that the cardiovascular disease only relate to Fried’s but not to REFS phenotype. Could you please provide more details about this? why would it be?

Response: The Fried frailty phenotype just focus on physical frailty, while the REFS takes into consideration multiple aspects. We think this could help explain the different findings. Previous studies have shown differences in patients identified through different scales. In addition, cardiovascular diseases are most likely to reduce patient’s physical performance, especially in acute hospital settings, while REFS captures chronic global multifactorial decline from a wide range of causes. More research is needed to explore this issue.