Author’s response to reviews

Title: Prognostic value of frailty in elderly patients with acute coronary syndrome: A systematic review and meta-analysis

Authors:

Qingyu Dou (ddqqking@126.com)
Wen Wang (wangwen83@outlook.com)
Hui Wang (derrywang2000@hotmail.com)
Yao Ma (mayao623@sina.cn)
Shan Hai (haishan923@163.com)
Xiufang Lin (sitaning00@163.com)
Ying Liu (lycherishu@qq.com)
Xinjun Zhang (alexzhang34@163.com)
Jinhui Wu (wujinhui@scu.edu.cn)
Birong Dong (birongdong@163.com)

Version: 1 Date: 23 Jun 2019

Author’s response to reviews:

Dear editor and reviewers:

Thank you very much for your letter and for the reviewer’s comments concerning our manuscript entitled “Prognostic value of frailty in elderly patients with acute coronary syndrome: A systematic review and meta-analysis”. Those comments are valuable and quite helpful for revising and improving our paper. We have studied comments carefully and have made corrections which we hope to meet with approval. Revised portion is marked in blue on the paper.

Editor Comments:

In addition to the referee comments, please address the following editorial points:
Please be aware of overlapping text with published studies and edit to rephrase into your own words. Please see the attached screenshots.

Response: Thanks for the editor’s important comment. We accepted your suggestion and rephrased these texts. We did not revise the content of Newcastle-Ottawa Quality Assessment Scale for accuracy and preciseness.

Please confirm all studies included were observational. If so please include a complete MOOSE checklist as an additional file.

Response: Thanks for the editor’s important comment. We confirmed all studies included were observational and supplemented MOOSE checklist as an additional file. According to the requirements of MOOSE checklist, we added the method and result of sensitivity analysis in the article.

The responds to the reviewer’s comments are as follows:

1. Albert Ariza-Sole (Reviewer 1): Interesting paper about a clinically relevant topic.

Although previously described, this is one of the biggest studies regarding the prognostic impact of frailty in ACS patients. Interestingly, it confirms the association between both frailty and prefrailty with poorer outcomes, independently form covariates.

Just a minor mistake. The reference 35 is cited as Julio’s study. The fist author of this study is Julio (Name) Núñez (surname). I suggest to cite as Nuñez's study.

Response: Thanks for the reviewer’s positive comment. We accepted the reviewer’s suggestion and made the corresponding change in the article.

Takaaki Senbonmatsu, MD., PhD (Reviewer 2): Reviewing the manuscript entitled, "Prognostic value of frailty in elderly patients with acute coronary syndrome: A systematic review and meta-analysis." by Dou QD. et al., overall, this is a clear, concise, and well-written manuscript about relevance between frailty in geriatric patients and ACS. Therefore, this manuscript will be acceptable after response to my concerns.

Concerns

#1. Line 129 to 131 in the Results, the authors mentioned " Of those, 9 were excluded after more detailed inspection of full texts. We finally identified 15 publications, including 8554 patients.". However, the authors need to show how to exclude 9 publications. What is detailed inspection? This is very important procedure. You excluded 9 publications despite after critique. Please explain how you exclude 9 publications.
Response: Thanks for the reviewer’s important comment. The detailed exclusion reasons were shown in Figure 1. Two descriptive studies were excluded because of improper study design. One study only reported quality of life outcomes and did not report mortality results. Three studies evaluated gait speed or grip strength instead of frailty. Two studies reported cardiovascular mortality or composite outcome not all-cause mortality, which led the HR/OR for all-cause mortality cannot be calculated. One study included non-elderly patients under 65 years.

#2. Table 1 displays the selected 15 publications. All clinical studies were performed after 2011. I think that you finally selected comparatively-new clinical studies. Is there any comment about this in the discussion? Because around 2005, the drug eluting stent, which is one of PCI therapy, showed up in the clinical area, and then PCI therapy was drastically progressive. Dual Antiplatelet Therapy (DAPT) that is the representative 2nd prevention of PCI was published in 1998.

Response: Thanks for the reviewer’s important comment reviewing crucial advances in coronary heart disease. The success in cardiovascular prevention has reduced the incidence of acute coronary syndromes (ACS) and has postponed the onset age of ACS. The progresses in the treatment of ACS (dual antithrombotic therapy and invasive strategy, e.g. the drug eluting stent) are significantly decreased the risk of ACS mortality and lead to a rapid increase in the proportion of old or very old patients. With the fast population ageing, the mean age of patients presenting with ACS increase steadily. For non-elderly patients, modern health-care systems are mostly organized around single-system illnesses. However, the elderly population with multiorgan problems is a heterogeneous group showing important divergences between chronological and biological age, which needs specific evaluation. Till recent years, with the development of geriatrics, the concept of frailty has gained popularity to explain, at least in part, the difference between chronological and biological age. Frailty is a practical, unifying notion in elderly patients that directs attention away from organ-specific diagnoses towards a more holistic viewpoint of the patient and their predicament. It is a reflection of biological rather than chronological age that shows up in stressful situations and, consequently, it may contribute to the heterogeneity in clinical outcomes within the elderly patient population. Distinction of frail elderly people from those who are not frail should therefore be an essential part of assessment in evaluation of a number of specific medical conditions, such as evaluation of surgical risk and cancer treatment. As a matter of fact, according to our literature search, the study by Ekerstad in 2011 was the first research to investigate the influence of frailty on ACS prognosis. Thereafter, several studies have associated higher mortality or adverse outcomes associated with frailty in elderly ACS patients with certain inconsistent data. This is the reason why we undertook a meta-analysis to investigate the influence of frailty on ACS prognosis. Our findings demonstrated that frailty significantly increases the risk of all-cause mortality by 2.65-fold, any-type CVD risk by 1.54-fold, major bleeding by 1.51-fold and hospital readmissions 1.51-fold in elderly ACS patients. By bringing quantitative evidence that frailty is critical for elderly ACS prognosis and analyzing possible adjustments of treatments, it allows practitioners to weigh up benefits and risks, help them to applicate appropriate management strategies and for patients to make properly informed choices.
Tong Liu (Reviewer 3): This present meta-analysis reports frailty constitutes addressable and significant prognostic value for adverse events in elderly patients after ACS. This review is well written and clearly presented.

Major comments:

1. Seven assessment tools of frailty are mentioned in the manuscript (line 144-154), how do these assessment methods evaluate the "prefrailty" in the subgroup analysis?

Response: Thank you for your interesting question. Frailty is the main problem and hotspot in geriatrics. However, regrettably, till now there is no gold standard for the frailty evaluation, which leads to some assessment methods lack "prefrailty" evaluation. Frailty can be evaluated in different ways, including self-perceived symptoms e.g. fatigue, appetite and objective tests, such as grip strength, walking speed and chair rise time. There are four assessment tools of pre-frailty in our manuscript. The EFS assesses cognitive impairment, dependence for activities of daily living, burden of illness, self-perceived health, depression, weight loss, medication issues, incontinence, social support, and mobility (using the timed “get up and go” test). Scores range from 0 (not frail) to a maximum of 17 (very frail). EFS > 7 is defined as frailty and EFS 4-6 is defined prefrailty. The Fried criteria address five domains of the frailty phenotype: (a) shrinking (weight loss of ≥10 pounds in the prior year); (b) weakness (decreased or weakened grip strength); (c) exhaustion (fatigue or declining endurance); (d) slowness (slower walking pace); and (e) low activity (decline in physical activity). It is examined according to frailty score with the following pre-specified groups: not frail (0 items); pre-frail (1–2 items); and frail (≥3 items). The SHARE-FI index is based on a standardized questionnaire addressing self-perceived fatigue, appetite, lack of energy or slowness, physical activity and handgrip strength measurement. The SHARE-FI score results in a continuous measure, and accordingly to its value, patients were classified into three groups: “frail,” “pre-frail,” and “non-frail.” FRAIL scale is a simple, interview-based tool that evaluates 5 items (fatigue, resistance, ambulation, concomitant diseases, and weight loss). Prefrailty is defined as the presence of 1 or 2 criteria, and frailty as the presence of 3 or more criteria.

Despite the difference in evaluation of frailty or pre-frailty, we found pre-frailty already significantly increased the risk of mortality before or after adjustment than robust group. Moreover, the incidence of the mortality between frailty and pre-frailty showed statistical significance before or after adjustment, indicating the group of frailty showed higher mortality than pre-frailty group. Frailty is dynamic and its earlier stages are potentially reversible. Therefore, early non-pharmacological intervention for prefrail patients also makes sense.

2. Please check the references in the paper, In literature search and study characteristics, the studies with Ref.'20,21'were not described in this section.

Response: Thank you for reviewer’s careful work. We made the corresponding change in the article.

3. Spelling mistake in line 117, "on-ST-segment' should be 'non-ST-segment".
Response: Thank you for reviewer’s careful work. We made the corresponding change in the article.

4. Line 223 and 231 shows "test for interaction: P < 0.05" which is inconsistent with the result description and "Statistical analysis" (line 122).

Response: Thank you for reviewer’s careful work. We made the corresponding changes in the article.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for editor and reviewer’s strict and careful work earnestly, and hope that the correction will meet with approval.

Once again thank you very much for your comments and suggestions.

Best regards!

Yours sincerely

Qingyu Dou