

Current Updates in Aging

Review Report

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Article Title: Management and Evaluation of the Pain in the Elderly Patients with Chronic Critical Illness: A Systematic Review

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Review Status: Revision Required

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Review Report

I have read with interest the article by Grazia D' Onofrio and colleagues. Following are my concerns:

1. Divide the abstract into: a) Introduction, b) Methods, c) Results, d) Conclusions.
2. Improve the English in the manuscript.
3. Please introduce a clear definition of "elderly patient".
4. Please insert a number for each references, as you named it in the body of the manuscript. Number of references is not present.
5. Introduce a paragraph describing "statistical methods".
6. In my opinion less has been reported about pathogenetic mechanisms implied in "aging" in your manuscript. The aging by molecular pro-apoptotic processes (Balestrieri ML, Rizzo MR, Barbieri M, Paolisso P, D'Onofrio N, Giovane A, Siniscalchi M, Minicucci F, Sardu C, D'Andrea D, Mauro C, Ferraraccio F, Servillo L, Chirico F, Caiazza P, Paolisso G, Marfella R. Sirtuin 6 expression and inflammatory activity in diabetic atherosclerotic plaques: effects of incretin treatment. *Diabetes*. 2015 Apr;64(4):1395-406), may affect the prognosis and disease progression in atherosclerotic plaque, conditioning as you introduced in the text, an unstable hemodynamic status in elderly patients. Please explain this point, reporting the sentence and the reference in the manuscript.
7. Similarly to pro-apoptotic processes, the loss of regenerative and reparative processes, as induced by endothelial progenitor cells (Marfella R, Rizzo MR, Siniscalchi M, Paolisso P, Barbieri M, Sardu C, Savinelli A, Angelico N, Del Gaudio S, Esposito N, Rambaldi PF, D'Onofrio N, Mansi L, Mauro C, Paolisso G, Balestrieri ML. Peri-procedural tight glycemic control during early percutaneous coronary intervention up-regulates endothelial progenitor cell level and differentiation during acute ST-elevation myocardial infarction: effects on myocardial salvage. *Int J Cardiol*. 2013 Oct 9;168(4):3954-62), may condition the unstable hemodynamic status during an hyperglycemic condition. In this reference authors have clearly expressed this point. Please report your considerations about, and call this reference in the manuscript.
8. An hyperglycemic status may lead to alterations in sympathetic tone, leading to alterations in autonomic balance (Rizzo MR, Sasso FC, Marfella R, Siniscalchi M, Paolisso P, Carbonara O, Capoluongo MC,

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Lascar N, Pace C, Sardu C, Passavanti B, Barbieri M, Mauro C, Paolisso G. Autonomic dysfunction is associated with brief episodes of atrial fibrillation in type 2 diabetes. *J Diabetes Complications*. 2015 Jan-Feb;29(1):88-92). This may induce atrial fibrillation, that may affect the prognosis in elderly patients. Please discuss this point, and introduce the reference in the manuscript.

9. You did not report data about the failing heart disease impact in your study population. In elderly, heart failure (HF) is growing disease impacting on the prognosis (Sardu C, Marfella R, Santulli G. Impact of diabetes mellitus on the clinical response to cardiac resynchronization therapy in elderly people. *J Cardiovasc Transl Res*. 2014 Apr;7(3):362-8). This point has to be discussed in your manuscript.
10. A part of this, you did not report the impact of telemonitoring systems in elderly. In last decades, telemedicine showed a great impact in chronic disease (Sardu C, Santamaria M, Rizzo MR, Barbieri M, di Marino M, Paolisso G, Santulli G, Marfella R. Telemonitoring in heart failure patients treated by cardiac resynchronisation therapy with defibrillator (CRT-D): the TELECARD Study. *Int J Clin Pract*. 2016 Jul;70(7):569-76). In my opinion I think that you may apply this concept to your study, as suggested by authors.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.