

Round 1

Dear Editor,

we are grateful for the opportunity to resubmit the revised manuscript entitled “**Frailty, sarcopenia and cachexia in heart failure patients: different clinical entities of the same painting**” following the reviewers’ comments. We appreciate the interest that the editor and the reviewers have taken in our manuscript and the constructive observations provided. Each of the issues raised has been carefully addressed. We believe the manuscript has significantly improved in the process. The paper was revised in consultation with all coauthors, and each author has given approval to its final form. We hope you will now find the study suitable for publication in your journal.

Reviewer 1: This review article suggests Frailty, sarcopenia and cachexia in heart failure patients: different clinical entities of the same painting. In general, this article bears significance and innovation. I recommend major revision for this article. The following comments are provided for the authors' consideration before accept. 1. For a better understanding of background and discussion, please cite the following literature in appropriate sites throughout the manuscript before accept. PMID:27815596, 31632964, 31737623 2. There are some spelling mistakes and format errors. 3. Can authors cite some clinical studies e.g. RCT or cohort studies for better elucidation?

Many thanks for you comments.

1) I put in the appropriate sites the references

2) I correct same spelling mistakes

*3) I add RCT trial in references: 30) **Rossignol P**, Masson S, Barlera S, Girerd N, Castelnovo A, Zannad F, Clemenza F, Tognoni G, Anand IS, Cohn JN, Anker SD, Tavazzi L, Latini R; GISSI-HF and Val-HeFT Investigators. Loss in body weight is an independent prognostic factor for mortality in chronic heart failure: insights from the GISSI-HF and Val-HeFT trials. *Eur J Heart Fail* 2015;**17**:424-33. [PMID: 25704364 DOI: 10.1002/ehf.240]*

*37) **Morley JE**, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, Cederholm T, Coats AJ, Cummings SR, Evans WJ, Fearon K, Ferrucci L, Fielding RA, Guralnik JM, Harris TB, Inui A, Kalantar-Zadeh K, Kirwan BA, Mantovani G, Muscaritoli M, Newman AB, Rossi-Fanelli F, Rosano GM, Roubenoff R, Schambelan M, Sokol GH, Storer TW, Vellas B, von Haehling S, Yeh*

SS, Anker SD; Society on Sarcopenia, Cachexia and Wasting Disorders Trialist Workshop Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc 2011;12:403-9. [PMID: 21640657 DOI: 10.1016/j.jamda.2011.04.014]

Reviewer 2, The present manuscript is a well-written mini-review covering clinically important aspects of cachexia, sarcopenia and frailty in patients with heart failure. All of the important consequences and associated conditions of this syndrome are described in an appropriate way for such an article type. This version of the manuscript has also been well adapted according to previous peer-reviews. I have only few minor objections. 1. It would be much easier to read the text if it is divided into appropriate paragraphs. Also, putting a number of commas throughout the text will make an additional improvement; the text could be rechecked by a native speaker. 2. The term “6-minute walk test” for the first time appears in the middle of page 6 (there is no page numbers!), but the abbreviation is provided 9 rows below. Moreover, it seems that there is no need for this abbreviation. In addition, all abbreviations must be checked up because it seems that many of them are not explained. Does HT mean heart transplantation? Why “Heart Transplantation” and “Literature” stands with capital letters? 3. The authors mentioned the role of testosterone as a possible therapeutic agent, but this hormone may play a role in the pathophysiology of this syndrome as well. In addition, growth hormone, ghrelin, thyroid hormone and insulin, may also play some role in this syndrome, so all those hormones should be briefly mentioned.

Really thanks for your comments

1) I divided in two distinct paragraphs; “BASIC PATHOPHYSIOLOGICAL OVERVIEW ” and “TERAPHEUTIC IMPLICATION” and I add some commas throughout the text as suggested. The text is revised by a native speaker

2) I use the The term “6-minute walk test” without abbreviation and I correct all the abbreviations and capital letters (i.e Heart Failure with reduced ejection fraction (HFrEF) and Heart Failure with preserved ejection fraction (HFpEF), heart transplantation (HT))

3)Many thanks for this point. I add in “BASIC PATHOPHYSIOLOGICAL OVERVIEW ” paragraph a brief description of hormones suggested in your comments.

“Higher levels of hormones and cytokines activities are both associated with muscle wasting, reduced fat tissue and bone mass. Few hormones are implicated in the pathophysiology in cachexia and sarcopenia. Growth hormone, insulin resistance and insulin-like growth factor-1 levels are all associated with muscle mass loss and consequently with a significant reduction of physical performance. Triiodothyronine in cachectic oncologic patients are increased compared to non-cachectic cancer patients and it is also normal in patients with benign weight loss. Ghrelin significantly inhibits the production of cytokines with inflammatory pathway and exhibits anti-cachectic activity both with growth hormone dependent and independent mechanisms. Low testosterone levels are usually common in all HF patients and contribute to the progression of cardiac cachexia, sarcopenia and frailty through altered peripheral vascular resistance, increased cardiac afterload, and decreased cardiac output.”

Round 2

Reviewer 1: For Review 1's comments: 1) I put in the appropriate sites the references. I failed to find one of them in the references. The authors shall be practical and realistic as they said.

Many thanks, i add in the text the references regarding the table 1 and figure 1. Onestly i didn' t understand the comments of reviewer 1, because as you can see in the manuscript the are the references (at the end of the manuscript from page 10) and put in the correct manner in the text.