Dear Editor:

We would like to thank Jouranl of Aging Pathobiology and Therapeutics for giving us the opportunity to revise our manuscript.

We thank the reviewers for their careful read and thouhtful comments on previous draft.We have resulted in a paper that is clearer,more compelling,and broader.The following summarizes how we responded to reviewer comments.

Below is our response to their comments.

Thanks for all the help.

Qiao-cong chen MD The first author

Revision-authors’ response

Reviewer B:
The authors have written an interesting review article on the association between osteoporosis and sarcopenia. Given below are my comments in no particular order.
1. Numerous spelling and punctuation errors abound (too many to even start highlighting).
Accoding to the referee’s suggestion,we have corrected the wrong words and sentence structure in red font detaleidly.

1. The title is misleading. The only recent advance topic that the authors actually describe is the genetic interaction and association between the two conditions. Make the title clear that it is focusing on the recent advances in genetics linking the two conditions.
In order to better describle this issue,we changed the title as “Recent advances in the genetic association between osteoporotic fracture and sarcopenia”.

3. References are poorly formatted. Eg see reference 13, author list is incorrect.

Using the Endnote X7 software,We have revised the references in NLM format,detailed in the references with red font.

4. Mix of reference styles has been used (AMA, vancouver, NLM - I can see all mixed)
Accoding to the referee’s suggestion,we have revised the references in NLM format,detailed in the references with red font.

5. The genes and loci that the authors describe, they do not describe well the clinical utility of how each could be targeted and how studies have reported this. A simple literature search reveals that some of the genes reported have already been targeted. Some discussion of therapeutic agents in the pipeline focusing on the genes and their products discussed would add value to the paper.

As suggested by the reviewer we have added the RANKL human monoconal antibody-denosumab for example to reveal the gene and their clinical utility.Detail in page 9,paragraph3 with red font.

6. Pointless abbreviations have been utilised. There is no value in shortening osteoporosis to OP and sarcopenia to SP since it makes the writing confusing to the reader. Writing should be clear.

Accoding to the referee’s suggestion,we have removed the abbreviations such as SP and OP.

7. Note that the studies showing association in patients of osteoporosis and sarcopenia have been there for quite some time. This is not a recent advance. The recent advance is the genetics of it. All of this should come under a section titled introduction.
Accoding to the referee’s suggestion,we have revised the title. We first discuss the clinical evidence and then the genetic evidence for interactive factors.This plays a link role between the preceding clinical evidence and the following genetic association between osteoporotic fracture and sarcopenia.

8. Introduction section should mention 1-2 lines about diagnostic criteria of both osteoporosis and sarcopenia. Since that itself is the exact definition. (T score and Z score).
Accoding to the referee’s suggestion,we have added the diagnostic criteria of osteoporosis and sarcopenia,respectively shown in line 38-41 of page1 and line 4-9of page 2.

9. Discuss whether a dose response curve exists with regards to degree of osteoporosis and sarcopenia. Eg is osteopenia less associated with sarcopenia and osteoporosis more?

The topic is interesting for our team,in our clinical studies have reported the prevalence of osteo-sarcopenia varied with diferent dignostic criteria of ostopenia,osteoporosis and sarcopenia in a small samples. Whether there are a dose response curve exists with regards to degree of osteoporosis and sarcopenia,we need more samples and prospective studies to confirm it.

**Reply to Reviewer C:**
The manuscript “Recent advances in the association between osteoporotic fracture and sarcopenia” by Chen et al provides a focus on how osteoporotic fractures in older people are at increased risk under conditions of sarcopenia. The authors first discuss the clinical evidence and then the genetic evidence for interactive factors. Although their arguments are based mainly on correlative data and not causal data, the manuscript is still quite informative and will be of interest to the geriatric community. However, there are areas of weakness that will need to be addressed as described in the following suggestions.
1. The manuscript has many typos, grammatical errors, and improper sentence structure. This reviewer has touched on a number of these as highlighted in yellow with suggested corrections in red font (see attached reformatted manuscript). This weakness will need to be addressed in detail.

Accoding to the referee’s suggestion,we have corrected the wrong words and sentence structure in red font detailedly.

2.  The addition of figures and tables would significantly enhance the strength and readibility of the manuscript. For example, in the first section an overview figure showing the general relationship between osteoporosis, fractures, and sarcopenia would be very helpful. Another example would be a figure on the Wnt signaling pathway as described in the text in the genetic section. Tables would be extremely helpful in providing an instant summary of the genes and gene variants discussed in the text. The more genes listed in the text the more need for a table.

To address the referee’s comment, we added talbe 1 with Published studies for the association between osteoporotic fractures and sarcopenia in page 4 and 5.Also,we added figure 1 for the role of WNT pathway in bone metabolism in page 8.

3. The summary section is quite weak. There should be some major projections on the types and strategy for not only treating but preventing the osteoporosis/sarcopenia/fracture triad. This does not have to be detailed but should describe some specific approaches that could be used in preclinical or clinical studies by targeting some of the genes described in the text. A figure would also be helpful. This is an opportunity to make some projections about the ability to extend healthy aging by enhancing mobility and decreasing the risk for fractures with increasing age.

Thanks to the referee’s comment, it is unclear on major projections on the types and strategy for not only treating but preventing the osteoporosis/sarcopenia/fracture triad in the summary section.we have revised the summary part,added RANKL-antibody as the genes reported have already been targeted to clinical drug treament and “CFDR-analysis may be a useful method in exploring the causal gene between osteoporotic fracuture and sarcopenia” as a example.we have used the cFDR method to identify the pleiotropic locion both bone and muscle including LPR5,FTO and PRRX1(unpublished data).The changes has been made on page 9,paragraph 2(line 16-20),3 and 4(line33-35).In the future,our team will do some replication and funcation experiments to verify the role of the gene in bone and mucsle metabolism.