Response to reviewer comments

Reviewer 1

The authors reviewed articles regarding cardiac amyloidosis focusing on imaging techniques. Wide-ranging issues, not only cardiac imaging but also epidemiology, clinical features, diagnosis, and treatment, are comprehensively covered. This is an interesting review article elucidating current progress in cardiac imaging for the diagnosis of systemic amyloidosis. It is timely to take topics of amyloidosis, particularly light chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis, because novel therapeutic options for these diseases, such as chemotherapy, TTR stabilizers, small interfering RNA, and antisense oligonucleotide, now appear one after another. The manuscript is well written, and I enjoyed reading it. I believe many physicians will be attracted to this article.

- We thank the reviewer's positive comments.

Although I do not have any critical comments, minor issues to strengthen this manuscript are raised as follows:

1. ATTR amyloidosis consists of hereditary ATTR (ATTRv) amyloidosis and wild-type ATTR (ATTRwt) amyloidosis (Biomedicines 2019; 7: E11). This issue should be clarified in the introduction section from the viewpoint of terminology, citing this article. In addition, patients with ATTRv amyloidosis tend to manifest cardiomyopathy, somatic neuropathy, and autonomic dysfunctions, while those with ATTRwt amyloidosis are characterized by cardiomyopathy and carpal tunnel syndrome (Biomedicines 2019; 7: E11). As this issue is important to understand clinical spectrum of ATTR amyloidosis, it should be mentioned in the "Presentation" section.

- We have added these terminologies ATTRv and ATTRwt to the introduction and clinical presentation sections for clarity, and referenced this article as suggested.

2. As for ATTRv amyloidosis, early-onset cases from conventional endemic foci in Portugal and Japan tend to have cardiac conduction disturbances leading to the necessity of pacemaker implantation, while late-onset cases from non-endemic areas usually manifest diastolic dysfunctions due to massive amyloid deposition (Arch Neurol 2002; 59: 1771-6). Pathological examinations revealed subendocardial amyloid deposition resulting in atrophy and degeneration of cardiomyocytes in conventional early-onset cases, whereas diffuse amyloid deposition throughout layers of myocardium unaccompanied by cardiomyocyte degeneration in late-onset cases, corresponding to the difference of clinical features (Neurology 2004; 63: 129-38). These issues should be incorporated citing relevant articles because they are important to understand the mechanisms of cardiac amyloidosis.

- We have added these descriptions into the presentation section, citing the reference as suggested.

3. Previous studies of ATTR amyloidosis indicate the presence of two types of amyloid fibrils from the viewpoint of morphology (i.e., short amyloid fibrils in late-onset patients and long amyloid fibrils in early-onset patients) (J Pathol 2005; 206: 224-32; J Neurol Sci 2009; 287: 178-84). A 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy may discriminate these two types of amyloid deposits (PLoS One 2019; 14: e0211983). I would recommend incorporating this issue by citing these studies.

- We have added these descriptions to the presentation and nuclear sections respectively, citing the references as suggested.

Reviewer 2
It was a pleasure to review the article on multimodality imaging of cardiac amyloidosis.

- We thank the reviewer for the positive comments.

I have a few minor/major revision comments.

1. Presentation section: Reduced EF or impaired systolic function is also a common presentation and not mentioned at all.

- This has been added to the presentation section.

2. Differential diagnoses: DCM should also be included.

- This information has been included.

3. Non imaging investigations: Other possible blood tests and biopsy from other sites need to be mentioned.

- This section has been updated. Blood test results have been included in the non-imaging investigations. We have further added biopsy from other sites into this section.

4. Cardiovascular magnetic resonance: Did you mean TI (inversion time scout) with the following phrases "Standard T1 scout and T2 imaging should also be performed." "and T1 inversion scout is helpful to time delayed imaging". Please check nomenclature especially in the CMR section. CMR section "of distribution is often subendocardial (especially for AL subtype) or transmural (especially for ATTR subtype or advanced disease affecting both ventricles)(34)." Please give image examples of these patterns, not very clear in this form for the reader.

- Thank you for the comment. We have altered the wording as suggested to TI inversion time scout should be performed and removed T2. We have updated the CMR section and nomenclature.

5. Nuclear medicine section is much more detailed than the others and also explains the methodology which was not done for echo and CMR-not good for consistency. Examples for this are matrix size etc. For example you don't mention the gadolinium dose for CMR but give tracer dose for nuclear. Frame rate for echo can be another example that was not included. Please either include those for all modalities or mention in title and introduction that work focuses specifically on nuclear medicine.

- We have updated the sections appropriately. We have added a comment for frame rate for echocardiography. We did explain the methodologies for CMR imaging (two-dimensional, Doppler and speckle-tracking for echocardiography, SSFP, late gadolinium enhancement, T1 and T2 imaging protocols) used for imaging cardiac amyloidosis. A greater emphasis and focus have been given to the nuclear medicine imaging section.

6. Table 4 "diffuse LGE" is a very vague description. Please amend.

- We have changed the statement to include difficulty in nulling the myocardium from diffuse amyloid infiltration. Diffuse, subendocardial or patchy LGE patterns may be observed.

7. Figure 3. LGE image on left upper panel not typical and diagnostic for amyloid, parametric T1 maps should be in color with DICOM LUT chosen on CVI42 software. I think map analysis section of software may be more demonstrative.

- The selected illustrative case example came from a real patient with TTR cardiac amyloidosis from our center. It demonstrates a diffusely abnormal global pattern of transmural delayed enhancement in the myocardium. It is known from published literature that the classic global subendocardial pattern of delayed enhancement is observed more frequently in AL amyloidosis (JACC: CARDIOVASCULAR IMAGING, VOL. 7, NO. 2, 2014). A T1 map in color has been provided.

Reviewer 3
In this manuscript, the authors aimed to discuss the clinical utility of multi-modality cardiac imaging in the contemporary evaluation and management of cardiac amyloidosis. They discussed echocardiography, cardiac magnetic resonance imaging and nuclear imaging in the non-invasive diagnosis and evaluation of cardiac amyloidosis.

My comments are as follows:
1) It was an up-to-date and highly scientific review article.
- We thank the reviewer for the positive comment.

2) Noncompaction of the left ventricular myocardium and Loeffler endocarditis should be present among the differential diagnosis. In this respect, articles of Gulel et al (Korean Circ J. 2018;48(7):655–657. doi:10.4070/kcj.2017.0348) and Celebi et al

(Int J Cardiol. 2008;128(1):e22–e24. doi:10.1016/j.ijcard.2007.04.160) should be mentioned in the text.

- We have added updated the differential diagnoses section, citing the references.

3) References should be rewritten according to the Journal's style.

- We have amended the reference style to fit the journal’s format.