**Author’s response to reviews**

**Title:** Coexistence of Aortic Valve Stenosis and Cardiac Amyloidosis: Echocardiographic and Clinical Significance

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**Author’s response to reviews:**

Response to reviewers

Dear Reviewers,

Thank you for the careful, and also helpful review of the manuscript.

Our detailed answers to the reviewers:

Reviewer 1:

1. Authors underline the fact that one of the key aims of the study was to establish the prevalence of AS in the group of the consecutive, unselected CA patients. However when taking into consideration the prevalence of AL and wTTR CA in a study group which does not reflect a prevalence in a general population and the specific character of the Centre in which the study was conducted (significant percentage of hematologic patients)
it is doubtful whether the study population can be actually described as consisting of the 'unselected patients'. On the other hand, the significant number of AL patients enrolled into the study should be considered as an advantage, differentiating it from the previous publications. The manuscript could benefit from the inclusion of the separate characteristic of AL patients.

This topic really can be a subject of discussion. First: We totally agree with the opinion of the reviewer that the significant number of AL patients in this study should be considered as an advantage. In the discussion part we introduce in detail the prior studies, performed in the clinical field of CA an AS, where TTR was the most common, or in some cases the only form of CA.

In our study we looked for AS among “consecutive” CA patients. As it is mentioned in the manuscript, our department has a haematology ward, but also a cardiology one. Patients with suspicion of CA are sent to our hospital from the whole country, and we have the greatest experience with CA in the country. Therefore the high ratio of AL patients is not necessarily a consequence of the presence of the haematology ward, but could also mirror the real prevalence of different CA subtypes. Authors from the National Amyloid Center, London, UK published their experiences in Lancet, 2016, with 5100 patients with systemic amyloidosis. Among systemic amyloid pts, between 2009 and 2012 they found, that AL was presented in 67%, wtTTR was 6.4%, mTTR was around 3.2%. Other forms gave the remaining part, but those ones almost never effect the heart. Therefore our findings regarding the distribution of the different cardiac subtypes, are close to those results.

Unfortunately, we don’t know the prevalence of the different subtypes in Hungary, but wtTTR is probably less frequent than in Western Europe, because the expected life expectancy and the ratio of very elderly people is significantly lower, and wtTTR is a disease of the elderly.

In conclusion, we don’t know right now, whether our “consecutive” patients represent an “unselected” CA population in Hungary or not, but probably it is close to it.

In the manuscript we tried to describe precisely the environment in which the study was conducted, and also the method of patient selection.

Minor comments:

1. Table 1 description is misleading; the percentage values are lacking; spelling mistake (NYHA) should be corrected.

The misleading title of table 1 was changed, cardiac biomarkers and echocardiographic parameters were incorporated to the title. Percentage values were calculated and put into the table. The spelling mistake was corrected.

2. Page 7 line 14: the word „table" should be removed
Finally, hemicolecction was performed without any major complication. The cardiac images of this patient are shown in figure 1.

1. There were no mentions about statistical analysis authors used in the methods section. Here by, I would like to suggest authors to describe details on statistics in the method section.

We summarized the used statistical analyses at the end of the methods section:

Since most of the variables exhibited skewed distributions, the descriptive statistics are presented as medians with interquartile ranges (IQR), or as percentages. The strength of the associations was calculated with the nonparametric Mann-Whitney test or the chi-square test, as appropriate.

2. I believe that there might be a technical problem..., there is no image related to the Figure 1 legend. Please check again and present it again.

We are sorry, that you could not see that figure, it must be a technical problem. The homepage of the journal generated a PDF file after the submission, which was send to us. This PDF file included the figure on the last page. We hope, that after resubmission there will be no technical problem.

3. Authors have presented a table showing the characteristics of patients with cardiac amyloidosis and aortic stenosis in table 2.

It would be better if authors provide further information on their clinical progress regarding medication they prescribed and clinical outcome including mortality, because authors have enrolled patients who diagnosed between 2009 and 2019.

Specific treatment of the AL pts for the plasma cell dyscrasia was driven by hematologists. In most of the cases, a combination of cyclophosmad-bortezomib and corticosteroid was introduced, but the whole spectrum of multiple myeloma medication was used, including lenalidomid, thalidomide, daratumumab and melphalan. Doxycylin was used in the last 4 to 5 years. Due to the very severe performance status two AL patients had no specific treatment and died within days after the diagnosis. Two patients had autologous bone marrow transplantation.

wtTTR pts did not receive any specific treatment. Four out of the six mTTR patients received 20 mg tafamidis, daily. The other two pts with TTR mutation had no perceptible neuropathy, therefore tafamidis therapy was not indicated. Generally, our CA patients had no ICD, and none of these 55 patients had heart transplantation.

Table 1 shows, that the vast majority of them had severe HF at the time of the diagnosis. Calculation of mortality rate is not simple, because the follow up period is no more than nine month in the cases of the latest included patients. So median survival cannot be calculated. We can calculate the median follow up time interval and the total mortality, which was 399.5 days.
(110.5-834.5) and 37/55 (67%). We think, the most correct way to describe mortality is to describe the nine month mortality rate, which was 23/55 (42%) for the whole CA patient population.

The most important elements of the above mentioned and detailed information was added to the original manuscript, in the Results section:

Here we summarize the most important therapeutic and mortality data of this patient population: Specific treatment of the AL patients for the plasma cell dyscrasia was driven by hematologists. In most of the cases, a combination of cyclophosphamide-bortezomib and corticosteroid was introduced first, but the whole spectrum of multiple myeloma medication was used, including lenalidomide, thalidomide, daratumumab and melphalan. Doxycyclin was used in the last 4 to 5 years. Two patients had autologous bone marrow transplantation.

wtTTR patients did not receive any specific treatment. Four out of the six mTTR patients received 20 mg tafamidis, daily. Generally, our CA patients had no ICD, and none of these 55 patients had heart transplantation.

Calculation of mortality rate is not simple, because the follow up period is no more than nine month in the cases of the latest included patients. We think, the most correct way to describe mortality in this case, is to describe the nine month mortality, which was 23/55 (42%) for the whole CA patient population.

Best regards,

Zoltan Pozsonyi