Reviewer's report

Title: ACTN3 R577X polymorphism and long-term survival in patients with chronic heart failure

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Reviewer: Kátia G. Santos

Reviewer's report:

The article is original, well-written and concise. The methodology used to address the research question is appropriate and there are few typo errors that can be easily corrected. However, some useful information is missing. I have some comments and suggestions that could improve the manuscript.

Discretionary Revisions

1) As the ACTN3 R577X polymorphism was not previously investigated in heart failure, additional information about it would be interesting, such as the chromosomal location and change at the DNA level (i.e. C/T).

Minor Essential Revisions

2) The authors refer to the 577X allele as it would be the polymorphism itself (Abstract section, third paragraph and Results section, second paragraph). The sentence “The frequency of the ACTN3 R577X variant allele was 39.0%” does not state which allele is the variant. By the context, one can infer that the X allele is the variant, but this is not always the case. Patients do not carry polymorphisms. Polymorphism is a genetic concept applied to the population. The population has or does not have certain polymorphisms. Subjects carry alleles, genotypes or haplotypes. Generic sentences as “R577X polymorphism in the ACTN3 gene was independently associated with worse survival in patients with chronic heart failure” (Abstract section, last paragraph) are acceptable in the title and conclusion, but some specification is necessary in the text. Only in the third paragraph of the Discussion section it is specified that the R allele is the wild-type allele.

3) Authors state in the Abstract section (third paragraph) and in the Results section (first paragraph) that “after mean follow-up of five years, 239 (51.6%) patients met the pre-defined study endpoint”. However, the survival curves (Figure 1) end shortly after the 60th month. So, it seems that 60 months do not correspond to the mean.

4) The last sentence of the last paragraph of the Abstract section states that “Further studies are necessary to ensure its use as a marker of risk for this syndrome”. As the susceptibility to the heart failure was not addressed in the manuscript, I think that the word “prognosis” would be more appropriate rather than “risk”.
5) Some reference is missing in the first paragraph of the Background section.

6) The association of the R577X polymorphism with all-cause death was evaluated by Cox proportional hazard model adjusting for age, gender, body mass index, ethnicity, LVEF, etiology, hemoglobin, and creatinine. Question: what were the criteria to include these covariates in the multivariate analysis? Were they chosen based on the univariate analysis or were they chosen based on their clinical relevance?

7) How many deaths occurred in both groups of patients (RR and RX + XX)? This information could be included in the Table 1.

8) Question: Why the chagasic etiology entered the Cox regression model (Table 2) as the reference category? Was it because it has the worst prognosis?

9) Typo errors: ‘carries’ instead of ‘carriers’ in Discussion section, fifth paragraph, ‘R577R’ instead of ‘R577X’ in Conclusion section, first paragraph, ‘Kg’ instead of ‘kg’ in Table 1, and ‘Chagastic’ instead of ‘Chagasic’ in Table 2.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.