**Author’s response to reviews**

**Title:** Predictors of one-year outcomes in chronic heart failure: the portrait of a middle income country

**Authors:**

Luciana Gioli-Pereira (lu_gioli@yahoo.com)

Fabiana Marcondes-Braga (fgmarcondes@gmail.com)

Sabrina Bernardez-Pereira (bernardezsabrina@gmail.com)

Fernando Bacal (fbacal@uol.com.br)

Fábio Fernandes (fabio.fernandes@incor.usp.br)

Alfredo Mansur (ajmansur@incor.usp.br)

Alexandre Pereira (alexandre.pereira@incor.usp.br)

José Krieger (jose.krieger@incor.usp.br)

**Version:** 1  **Date:** 01 Sep 2019

**Author’s response to reviews:**

Reviewer reports:

Peter Bramlage, MD (Reviewer 1):

1) It is likely not representative for the Brazilian population and no particular emphasis has been made to provide evidence for representativeness. As such the event rates need to be perceived with caution.

Answer: Indeed, we agree with the lack of representativeness of the population. This limitation is presented in the revised discussion section.

2) Patients were enrolled at different time point within 2 years after the diagnosis of lowEF defined as being < 50%. This may introduce bias into the event rates as rates be different during early compared to late FU.

Answer: This is an important point raised by the reviewer. Indeed event rates in heart failure have been shown to differ regarding not only the follow-up time, but also the moment of enrollment (hospital admission versus outpatient setting, for instance). Here we provide only one-year events incidence. We will work with longer FU incidence rates as well as the different predictive value of variables for different FU times in future work.
3) Variables selected for the association studies are not complete by far and the authors should make transparent what they have and which variables were selected for the analysis and why.

Answer: Variables considered potential predictors of worse prognosis in heart failure were tested in an univariate analysis (age, gender, ejection fraction, hemoglobin, sodium, blood urea nitrogen, BNP, systolic blood pressure, high sensitive troponin). Variables which analysis resulted in \( p < 0.04 \) were included in a multivariate analysis (ejection fraction, blood urea nitrogen, BNP, systolic blood pressure, high sensitive troponin).

This information were included in revised table 2.

4) Event rates are variables associated with events are not discussed in a broader context in an attempt to elucidate the critical variables for a Brazilian HF population.

Answer: Studies in chronic heart failure are scarce in the Brazilian population. Thus, it is not known for certain critical variables in our population, except in acute patients as in the BREATHE Registry (Brazilian Registry of Heart Failure - Clinical Aspects, Care Quality and Hospitalization Outcomes. Arq Bras Cardiol. 2015 Jun; 104(6):433-42). We have added this into the revised discussion section.

Flavia Balloca (Reviewer 2):

Question: “only 700 patients have been enrolled of more than 2000 screened; could the authors provide some details about the reasons for the exclusion? And how did you managed the data of the 67 patients that had only the first telephone contact?”

Answer: In fact, we obtained an expressive number of eligible patients, that for various reasons could not be included.

More specifically, the reasons were described below and in the revised flowchart legend:

- Ejection fraction \( \geq 50\% \) or echocardiogram with a date exceeding 2 years of acquisition (316);

- Patients without echocardiogram at the time of the invitation (clinical diagnosis of HF only) (587);

- Age \( \geq 80\) years at the time of inclusion (84);

- Patient without telephone contact for recruitment (334);

- Refusal of the eligible patient or responsible person to participate (230);

- Death before the invitation for inclusion (63).

Regarding the 67 patients that had only the first telephone contact, we consider the events occurred in this period of follow up.

We have added this information in the revised Methods section.
Question: “a significant number of patients had a chagasic etiology: even though the results regarding heart failure etiologies is beyond the purpose of this article, it would be useful to add some data on this form of heart failure, as long as it is peculiar of the Brazilian population and differs in its clinical course and prognosis from other forms of HF;”

Answer: Chagas disease is an important etiology of HF mainly in South America. Recently, Nadruz et cols evaluated the population attributable risk (PAR) of Chagas cardiomyopathy for 2-year mortality among patients with HF enrolled at years 2002-2004 (era 1) and 2012-2014 (era 2). The era 2 population is part of our cohort and the results found were that although the absolute death rates decreased over time in the Chagas cardiomyopathy and non-Chagas cardiomyopathies groups, the PAR of Chagas cardiomyopathy for mortality increased among patients with HF. Therefore, the current knowledge indicate that of all etiologies, Chagasic HF has the worst prognosis. Heart. 2018 Sep;104(18):1522-1528.
We have added this comment into the revised discussion section.

Question: “ is the table reporting drug therapy comprehensive of all medications taken by the patients? Because no antiplatelet therapy is reported, while more than 20% of the patients have ischemic disease;”

Answer: In fact, patients make use of a series of medications, among them, many times, antiplatelet drugs. In the manuscript we have chosen to highlight the medications for HF treatment.

Question: “ were all variables studied tested in the univariate analysis?”

Answer: Yes, we have conducted both univariate and multivariate analysis for all selected covariates. This information is better explained in revised Table 2.

Question: “no data on previous history- like previous admission for heart failure - or other relevant comorbidities - like lung disease - (except for renal failure) are reported, while these variables may play a role in survival, as demonstrated by some publications like Dokainish "Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study”

Answer: We have collected data about previous heart failure admissions as well as other relevant comorbidities including lung diseases, cancer, thyroid diseases and others.
We have added these information in the revised table 1.

Umberto Barbero (Reviewer 3):
Question: “Page 4 line 16: change "mortality predictor's" to "mortality predictors" (no need of 's)"
Answer: The requested correction was performed.

Question: “Regarding heart failure etiology distribution, we observed a predominance of hypertensive (26.0%), ischemic (21.9%) and chagasic (17.0%) forms of cardiomyopathy. Chagas disease is still a major concern and given the particularly high number of patients with
this disease in Brazil otherwise rare in normal trial on HF, I suggest that a sub-analysis on this group should be added to the paper.”

Answer: We agree with these data are very interesting and should be better explored. In the first version of this manuscript, we included data on etiologies, but we were advised to analyze these data in another report. Thus, we chose not to highlight any association with specific etiologies. A new manuscript describing differences regarding the etiologies will be prepared.

Question: “previous CABG and previous PCI should be added in table 1.”

Answer: The information requested had been added in revised table 1.

Question: “How may patients were GUCH? And how many were HIV infected?”

Answer: There were not GUCH in our cohort. The information about HIV patients were added in the revised table 1.

Question: “in Table 1 in the drugs section is reported ACE-i and "ACE-i or ARB": it should be corrected with patients allocated to one or the other category.”

Answer: The requested correction was performed.

Question: “The authors enrolled only patients with reduced EF: why HFpEF patients were not included? This fact should be explained in methods and added in the limits. Furthermore, given the actual interest in HFmrEF characterization I suggest to repeat multivariate analysis in both subgroup of HFmrEF and HFrEF if possible.”

Answer: This study was specifically designed to study predictors of clinical deterioration in patients with reduced systolic fraction. We have added a comment of this limitation in the respective section.

Question: “Most of the included individuals were in NYHA class I/II (81%) at enrollment. As the authors recognize this is due to the clinic status of the majority of them but it should also be added in limits since the predictor they found represent reliable predictor in style CHF patients.”

Answer: This is correct. Our results should be understood in the context of a stable-outpatient heart failure population. We have added this in the discussion section.

Question: “The SEATTLE heart failure model is cited but the numbers resulting from its application on the study population is not reported in any table.”

Answer: We actually chose to discuss the SEATTLE model and not apply it in our population. The reasons are related to the need for recalibration of the score for application in different populations as cited by the authors.

Question: “Limits section should be separated from discussion.”
Answer: The requested correction was performed.

Question: “Reference 12 refers to 2012 ESC Guidelines on HF but the newest ESC guidelines about this topic are the ones released in 2016. This reference should be updated.”

Answer: The requested correction was performed.