Author's response to reviews

Title: Plasma NT pro-BNP, hs-CRP and big-ET levels at admission as prognostic markers of survival in hospitalized patients with dilated cardiomyopathy: a single-center cohort study

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Version: 4 Date: 28 April 2014

Author's response to reviews: see over
Dear Editors and Reviewers,

Thank you for your letter and comments concerning our manuscript titled, “Plasma NT pro-BNP, hs-CRP and big-ET levels at admission as prognostic markers of survival in patients with dilated cardiomyopathy.” (Ms. 2015117270120605). We are pleased to answer the reviewers’ questions, and we have revised our manuscript according to their suggestions. The revised portions are marked in red in this updated version. Our point-by-point responses to the concerns are provided below.

Sincerely,

Wei Hua

April 6, 2014
Reviewer's report
Title: Plasma NT pro-BNP, hs-CRP and big-ET levels at admission as prognostic markers of survival in patients with dilated cardiomyopathy
Version: 3
Date: 20 February 2014
Reviewer: Nicole Ebner

Reviewer's report:
Li et al. analyzed predictors of mortality in patients with dilated cardiomyopathy (DCM). They followed 622 patients over a mean of 2.6 years and showed that NT-pro BNP and hs CRP are independently predictive for mortality with a cutoff point of NT-proBNP<2247 pmol/L and hs CRP <3.90 mg/L. This manuscript is very interesting and NT proBNP seems to be a strong predictor of adverse outcomes in patients with DCM.

Discretionary Revisions:
I was confused about such high cutoff value of NT-proBNP. In literature mostly a lower cutoff value of NT-proBNP were used. (Prastaro M et al. Eur J Echocardiogr 2011, 12(7):506-13. doi: 10.1093/ejechocard/jer070) used a NT-pro-BNP cut-off of 1480 pg/mL (174.64 pmol/L) to identified LA dysfunction. Also from literatureTigen K et al. (Heart Lung Circ. 2007;16(4):290-4) showed that the event free survival was found to be significantly lower in patients with NT proBNP levels >4500 pg/ml (>531 pmol/L). The ESC Heart Failure guidelines postulated a NT-pro BNP value of 300 pg/ml (35.4 pmol/L) which is much lower than the cutoff point that was used in this manuscript. Mahadavan G et al. recently (Curr Opin Cardiol. 2014, 29(2):160-6. doi: 10.1097/HCO.0000000000000036) stated that Interleukin 1-beta is also useful for risk stratification. May be it is additionally useful to measure IL-1ß in these patients.

Response: We have used a median for describing the NT pro-BNP in Table 1 because the values were not normally distributed, and the median was much smaller than the mean; however, the cutoff for NT pro-BNP did not change. There was variability in the
values of BNP and NT pro-BNP in various studies, and the values in the present study were much higher than those in most chronic heart failure studies; however, a few studies also found the difference, such as a study that found that the plasma N-BNP levels were significantly higher for infants with heart failure (median: 18452 pg/mL; range: 5375-99700 pg/mL) compared to infants with lung disease (median: 311 pg/mL; range: 76-1341 pg/mL) (Cohen S, Springer C, Avital A, Perles Z, Rein AJ, Argaman Z, Nir A. Amino-terminal pro-brain-type natriuretic peptide: heart or lung disease in pediatric respiratory distress? Pediatrics. 2005 May; 115(5):1347-50). The reason that our cutoff was larger than that in other studies may be because of the higher proportion of patients in NYHA classes III and IV and more seriously ill heart patients at admission in Chinese hospitals. I am sorry we did not determine the IL-1 beta levels in the present study.

Minor Essential Revisions:
Page 8: please change „1119 patients with DCM“ in 622 patients with DCM
Response: We have corrected the error in the revised manuscript (page 7, line 19)

Page 8 “For mortality, the optimal cutoff of 0.95 pmol/L...” please specify that this cutoff was for bigET.
Response: We have clarified this on page 7, line 21.

References are not all in the same style, for example some journals are kursiv and some not. The actual literature in the manuscript is from 2008. It would be helpful to update your references.
Response: We have corrected the references as you suggested.
Reviewer's report

Title: Plasma NT pro-BNP, hs-CRP and big-ET levels at admission as prognostic markers of survival in patients with dilated cardiomyopathy

Version: 3 Date: 7 March 2014

Reviewer: Otto Mayer

Reviewer's report:
The study represents prospective mortality cohort study in the setting of patients with dilated cardiomyopathy (DCM) with respect to concentration of some biomarkers (namely NTproBNP and hsCRP) at admission for hospitalisation for cardiac decompenzation. Despite abundance of studies with NTproBNP or CRP, the power of present analysis is relative large cohort of patients with less frequent disease.

I have following comments/points requiring revisions:

Abstract (and other section):

1. I cannot agree with the term „neurohormones“ (at least CRP is not a neurohormone and I have doubts about this classification also in NT-proBNP or bigET).

Response: We have corrected the terms in the revised manuscript.

2. It should be also emphasized, that patients were hospitalized for cardiac decompenzation (and not for other causes) – perhaps also in title.

Response: We have added the information on page 5, line 15, and in the title, we emphasized that patients were hospitalized.

Methods:

3. selection of subjects should be described more in detail (all DCM patients hospitalized during selection period were included or also those with follow-up data?).

Response: The hospitalized patients were all admitted between January 2005 and September 2011 and did not have a secondary cause of cardiomyopathy. We have added the information on page 5, lines 15-16.
4. I am also lacking the information in which extend was „an apparent secondary cause of cardiomyopathy” ascertained (by medical history only? excluding CHD etiology using coronary angiography? were patients with history of arterial hypertension excluded?).

**Response:** We have added the information on page 5, lines 17-23 and on page 6, line 1.

5. The timing of blood collection for biomarkers should be also clearly stated (in the course of admission blood collection? during first 24 hours?... ) , because of its possible rapid change during hospitalisation.

**Response:** Blood collection for determining the levels of the biomarkers was performed the day after admission, and we have added that information on page 6, line 8.

**Results & Tables:**

6. The cross sectional values of baseline characteristics in all sample should be stated (currently, only subgroups are mentioned on table 1).

**Response:** We have added the data in the revised Table 1 and Table 2.

7. What was the range (maximum) of hsCRP and was its elevation due to intercurrent inflammatory illness excluded?

**Response:** The range of hsCRP was 0.1-17.9 mg/L, with a median of 2.62 mg/L (1.34-7.67 mg/L); we did not exclude patients with potential inflammatory illnesses because without more detailed clinical investigations, it is not easy to determine which patients with heart failure have respiratory inflammatory illnesses and which patients do not.

8. I am lacking information about statin treatment proportion (which should be event. also added into regression model) and also about antidiabetics.

**Response:** A total of 23.4% of the patients were being administered statin treatment; in Table 1, just the six most common medicines are listed, and some medicines such as
statins were not included.

We did not analyze the data based on the usage of medicines in the Cox models, because the record data of medicines usage just at enrollment has a limited mean, and we have no data on the medicines usage for patients cover a long-term.

9. It should be also interesting to mention the rehospitalisations for heart failure (if these data are available)

Response: Unfortunately, we do not have any data regarding the re-hospitalizations.

Minor points:

Discussion: another studies with NTproBNP or CRP in the setting of DCM should be discussed (if any). Also potential clinical utility of results should be mentioned (BNP guided therapy?)

Response: As you suggested, the data have been added to the Discussion section on page 10, lines 16-21.
Reviewer’s report
Title: Plasma NT pro-BNP, hs-CRP and big-ET levels at admission as prognostic markers of survival in patients with dilated cardiomyopathy
Version: 3 Date: 4 March 2014
Reviewer: Frank Dini

Reviewer’s report:
In the study: “Plasma NT pro-BNP, hs-CRP and big-ET levels at admission as prognostic markers of survival in patients with dilated cardiomyopathy” Xiaoping Li and co-workers address the question whether the assessment of different peptides and cytokines were useful to risk stratify patients with HF secondary to dilated cardiomyopathy.
This is a well conducted and interesting study, but I have several concerns that the authors should address.

MAJOR CONCERNS
To this reviewer, it is not clear why the authors decided to determine circulating levels of NT pro-BNP, hs-CRP and big-ET at admission rather than at discharge. This should be considered a limitation, unless a specific reason could account for their decision.
Response: I have added this limitation to the limitation section in the revised manuscript.

The determination of cut off values for prognostic threshold levels of NT pro-BNP, hs-CRP and big-ET by ROC analysis should be described in the first paragraph of the results. This would facilitate the reader to understand the Kaplan-Meier results.
Response: Based on your suggestion, the paragraph describing the ROC analysis was made the first paragraph of the Results section in the revised manuscript.

Big-ET level was not an independent predictor of the outcome, therefore, I would not have spent very much space in the discussion, to describe its significance. In my opinion, the authors should focus especially on the value of combined
assessment of NT pro-BNP and hs-CRP to risk stratify patients with HF.

Response: I have deleted the sentences about the big-ET in the Discussion section in the revised manuscript.

MINOR CONCERNS
The quality of Survival figures are not satisfactory. Please improve them. Moreover, due to the limited number of patients remained, they should better be truncated at 60 months.

Response: I have revised Figure 1 as you suggested.

Pay attention to acronyms and abbreviations. Sometimes, heart failure is used instead of HF.

Response: I have revised the abbreviations in the revised manuscript as you suggested.