Reviewer's report

**Title:** Prognostic value of short-term follow-up BNP in hospitalized patients with heart failure

**Version:** 0  **Date:** 06 Mar 2017

**Reviewer:** T Mueller

**Reviewer's report:**

**GENERAL STATEMENT:**

This is a manuscript on a cohort of 240 patients admitted to hospital due to heart failure. BNP plasma concentrations were measured twice, first at admission to hospital and second within 90 days after admission to hospital. Outcome measure was all-cause mortality, and the median follow up time was approximately 700 days. The authors found that an increased concentration of BNP measured in the plasma samples drawn at admission was not of prognostic value. In contrast, an increased BNP concentration obtained within 90 days after admission to hospital were predictive for all-cause mortality, such as the BNP percent change between the first and second blood collection.

**SPECIFIC COMMENTS:**

(1) The results of this study are mainly confirmatory as it had been published previously that the predictive value of BNP concentrations measured in samples of patients with acute heart failure at admission to hospital might be inferior to e.g. the predictive value of BNP concentrations measured in samples of patients at discharge from hospital (e.g., "wet" vs. "dry" BNP). Furthermore, the study sample of 240 patients is rather small in this study.

(2) I cannot understand the study design. In reference #16 (Eur J Heart Fail 2014;16:700-8), the authors stated that they recruited 2066 consecutive patients with acute heart failure in a multi-center study from March 2011 to April 2012. The authors further stated that the scheduled enrolment of 5000 patients is expected to be complete in 2014, with a planned follow-up period through 2016. In addition, the authors described that they were establishing this registry to elucidate the overall clinical characteristics, current treatment patterns, and outcomes of patients with AHFS in Korea and to compare this registry with other registries to expose regional heterogeneity. In the present work they tried to evaluate 427 consecutive patients who were recruited between April 2011 and December 2013. This discrepancy should be clarified in a revised manuscript.
(3) What was the concrete study hypothesis of the present work?

(4) The authors should clarify in a revised manuscript, whether the present work is a prospectively or retrospectively conducted study. It seems that it was a post hoc decision to evaluate the predictive value of BNP in this cohort (from blood samples drawn in time course). Which study protocol was approved by the ethics committee? In addition, is the present work an observational cohort study without any study-specific intervention - this should be clarified in a revised manuscript as well. Or was the second BNP measurement performed in samples drawn within 90 days after admission to hospital a study specific intervention?

(5) The authors obviously had 427 consecutive patients with acute heart failure to be eligible for this study within a recruitment phase of 33 months (April 2011 to December 2013). This means they had approximately 13 patients per month with acute heart failure at their hospital. At least for me, this seems to be a rather low number. The authors are advised to comment on this in a revised manuscript.

(6) The authors obviously tried to evaluate 427 patients with heart failure but - in fact - they analyzed only 240 patients due to several exclusion criteria. In a revised manuscript, it should be stated how many patients were excluded for which reasons. The respective flow chart (i.e., Figure 1) should be modified accordingly. The exact definitions of the exclusion criteria are currently missing.

(7) The diagnosis of acute heart failure should be better described in a revised manuscript. Currently, one has the impression that heart failure was diagnosed if lung congestion was present or if there was an indication of structural cardiac disease of left ventricular systolic dysfunction. Such is not an adequate definition of acute heart failure. In addition, it is somewhat astonishing that the authors had 53% patients with HFpEF with these definitions.

(8) What was the rationale for "selecting three months as an endpoint for the short-term follow-up BNP value after discharge"? This decision should be justified in a revised manuscript.
With respect to statistical analysis, I would recommend to use only median (25th-75th percentiles) for all metric and ordinal data (but not using mean +/-SD). Accordingly, only the Mann Whitney U-test should be used for all metric and ordinal data. Further, I would strongly recommend to stratify the cohort according to median BNP concentrations at admission and at discharge from hospital and according to the median percent changes (but not by quartiles).

The authors are advised to provide results on whether BNP (initial, follow up and percent change) is an independent predictor of outcome and on whether this analyte adds on top of the prognostic value of clinical variables and as well as other biomarkers. The authors should, thus, consider using multivariate Cox-regression models and reclassification analyses such as ROC curve analyses, net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Specifically, I would like to see univariate and multivariate risk ratios (95% CI, p-values) in Table 2. In this table, the first row should indicate the variables of interest, the second row should indicate univariate risk ratios (95% CI, p-values) of the variables of interest, and the third row should indicate multivariate risk ratios (95% CI, p-values) of the variables of interest (either inclusion model or stepwise procedure). Thus, Tables 3 and 4 could be omitted.

Similarly, Figure 2 should show Kaplan Meier curves for BNP (initial, follow up and percent change) according to the median values. What about the censored data in these graphs?

To my opinion, Supplementary Table 1 could be omitted as it does not add relevant information to the proposed study question.

At which time point in relation to the admission of the patients to hospital was echocardiography performed? Which echocardiographic parameters were evaluated and with which methods? What about a second echocardiogram after three months?
(15) At which time point in relation to the admission of the patients to hospital was the second blood collection for BNP measurements performed (median time, range, 25th-75th percentiles)?

(16) I would recommend changing the follow-up time. The authors enrolled their patients from April 2011 to December 2013. The status of all-cause mortality was collected for each study participant in February 2016. This would give the opportunity to obtain a complete 2-year follow up for each patient (without any censored data). For example an appropriate statement in a revised manuscript could be as follows: "The endpoint of the present investigation was defined as all-cause mortality, and the study participants were followed up for 730 days from the time they were admitted to hospital or until death if occurred earlier. Mortality data were obtained from the National Death Records. All 240 patients received follow-up."

(17) The authors should provide data on the patients' medication. Were the medications obtained at admission or at discharge from hospital?

(18) Isn't it a bit "unfair" for the initial BNP to exclude those patients who died in hospital or in the time until the second blood collection after three months? The authors should discuss this issue in a revised manuscript.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
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