Author’s response to reviews

Title: Plasma Brain Natriuretic Peptide as A Surrogate Marker for Cardioembolic Stroke

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Author’s response to reviews: see over
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Sabina Alam, PhD
Editor
BioMed Central

Dear Prof. Sabina Alam

Thank you for your letter of August 11, 2008, concerning our manuscript, “Plasma Brain Natriuretic Peptide as A Surrogate Marker for Cardioembolic Stroke ” by K. Yukiiri et al. [2126130049211808], that was requested a revision for publication in BioMed Central. We are enclosing a revised version of the manuscript, in which we have attempted to make additional changes as suggested.

We believe that we can respond satisfactorily to the concerns of the reviewer. In particular, point-by-point responses to each of the criticisms are given, as you had requested.

We hope that our work will now be found suitable for publication in BioMed Central. We thank you and the reviewers for the detailed comments and suggestions that have improved the manuscript.

Sincerely yours,

Naohisa Hosomi, MD.
Reviewer 1

Reviewer's report:
In this study, it is seen that AF and heart failure are more in cardioembolic group. Cardiac morphology is in disorder similarly in cardioembolic group.

Response to the reviewer’s comment,
Thank you for the comments.
As the reviewer mentioned, the cardioembolic stroke patients should have an evidence of cardiac diseases, which can be an embolic source of cardioembolic stroke. Therefore, in the present study, cardioembolic stroke patients had more atrial fibrillation, heart failure, and the disorder of cardioechographic parameters.

In this study, inclusion and exclusion criteria have not clearly been defined (For example; have valve diseases been removed?)

Response to the reviewer’s comment,
Thank you for the comment.
In the present study, we have included all the ischemic stroke patients who admitted our hospital within 24 hours after their stroke onset, except who did not give written informed consent, during the evaluation period. We have no exclusion criteria. There are the patients who had valve diseases in this study. We added the information about the valve diseases in manuscript.

What was the primary disease that increased LA dimension so much in cardioembolic group? (Mitral stenosis, Mitral regurgitation, RESTRICTIVE KMP, HEART FAILURE, COR PULMONALE;)

Response to the reviewer’s comment,
Thank you for the comment.
The information of mitral stenosis and mitral regurgitation were inserted in the manuscript. However, there are a limited number of patients who had those valve diseases. And, we had no patient with restrictive cardiomyopathy or cor pulmonale. However, aging[1] and atrial fibrillation[2], themselves, also associated with increased
LA dimension. Therefore, in the present study, the primary diseases of increased LA dimension were aging and atrial fibrillation.

BNP does not increase or increases very little in lacunar infarcts, what was the rate of lacunar infarct?

Response to the reviewer’s comment,
Thank you for the comment.
There are 24 atherothrombotic stroke, 21 lacunar stroke, and 24 undetermined subtype of ischemic stroke in non-cardioembolic stroke. We have inserted the information of patient distribution in non-cardioembolic patients of atherosclerotic infarction, lacunar infarction, or undetermined case.

What was the normal intervals of BNP? Was there a control group?

Response to the reviewer’s comment,
Thank you for the comment.
In the present study, we had no control patient, since our purpose of the present study is to find the surrogate marker of cardioembolic stroke among the ischemic stroke. The patients with cardioembolic stroke were compared with the patients with non-cardioembolic patients. Our normal range of BNP is less than 18.4 pg/ml.

Was INTRA and interobserver evaluation made?

Response to the reviewer’s comment,
Thank you for the comment.
To estimate the reproducibility of measurements of dimension and flow velocity with echocardiography, the echocardiography of 10 volunteers were evaluated by 10 trained cardiologists who were not involved in this study. Intraobserver coefficients of variation of dimension and flow velocity of echocardiography were 7.0 and 9.2%, respectively, and interobserver coefficients of variation of dimension and area of echocardiography were 9.6 and 10.8%, respectively.
We have inserted this information in the manuscript.
What was the reason of the difference of E/A rate between the two groups (Restrictive KMP?)?

Response to the reviewer’s comment,
Thank you for the comment.
All of the cardioembolic stroke patients with paroxysmal Af were in sinus rhythm when they have admitted in the present study. In those patients, their left atrium is still in stunning condition. Therefore, E/A was high (1.7±0.6) in the paroxysmal Af patients.

How were the diastolic functions between the two groups?

Response to the reviewer’s comment,
Thank you for the comment.
In our cohort, there is no patient with diastolic dysfunction.

How can researchers explain the reason of BNP increase in stroke if there is no connection between BNP and LVEF?

Response to the reviewer’s comment,
Thank you for the comment.
In the present study, we have evaluated the factors, which influenced on plasma BNP. From this result, we have found that increased plasma BNP was associated with atrial fibrillation, heart failure, chronic renal failure, and LA diameter in ischemic stroke patients. We think LV ejection fraction was covered with heart failure. And, it is also widely known that stressed LA is one of the cardiac sources to secreting BNP.

What kind of difference was there between the two groups regarding BNP when the group AF and the group that was not AF were evaluated? Was the non-cardioembolic group that was not AF similar to the cardioembolic group?

Response to the reviewer’s comment,
Thank you for the comment.
From our results, Af was a strong predictor of increased plasma BNP. Therefore, the patients with Af showed high BNP (102.5±33.0) than without Af (60.1±48.2). Importantly, although Af is one of the main reasons in increased plasma BNP, cardioembolic stroke was still predicted with plasma BNP independent from Af.

It is known that medical medication (beta blocker, ACE inb, AT receptor blockers, etc.) is effective on BNP. Was the medication of both groups similar?

Response to the reviewer’s comment,
Thank you for the comment. We have inserted and analyzed the information on pre-medication at ischemic stroke. However, we could not find any independent predictor on plasma BNP in the present study.

**Reviewer 2**

**Reviewer's report:**
The work presented here is interesting and useful. However I see points needing clarification.
Firstly the authors report a high frequency of cardioembolic stroke (50% of all strokes). It is surprisingly high in comparison with the majority of series. Is there some type of selection of patients? Where they admitted in a really consecutive manner? Is the heart diseases rate higher in Japan than in other countries?

Response to the reviewer,
Thank you for the comment. Our hospital is high care centered hospital. Therefore, usually heavy symptomatic patients have admitted. And, in the present study, we have evaluated the patients who had admitted within 24 hours after their stroke onset. We think this is the other reason of the high distribution of cardioembolic patients in this study. Hospital based selection bias can be exist. We had no exclusion criteria for this study. And it is held on consecutive manner. From the Japan Standard Stroke Registry Study data, cardioembolic stroke hold around 25% of ischemic stroke. This is similar level to the western countries.
Additionally the authors did not mention strokes of undetermined cause, which are very frequent according to the TOAST classification.

Response to the reviewer,  
Thank you for the comment.  
Ischemic stroke of undetermined cause was included in noncardioembolic stroke. We have revised the manuscript.

It would be interesting to know the frame time in which the blood samples were withdrawn.

Response to the reviewer,  
Thank you for the comment.  
We have shown duration after ischemic onset to BNP measurement. It was the time in which the blood samples were collected.

Minor points  
There is no need to repeat statistical values in the discussion.

Response to the reviewer’s comment,  
Thank you for the comment.  
According to the reviewer’s comment, we have deleted the statistical values in the discussion.

The manuscript would improve by adding more bibliographic references as the authors state that there is no many reports on this issue. A more extensive search should be made.

Response to the reviewer’s comment,  
Thank you for the comment.  
We have made additional discussion on plasma BNP in acute ischemic stroke including recent reports.
In the regression model the dependent variable should be indicated in the legend.

Response to the reviewer’s comment,
Thank you for the comment.
We have added the variable information in the table legends.

References: