Peer review file
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Reviewer A

This is a retrospective cohort study to assess the influence of pre and/or postop BNP levels on 30-day or overall mortalities in patients undergoing various type of open heart surgeries using CPB. The authors found that preop BNP was not associated with mortalities, while postop BNP was associated with mortalities especially in patients with high BNP levels. They concluded that postop BNP can be an useful surrogate maker to predict mortality. The whole manuscript was very well written and presented with robust statistical analyses.

Major points;

Comment 1. First of all, BNP is a well-known serum biomarker used in daily practice in cardiovascular medicine to monitor clinical status, and correlates with severity of overall outcomes. In terms of preop BNP in cardiac surgery, this can be used as a marker to see how optimal the patients have been managed medically prior to surgery, particularly in patients with heart failure / valvular heart disease. However, postop BNP is just a pin-point marker after given surgeries, which may indicate how invasive the procedure was. In other words, this is not something the surgeons can easily control during surgery. As discussed in the manuscript, when the procedure is more invasive (longer CPB time and cross-clamp time, more complex procedure, etc), the postop BNP can be higher. Therefore, this can be utilized to sort out the sicker group of patients who need more careful attention both immediately postop period and during later follow-up.

Reply 1: I agree with your comment. As you mentioned, preoperative BNP only reflects the patient's preoperative condition. This may be why preoperative BNP levels was not associated with postoperative mortalities in our study. By the way, postoperative BNP levels may reflect the patient's preoperative condition as well as intraoperative and immediate postoperative conditions. As described in the manuscript, longer CPB time was identified as the most significant factor associated with elevated postoperative BNP level in the multiple linear regression analysis. Other than CPB time, other factors such as female sex, high Euro score, longer CPB time, and low LVEF were also associated with increased postoperative BNP level. In addition, postoperative acute changes in

systolic or diatolic function might increase the postoperative BNP level as described in the discussion. Therefore, as you comment, measurement of postoperative BNP level may be very simple and reliable method to sort out patients at risk of death after cardiac surgery.
Changes in the text: none.

Comment 2. In daily clinical setting, higher BNP levels can be observed in patients with chronic kidney disease, likely due to its metabolism. According to the whole analyses, postop AKI was the strongest marker to predict the outcomes, which has been well recognized in other studies. Please discuss more the influence of AKI in relation with higher BNP.
Reply 2: I appreciate your critical comment. As you comment, BNP level can be affected by renal function because of clearance mechanism. NT-pro-BNP is known to be only excreted by the kidney, so alterations in renal function may influence NT-pro-BNP level to a great extent. However, in case of BNP, its clearance occurs by at least 3 different pathways including excretion in urine. Therefore, postoperative high BNP level may be an outcome of various factors such as ischemic/reperfusion injury, cardiac dysfunction as well as renal function. In addition, correlation (pearson's coefficient value) between postoperative creatinine and postoperative BNP level was 0.18 which is considered as negligible or weak. I added this explanation in the discussion section.
Changes in the text: I added "Also, postoperative alterations in renal function might affect the increased postoperative BNP level because one of the BNP clearance mechanisms is urinary excretion. However, postoperative creatinine level did not show significant correlation with postoperative BNP level in our study (r =0.18)" in the discussion section. Please see page 9-10, line 213-216.

Comment 3. Table 5; 30-day mortality: postop BNP ranged 170 to 282 had lowest mortality, not < 170 (OR 4.1). Why do the authors think that lowest postop BNP patients did not have lowest mortality.
Reply 3: I appreciate your valuable comment. Number of deaths in each quartile for 30-day mortality was six, two, six, and 23 from the lowest to the top quartile, respectively. Even though 2nd quartile was the one with the lowest death rate, number of deaths in the three quartiles at the bottom was similarly low compared to the top

quartile. This means the relation between 30-day mortality and postoperative BNP was not linear. That is, the association becomes strong from the certain level of postoperative BNP level. Therefore, I performed ROC curve and the cut off value was the same as the postoperative BNP level of top quartile.
Changes in the text: none.

Minor points;
Comment 1. P3. L67. This sentence does not make sense. Please correct.
Reply 1: I appreciate your pointing out the mistake. I corrected the sentence.
Changes in the text: CPB wad deleted by mistake during previous revison. I added "CPB" at the end of the sentence.

Comment 2. Table 1; there is no mention of ECMO and AKI. Please correct on the foot note
Reply 2: I deleted the footnotes for ECMO and AKI.
Changes in the text: I deleted the footnotes for ECMO and AKI in the table 1.

Comment 3. Table 2, 3,4; Procedures: "alve+CABG" should be "valve+CABG".
Reply 3: I appreciate your pointing out the mistake. I corrected the error in the table 2, 3, 4.
Changes in the text: I corrected the error "alve+CABG" to "valve+CABG" in the table 2, 3, 4.

Reviewer B

General comments:
In this study authors have evaluated the prognosis of pre-operative and post-operative BNP values in patients undergoing cardiac surgery.
They found that preoperative BNP level was not associated with mortality after cardiac surgery while postoperative BNP level was associated with 30-day and overall mortality after cardiac surgery, particularly in patients with high levels (≥484 pg/mL).
The topic of the study is of interest; however, there are some methodological concerns raised mainly from the retrospective nature of the analysis.

Specific comments:

Comment 1. The retrospective nature of the analysis limits conclusions.

BNP testing was ordered and measured without a standard protocol but at clinicians clinical decision that might induce significant bias to the study results.

BNP levels can vary according to volume status, renal function and acute decompensation of cardiopulmonary disease.

So preoperative BNP levels can be different, if measured 1 month prior or at the day of surgery.

Reply 1: I agree with your concerns. The interval from the preoperative BNP measurement to operation varied due to the retrospective nature of the study. As described in the method section, the median interval between preoperative BNP measurement and the operation was 1 day (IQR 1-3 days). The distribution of the timing of preoperative BNP measurement prior to surgery was as follows: ≤1 day (64.4%), 2–7 days (28.5%), and 8–30 days (7.1%). We performed the analysis to evaluate the influence of the interaction between the timing of preoperative BNP and the outcomes (30-day mortality and overall mortality). The interaction did not show any significant effect on either 30-day (p=0.15) or overall (p=0.22) mortality. Subgroup analysis was performed according to the timing of preoperative BNP measurement (≤1 day, ≤7 days and ≤30 days). Multivariable analysis showed no significant association with 30-day mortality and overall mortality in patients with preoperative BNP measurement at ≤1 day (OR 1.00, 95%CI 0.93-1.07, p=0.89, HR 0.99, 95% CI 0.94-1.03, p=0.55), ≤7 days (OR 1.01 95% CI 0.97-1.05, p=0.71, HR 1.00, 95% CI 0.98-1.02, p=0.94) and ≤30 days (OR 1.01 95% CI 0.98-1.04, p=0.63, HR 1.00, 95% CI 0.98-1.02, p=0.79). Therefore, the diverse timing of preoperative BNP measurement might not induce significant bias to the study results. However, I added this limitation in the limitation section.

Changes in the text: I added this limitation. Please, see page 10-11, line 236-7.

Comment 2. Similarly the post-operative BNP levels can be influenced by several haemodynamic parameters while the haemodynamic status of cardiac surgery patients may vary during the ICU course.

It would be important to know the reason for BNP ordering.

Patients with better haemodynamic status profile may not have been ordered a BNP testing; Study results for this reason on BNP diagnostic accuracy might be

overestimated.

Reply 2: I absolutely agree with your comment and concerns. As with preoperative BNP measurement, postoperative BNP measurement order was in so called 'set postoperative order' in our department which consisted of all the examinations and medications required in the postoperative period. That is, postoperative BNP testing was not performed by a physician's judgement based on hemodynamic status. Unfortunately, missing postoperative BNP testing was due to not following 'set order' because repetitive BNP testing during the same admission was not covered by medical insurance in our country. Therefore, as described in the manuscript, patients with postoperative BNP level were 1,208 patients among the entire 1,642 patients.

Changes in the text: none.

Comment 3. Information with regards to medical treatment is missing. Please provide available data.

Reply 3: I agree with your comment. Unfortunately, data for postoperative medical management such as inotropic supports was not available in this study as mentioned in the discussion section. Even though other similar studies (reference 12, 19) did not showed data for postoperative medical management, I added this factor in the limitation section and I will try to consider including postoperative medical information in the further study.

Changes in the text: I added this factor in the limitation section. Please, see page 10, line 237.

Comment 4. Please provide ROC curve analysis for independent predictors of mortality (AUC, CI, p value and sensitivity, specificity for the best cut-off value selected)

Reply 4: I appreciate your comment. AUC, CI, p value was 0.65, (0.58-0.71), $p<0.001$ for overall mortality and 0.71, (0.61-0.82), $p<0.001$ for 30-day mortality, respectively.

Changes in the text: I added this values in the manuscript. Please, see page 9, line 196, 198.

Comment 5. Editing is required in the whole manuscript.

Check abbreviations in Table 1

Reply 5: I appreciate your comment. I doublechecked all the abbreviations in the Table

1. There is no mention of ECMO and AKI in the footnotes. I deleted the footnotes for ECMO and AKI. Also, other errors were doublechecked.

Changes in the text: I deleted the footnotes for ECMO and AKI in the table 1. I added 'CPB' in page 3, line 67. "alve+CABG" in the table 2, 3, 4 was corrected to "valve+CABG".