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Pre-Operative Serum Brain Natriuretic Peptide and Risk of Acute Kidney Injury after Cardiac Surgery

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Abstract

Background—Acute kidney injury (AKI) following cardiac surgery is associated with poor outcomes and is difficult to predict. We conducted a prospective study to evaluate whether pre-operative brain natriuretic peptide (BNP) levels predict postoperative AKI among patients undergoing cardiac surgery.

Methods and Results—The TRIBE-AKI Consortium enrolled 1,139 adults undergoing cardiac surgery at six hospitals from 2007–2009, who were selected for high AKI risk. Pre-operative BNP was categorized into quintiles. AKI was common using Acute Kidney Injury Network definitions; at least mild AKI was a ≥0.3mg/dL or 50% rise in creatinine, n=407 (36%), and severe AKI was either a doubling of creatinine or the requirement of acute renal replacement therapy, n=58 (5.1%). In analyses adjusted for pre-operative characteristics, pre-operative BNP was a strong and independent predictor of mild and severe AKI. Compared with the lowest BNP quintile the highest quintile had significantly higher risk of at least mild AKI (risk ratio [RR] 1.87; 1.40–2.49) and severe AKI (RR 3.17; 1.06–9.48). After adjustment for clinical predictors, addition of BNP improved the area under the curve to predict at least mild AKI (0.67 to 0.69, p=0.02) and severe AKI (0.73 to 0.75, p=0.11). Compared with clinical parameters alone, BNP modestly improved risk prediction of AKI cases into lower and higher risk (continuous net reclassification index at least mild AKI 0.183; 0.061, 0.314; severe AKI 0.231; 0.067, 0.506).

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Conclusions—Pre-operative BNP level is associated with post-operative AKI in high-risk patients undergoing cardiac surgery. If confirmed in other types of patients and surgeries, pre-operative BNP may be a valuable component of future efforts to improve pre-operative risk stratification and discrimination among surgical candidates.

Keywords

brain natriuretic peptide; cardiac surgery; acute renal failure; creatinine

Introduction

Acute kidney injury (AKI) is a common complication during the early post-operative period after cardiac surgery, with rates up to 40% depending on how it is defined.[1,2] Even mild elevations in serum creatinine (0.3 mg/dL, or 26 μmol/L) are independently associated with adverse outcomes, including prolonged length of hospitalization as well as short- and long-term mortality.[3–5] Consequently, there has been a renewed effort towards better understanding the risk factors of AKI in order to develop potential preventive and therapeutic strategies. Several risk-stratification algorithms exist that identify such risk factors in the pre-operative (demographics, co-morbid conditions), intra-operative (type of surgery, acuity of surgery), and post-operative (cardiovascular complications) periods.[6–9] In addition, recent studies suggest natriuretic peptide biomarkers may help inform AKI risk.[10–12]

Cardiovascular disease and heart failure are highly prevalent among those who undergo cardiac surgery, contributing to hemodynamic stress that may be poorly characterized by clinical history. Consequently, natriuretic peptide biomarkers that better characterize this underlying physiology have become well established in the diagnosis and management of patients with heart failure. These biomarkers provide important prognostic information across a variety of clinical settings including stable and unstable coronary disease, valvular disease, and cardiac surgery.[13] Pre-operative elevations of B-type natriuretic peptide (BNP) and its precursor, *N*-terminal pro–B-type natriuretic peptide (NTproBNP), before cardiac[10–12,14–20] and noncardiac[21,22] surgery are strongly predictive of post-operative events including cardiovascular complications (myocardial infarction, heart failure, arrhythmias, cardiogenic shock), prolonged length of stay (intensive care unit and hospital), and mortality (short- and long-term). However, associations between natriuretic peptides and AKI remain unclear because previous studies are limited by small sample sizes, retrospective study designs, and suboptimal characterization of AKI.[10–12] In the current study, we evaluated whether BNP elevations both before and after surgery are associated with AKI.

Methods

Study Sample

We conducted a prospective cohort study of adults undergoing cardiac surgery (coronary artery bypass grafting [CABG], surgery for valve disease and both) at six academic medical centers in North America between July 2007 and December 2009. In order to include sufficient study outcomes, all enrolled patients were at high risk for AKI defined by the presence of one or more of the following criteria: pre-existing renal impairment (baseline serum creatinine > 2 mg/dL [177 μmol/L]), ejection fraction <35% or grade 3 or 4 left ventricular dysfunction, age > 70 years, diabetes mellitus, concomitant CABG and valve surgery, or repeat revascularization surgery. Adult patients were excluded if they had evidence of AKI prior to surgery, prior kidney transplantation, pre-operative serum creatinine level > 4.5 mg/dL (400 μmol/L) or end-stage renal disease. All participants

provided written informed consent and the study was approved by each institution's research ethics board. This clinical study was registered at Clinicaltrials.gov as NCT00774137.

Study Protocol

Preoperatively, a blood sample was collected, centrifuged and processed, aliquoted in 0.5 cc vials, and stored at −80°C. Because many studies evaluating BNP used post-operative levels,[12,14,15,18–20] we also conducted secondary analyses to evaluate whether relative or absolute increases in post-operative BNP levels independently predict subsequent AKI (post-operative level minus pre-operative level). The first post-operative samples were collected soon after admission to the intensive care unit (mean (SD) 0.6 (1.6) hours post-operatively) and the day one post-operative samples were collected on the morning of the first post-operative day in the intensive care unit (mean (SD) 16.0 (5.0) hours post-operatively). These samples were also centrifuged, processed, aliquoted, and stored. One pre-operative sample vial and each postoperative sample vial were used for biomarker measurements without any additional freeze-thaw. BNP measurements were conducted in a large batch using a Biosite Triage meter (Biosite Corporation, San Diego, CA). Pre-operative creatinine was measured as part of routine clinical care in each hospital's clinical lab. Estimated glomerular filtration rates (eGFR) were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[23] Secondary pre-operative predictors were used for multivariable adjustment, and were obtained from the patient and the clinical record, using standardized definitions of the Society of Thoracic Surgeons (STS) data collection tool. We chose all variables that had been included in the prior STS registry risk-assessment tool for predicting AKI after cardiac surgery, as well as others related to kidney function estimation. These included demographics (age, sex, race), comorbidities (hypertension, diabetes mellitus, heart failure, prior myocardial infarction), and surgery characteristics (elective or urgent; bypass, valvular surgery, or both; prior cardiac operation). Patients requiring emergent surgery were excluded from this study.

AKI was determined by the daily creatinine measurements during the entire hospital stay. At least mild AKI was defined by creatinine criteria for Acute Kidney Injury Network (AKIN) stage 1 or higher: an absolute creatinine increase ≥ 0.3mg/dL or a ≥ 50% relative increase.[24] Severe AKI was defined by AKIN Stage 2 or higher: either a doubling of creatinine or the requirement of acute renal replacement therapy. Although AKIN criteria define creatinine changes occurring within a 48 hour period, the time required for creatinine elevations to occur depends on the half-life of excretion such that patients with lower levels of kidney function require longer periods of time to reach a new equilibrium state after a decrease in kidney function following acute injury. Because patients in this study included those at high-risk for AKI many of whom have lower levels of kidney function, we defined AKI according to AKIN criteria for creatinine changes that occurred during the entire hospital stay. Nonetheless, a sensitivity analysis using AKI events within the first 48 hours post-operatively was also conducted. Additional outcomes that were collected during the study included in-hospital death or requirement of acute renal replacement therapy, and lengths of stay in the intensive-care unit and hospital.

Statistical Analysis

We graphically evaluated the functional relationship of BNP with each outcome (at least mild AKI and severe AKI) using restricted cubic splines. Based on the spline regression we used log-transformed serum BNP when it was included continuously in models (pre-operative BNP (Figure 1) and post-operative BNP (Supplemental Figure 1). Using pre-operative BNP values we categorized our cohort into quintiles. We assessed linear trends by the Cochran-Armitage test for dichotomous outcomes and the Jonckheere-Terpstra test for continuous outcomes. We compared continuous variables with two-sample t-test or

Wilcoxon rank sum test and dichotomous variables with the chi-square test or Fisher's exact test. We determined the crude and adjusted relative risks of AKI with multivariable Poisson regression.[25] We adjusted for covariates that have been used in previous studies for prediction of AKI after cardiac surgery,[8] including patient demographics (age [per year], gender, race), clinical risk factors (e.g. baseline eGFR, hypertension, diabetes) and operative characteristics (e.g. elective or urgent procedure and use of cardiopulmonary-bypass). In addition, site was included as a fixed effect in multivariable models. We tested for interactions for CKD, diabetes, chronic heart failure, elective/urgent, and age. The area under the receiver operating characteristic curve (AUC) was used to determine the ability of the multivariable models to discriminate between AKI cases and non-cases. We used likelihood ratio tests (LRT) to evaluate whether the addition of serum BNP to the clinical model improved the accuracy of AKI risk prediction.[26] As a second step to evaluate the impact of BNP on AKI risk prediction, we determined the continuous Net Reclassification Index (NRI) and the Integrated Discrimination Improvement (IDI) indices.[27–29] Log-transformed continuous BNP values were used to assess its discriminatory ability (ROC curve analysis) and impact on risk prediction (continuous NRI and IDI analysis). Bootstrap confidence intervals were reported for AUCs and reclassification indices (continuous NRI, IDI, rIDI). All analyses were completed separately for each outcome (at least mild AKI and severe AKI). Although urine albumin-to-creatinine ratio (UACR) may be an important risk factor for AKI,[30] seven existing risk models for AKI have not included it,[6–9,31–33] thus, we did not include UACR in our primary models. However, all analyses were repeated with the addition of UACR to our clinical model to demonstrate the improvement in AKI risk classification conferred by BNP even when we accounted for this important emerging AKI risk factor (Supplemental Tables 1–2 and Supplemental Figure 2).

In secondary analyses we evaluated post-operative BNP independently, as absolute change from pre-operative levels, and as a relative change from pre-operative levels. This was done to determine whether post-operative BNP levels independently predict subsequent AKI. We performed all analyses in SAS version 9.2 (SAS Institute, Cary, NC, USA) and R 2.11.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 1,219 adults enrolled into this study, 76 participants did not have pre-operative serum BNP results and 4 patients underwent emergent surgery, leaving 1,139 subjects for analysis. The average age was 72 years (SD10) and 68% (n=776) were men. Most subjects were white (94%; n=1,066). Among the surgical procedures, 48% (n=548) were CABG only, 29% (n=331) were valve only, and 23% (n=260) were both; 80% of surgeries were primary elective and 13% were re-operations. Pre-operative kidney function was not decreased for most participants (mean ± standard deviation; creatinine 1.09 ± 0.34 mg/dL (96 ± 30 μmol/L) and eGFR 67 ± 19 mL/min per 1.73m^2). Heart failure was common with ejection fraction <40% in 21% and diagnosis of heart failure in 26% (the presence of both characteristics was present in 11% of participants). When we compared baseline characteristics across quintiles of BNP (Table 1), the most striking differences were that persons in the highest BNP quintiles were older, more likely to have hypertension, heart failure, reduced ejection fraction, and reduced kidney function, and were more likely to undergo a combined bypass and valve surgery. Those in the highest BNP quintile were less likely to be male or to have diabetes.

During the post-operative period, 407 patients (36%) had at least mild AKI and 58 (5.1%) patients had severe AKI. Patients who developed AKI were more likely to have a history of congestive heart failure, undergo combined CABG and valve repair surgery, have longer cardiopulmonary bypass time, require a post-operative intra-aortic balloon pump, and had a

higher pre-operative serum creatinine. The incidence of both at least mild AKI and severe AKI increased across quintiles of BNP (Figure 2; p-value for trend <0.001 and 0.002 for AKI and severe AKI, respectively). The risk of at least mild AKI increased across quintiles of BNP, with an approximate doubling in AKI risk for the highest compared with the lowest BNP quintile (Table 2). This relationship was only minimally attenuated after adjusting for patient demographics, clinical risk factors, and operative characteristics. Quintiles three through five remained independently associated with at least mild AKI and had BNP cutpoint values similar to those identified in prior studies (approximately 50, 100, 250 pg/mL).[21,22] Associations between BNP quintiles and at least mild AKI did not differ significantly when stratified by those with varying degress of kidney function (low vs. high creatinine or CKD vs. no CKD; interaction p-values 0.9 and 0.06, respectively), or type of surgery (IABP vs no IABP, pump surgery vs no pump surgery, and elective vs non-elective surgery; all interactions, p>0.3). Restricting at least mild AKI events to the first 48 hours post-operatively also did not differ alter the associations observed with quintiles of BNP.

The risk of severe AKI increased across the first three BNP quintiles then plateaued (Table 2). This corresponded to a four-fold risk among the highest compared with the lowest BNP quintile. This relationship was attenuated slightly after adjusting for patient demographics, clinical risk factors, and operative characteristics. Quintiles three through five remained independently associated with severe AKI. When examining the association with other postoperative outcomes, the fifth quintile was associated with the greatest risk of in-hospital death or dialysis. In addition, BNP quintiles were associated with linear increases for lengths of stay in both the intensive care unit and hospital.

The ROC curve for the outcome of AKI had an AUC of 0.60 (SE 0.02) using BNP levels alone, and 0.67 (0.02) using the pre-operative risk variables of the clinical model (Table 3). Addition of BNP to the clinical model provided a modest incremental increase to 0.68 (0.02) (LRT p=0.01). When stratified by time after cardiac surgery (≥3 days [n=160], ≥5 days [n=85]), risk prediction improved (AUC for ≥3 days 0.74 (0.02) and for ≥5 days 0.79 (0.03)). For the severe AKI outcome, the AUC was 0.63 (0.03) for BNP alone, and 0.73 (0.04) for pre-operative risk variables alone. The AUC improved moderately to 0.74 (0.03) with the addition of BNP to the clinical model, though the p-value for the LRT was not significant (p= 0.06). In addition to the AUC, we used the continuous NRI and IDI to determine whether BNP materially impacted at least mild AKI risk classification. For patients with and without at least mild AKI, a scatterplot of these results (Figure 3) demonstrates the higher or lower predicted risks according to the clinical model alone versus the model with pre-op serum BNP included. Among the patients with AKI, 206 had higher predicted risk (above the diagonal line) while 193 had lower predicted risk in the new model. Among the patients without AKI, 412 had lower risk in the new model while 304 had higher risk in the new model. The continuous NRI is calculated by the net reclassification of the proportion of patients that move toward the correct direction indicated by the actual outcome ((206–193)/399 + (412–304)/716 = 0.183; 0.061 – 0.314). Continuous NRI among those with at least mild AKI (0.033; −0.043, 0.110) was smaller than among those without at least mild AKI (0.151; 0.068 – 0.226), providing an improvement in risk prediction among controls than cases, although the overall performance was weak.[28] The IDI was 0.014 (0.004, 0.031) and relative IDI was 16.3% (9.3%, 21.8%). Similarly, continuous NRI for severe AKI was 0.231 (−0.067, 0.506), and the IDI was 0.004 (−0.001, 0.023) and relative IDI was 8.8% (2.6%, 16.5%). Additional analyses demonstrated that the addition of UACR to our clinical model did not substantively alter the improvement in AKI risk classification conferred by BNP (Supplemental Tables 1–2 and Supplemental Figure 2).

In secondary analyses to evaluate the association between post-operative BNP levels and AKI, immediate (0–6h; Figure 4) and day 1 (data not shown), post-operative levels differed

significantly between cases and non-cases for both at least mild and severe AKI. Despite these differences, median changes in BNP levels between pre-operative and immediate post-operative levels differed slightly for at least mild AKI (cases −23.4 vs non-cases −15.5pg/mL, p=0.024) and were similar for severe AKI (cases −32.8 vs non-cases −17.0 pg/mL, p=0.62), suggesting that the association between post-operative BNP and AKI may be largely dependent upon pre-operative BNP levels. Similarly, median changes in BNP levels between pre-operative and day one postoperative levels were similar for at least mild AKI (cases 127.3 vs non-cases 114.2pg/mL, p=0.31) and severe AKI (cases 166.7 vs non-cases 118.7pg/mL, p=0.10). Finally, the AUC for the outcomes of at least mild and severe AKI were all less than 0.60 using either absolute or relative changes in serum BNP between pre-operative levels and both the immediate and day one post-operative levels

Discussion

In this large, contemporary, multi-center, prospective study of patients undergoing cardiac surgery who were selected for high AKI risk, the incidence of AKI was high, particularly among patients with greater comorbidity and impaired baseline kidney function. Although there are several well-known risk factors for AKI,[6–9] associations between natriuretic peptides and AKI remain unclear. We found that pre-operative BNP, a biomarker of hemodynamic stress, is a strong and independent predictor of at least mild and severe AKI. The addition of BNP to known clinical parameters provided modest improvements in risk discrimination, as demonstrated by absolute increases in the AUCs of 0.02–0.03. Similarly risk classification was only modestly improved as demonstrated by continuous NRIs of 0.23–0.38. These findings inform the role of BNP when considering how to best stratify the risk of AKI in the cardiac surgery setting.

The prognostic importance of natriuretic peptides has been well described in both the non-cardiac and cardiac surgery settings. The results from sixteen unique studies were reported in two separate systematic reviews that identified strong associations of elevated BNP and NT-proBNP levels with cardiac events and mortality.[21,22] Although various cut-points were used to define elevated BNP levels, the average number of patients with elevated BNP levels was 1 in 4.[22] Despite some differences in study inclusion criteria, outcome definitions and analytic methods, both reviews estimated that elevated pre-operative BNP levels were associated with higher risk of cardiovascular outcomes (including cardiac death) to a similar extent. Further, this association appeared independent of conventional risk factors,[22] although moderate heterogeneity in past study results limits inferences in this regard. Despite differences in analytic methods that may preclude direct comparisons with non-cardiac surgery studies, similar findings were observed among studies of patients undergoing cardiac surgery. The majority of these studies evaluated associations between BNP and mortality[10–12,14–20] and cardiovascular complications,[10,11,14,17–20] while some also examined length-of-stay.[10,11,15–18] Most past studies were limited to fewer than 200 patients with only one large study that included over 1,000 patients.[16] In the present study, we found that higher levels of pre-operative BNP were associated with higher incidence of post-operative mortality and longer lengths of stay in both the intensive care unit and hospital.

Few studies have examined the association between natriuretic peptides and risk of AKI following cardiac surgery. Although post-operative renal impairment is described as a study outcome in two recent studies,[10,12] the findings are limited by small study sizes (both <500 patients) and limited information regarding the observed incidence or associations with BNP levels. However, in one small study (n=135),[11] pre-operative NTproBNP levels were significantly higher among those who developed post-operative renal failure (defined as a 50% increase in serum creatinine or greater; median 1728 vs 194 ng/L, p<0.001). When

AUCs were examined for predicting renal failure, pre-operative NTproBNP (AUC 0.86, 95% CI 0.78 to 0.94) was more predictive than either the euroSCORE[34] or ejection fraction. Similarly, we found that pre-operative BNP levels were significantly higher among those who developed postoperative AKI. Quintiles of BNP were linearly associated with risk of at least mild AKI, whereas a risk threshold was observed above intermediate BNP levels when evaluating severe AKI. Because patients in our cohort were selected for high AKI risk, they represent a relatively homogenous high-risk population. It is possible that BNP may provide greater risk discrimination in more heterogeneous populations, such as in past studies which enrolled individuals at low- and medium-risk of AKI.[11,34] Although many studies evaluating BNP in cardiac surgery have examined both pre-operative and post-operative levels,[12,14,15,18–20] the relative advantages of each remain unclear. Consequently, we also assessed associations with post-operative BNP levels and found that pre-operative levels were more informative in predicting AKI.

The prognostic value of natriuretic peptide levels in the pre-operative setting is most likely related to their ability to measure small changes in right or left ventricular function among those with systolic or diastolic abnormalities, whether or not they are symptomatic. Ventricular myocardial wall stress stimulates natriuretic peptide secretion in the setting of volume expansion or pressure overload. Consequently, natriuretic peptides have prognostic abilities across a variety of conditions involving hemodynamic stress in addition to heart failure, including stable and acute coronary artery disease, sudden cardiac death, cardiac arrhythmias, pulmonary embolism, stroke, and septic shock.[13] Our findings add to these prior observations by demonstrating that pre-operative BNP levels also independently predict post-cardiac surgery AKI. Further, this relationship is supported by early physiologic studies as well as recent clinical observations. In classic physiologic experiments, increased venous pressure reduced renal blood flow and urine flow.[35] The magnitude of this effect proved even greater than equivalent decreases in arterial pressure.[35] More recently, venous congestion has been demonstrated to be strongly associated with AKI among patients with heart failure,[36–38] as well as those with atherosclerotic cardiovascular disease.[39] Because of greater recognition of the importance of venous congestion, the clinical trial focus is shifting from addressing impaired cardiac output and inadequate arterial filling to renal-sparing treatment strategies that reduce venous congestion.[40,41]

Within the peri-operative setting, reducing the risk of AKI following cardiac surgery has been a focus of growing importance. The primary emphasis has been on optimization of hemodynamic status throughout the peri-operative course because a variety of studies have suggested that such measures decrease the risk of AKI.[42] Despite the perceived importance of intra-operative hypo-perfusion as the dominant mechanism behind AKI following cardiac surgery, tight control of mean arterial pressure has not been consistently shown to reduce the risk of AKI. As observed in physiologic studies outside of the surgical setting, increased venous pressure may confer greater risk of post-operative AKI than decreased arterial pressure. Thus, reductions in elevated venous congestion prior to or during cardiac surgery may provide a novel approach to reducing the risk of AKI after cardiac surgery. Outpatient natriuretic-guided therapies have been effective in reducing heart failure deaths and re-hospitalizations.[43] Similarly, serum BNP may provide a non-invasive indicator to evaluate the efficacy of peri-operative reductions in hemodynamic stress related to either volume expansion or pressure overload conditions.

This study is the largest, multi-center study to date to assess the association between BNP and post-operative AKI risk. Although the focus of our evaluation was on the relationship between pre-operative BNP and AKI, the risks associated with post-operative BNP and corresponding changes from pre-operative levels were also assessed. The diverse settings of the six institutions also ensured a broad inclusion of high-risk cardiac surgery patients.

However, this study does have important limitations. Many studies evaluating natriuretic peptides have used NT-proBNP instead of BNP, which may be more influenced by factors such as body mass index. However, because BNP is less influenced by kidney function, it is the more reliable natriuretic peptide in this setting.[44] We were also able to account for the factors that strongly affect BNP levels such as age, gender, and kidney disease. However, other factors could not be accounted for, including pulmonary disease, severity of cardiac disease (e.g., severity of pre-operative myocardial infarction, hypotension or atrial fibrillation), and body mass index. Limited cases of AKI requiring dialysis, as well as a lack of data on pulmonary disease and limited data on heart failure classification precluded application of our study data to existing risk models.[7,8] In addition, our patients were mostly white limiting the generalizability of these findings to other populations. Nonetheless, all studies using natriuretic peptides suffer from limitations related to the biologic variability and intra-individual variation.[13,43] Although our study had a very large number of at least mild AKI cases, we had few patients with severe AKI, including dialysis-requiring AKI (n=17, 1.5%). Therefore, the ability of BNP to predict risk for these outcomes could not be reliably assessed in our study. Finally, some predictors of AKI (pre-operative cardiogenic shock, intra-abdominal pressure) were not available, limiting our ability to determine whether BNP levels remain independent of these factors. In order to develop the best AKI risk model, future efforts should simultaneously evaluate markers of kidney filtration (eg, serum creatinine, cystatin C, UACR), injury (e.g., urine neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, interkeukin-18, etc.), and hemodynamics (e.g., BNP). This multi-marker approach will then establish whether BNP is associated with AKI after simultaneously accounting for changes in other biomarkers that reflect different aspects of the AKI process. Our current results suggest that BNP will certainly need to be included in that development process.

In conclusion, we found that elevated pre-operative BNP levels were strongly associated with greater AKI risk. BNP was linearly associated with risk of at least mild AKI, whereas for evaluating severe AKI, a risk threshold was observed above intermediate levels of BNP. If confirmed in other populations not selected for high AKI risk, BNP may be a valuable component of future efforts to improve pre-operative risk stratification and discrimination among surgical candidates. These findings raise the possibility that pre-operative therapies to reduce hemodynamic stress indicated by elevated BNP levels may be effective in mitigating the high risk of AKI among select patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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CLINICAL PERSPECTIVE

Cardiovascular disease and heart failure are highly prevalent among those who undergo cardiac surgery, contributing to hemodynamic stress that may be poorly characterized by clinical history. Consequently, natriuretic peptide biomarkers that better characterize this underlying physiology have become well established in the diagnosis and management of patients with heart failure. In this study, 1139 adults who underwent cardiac surgery were evaluated from 6 centers to establish whether pre-operative brain natriuretic peptide (BNP) levels predict postoperative acute kidney injury (AKI; defined by Acute Kidney Injury Network definitions; at-least mild AKI was a >0.3mg/dL [26 μmol/L] or 50% rise in creatinine, and severe AKI was either a doubling of creatinine or the requirement of acute renal replacement therapy). In this high-risk cohort, AKI was common (at-least mild AKI, n=407 [36%]; severe AKI, n=58 [5.1%]). After adjusting for different pre-operative characteristics, pre-operative BNP was a strong and independent predictor of mild and severe AKI. Compared with the lowest BNP quintile, the highest quintile had significantly higher risk of at-least mild AKI (risk ratio [RR] 1.87) and severe AKI (RR 3.17). After adjustment for clinical predictors, addition of BNP improved the area under the curve to predict at-least mild AKI and severe AKI. When compared with clinical parameters alone, BNP also improved risk prediction of AKI cases into lower and higher risk. Pre-operative BNP level is associated with post-operative AKI in high-risk patients undergoing cardiac surgery and may be a valuable component of future efforts to improve pre-operative risk stratification among surgical candidates.

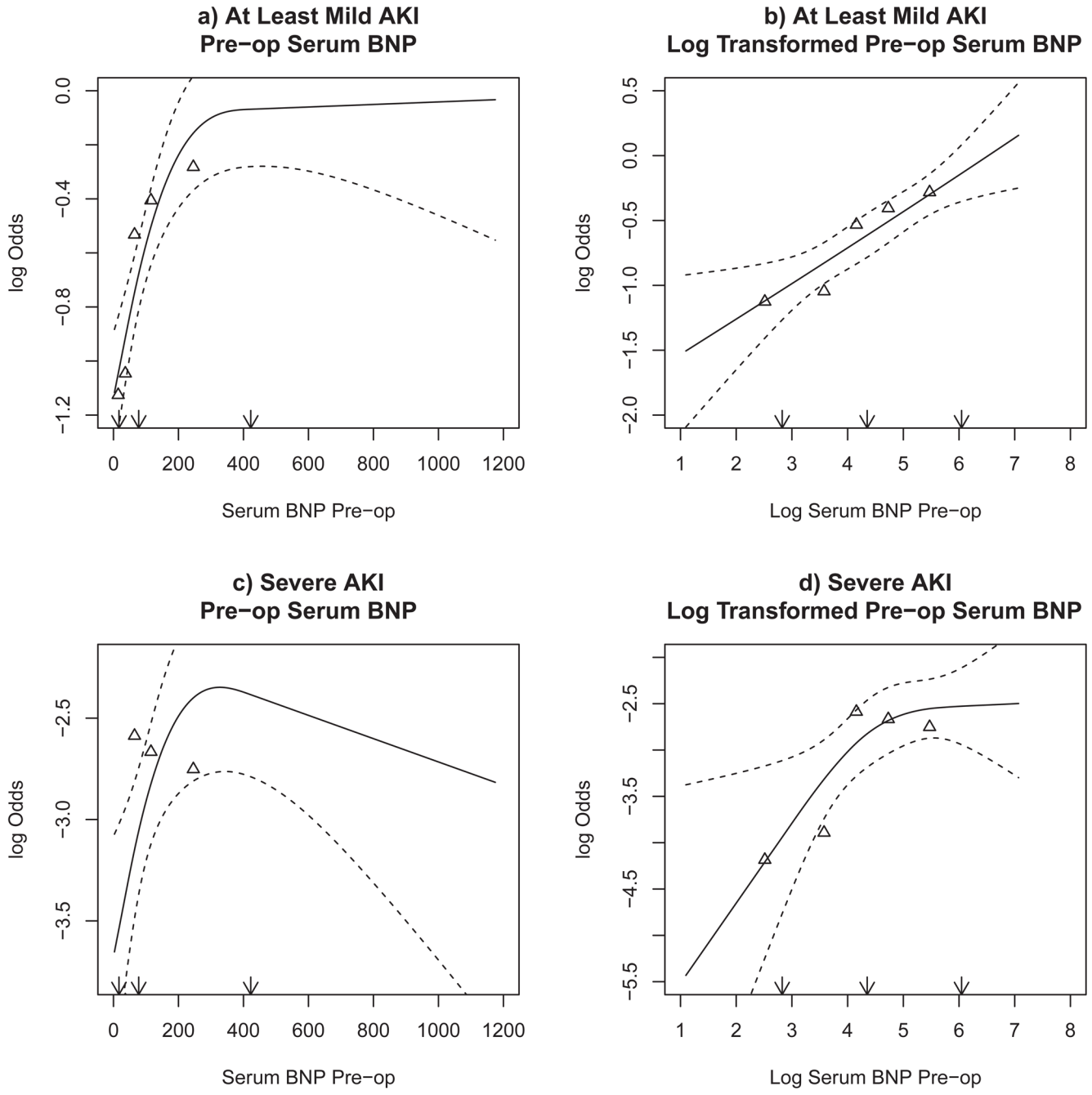

Figure 1.

The relationship between serum BNP and AKI (at least mild AKI, panels **A** and **B**; severe AKI, panels **C** and **D**) by spline regression modeling. Serum BNP was log-transformed in **B** and **d**. The curves represent restricted cubic splines with knots estimated by the arrows on the abscissa. Triangles denote the empirical logits. Abbreviations: Acute kidney injury (AKI), brain natriuretic peptide (BNP)

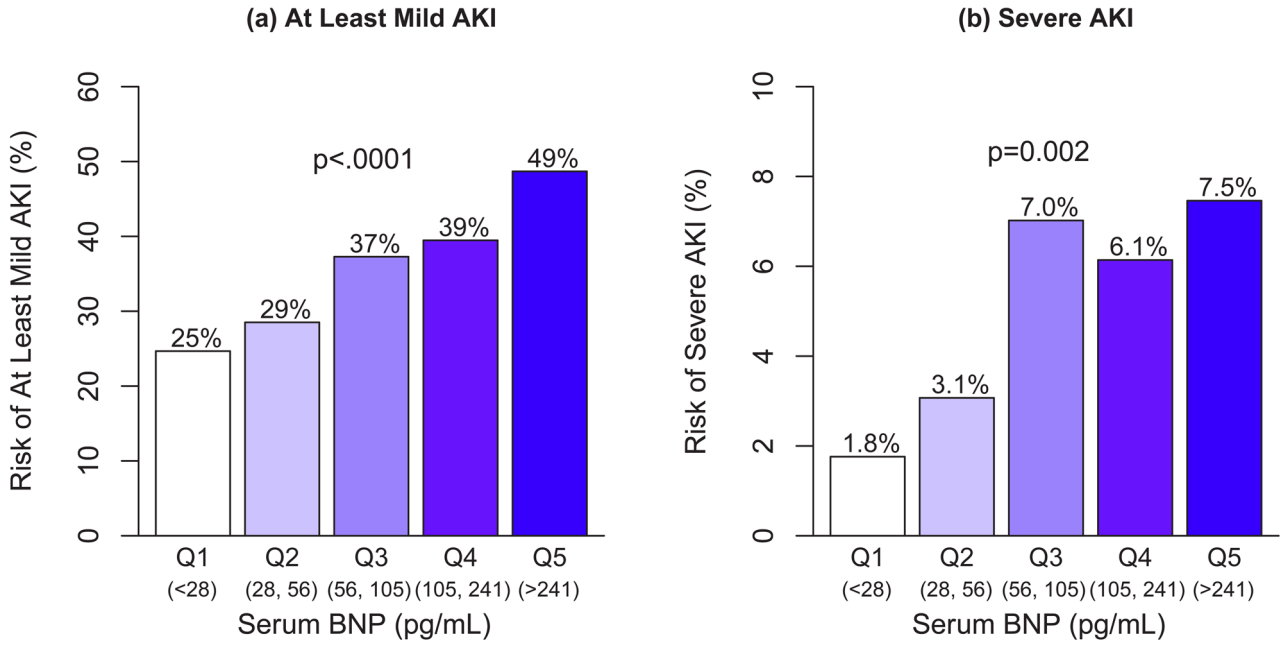

Figure 2.

Incidence of At Least Mild AKI (a) and Severe AKI (b) by Quintiles of Pre-operative BNP. AKI defined as during entire hospitalization, at least mild AKI (**A**) defined as ≥50%, ≥0.3 mg/dL or dialysis; severe AKI (**B**) defined as ≥100% or dialysis. BNP measured in pg/mL. Abbreviations: Acute kidney injury (AKI), brain natriuretic peptide (BNP)

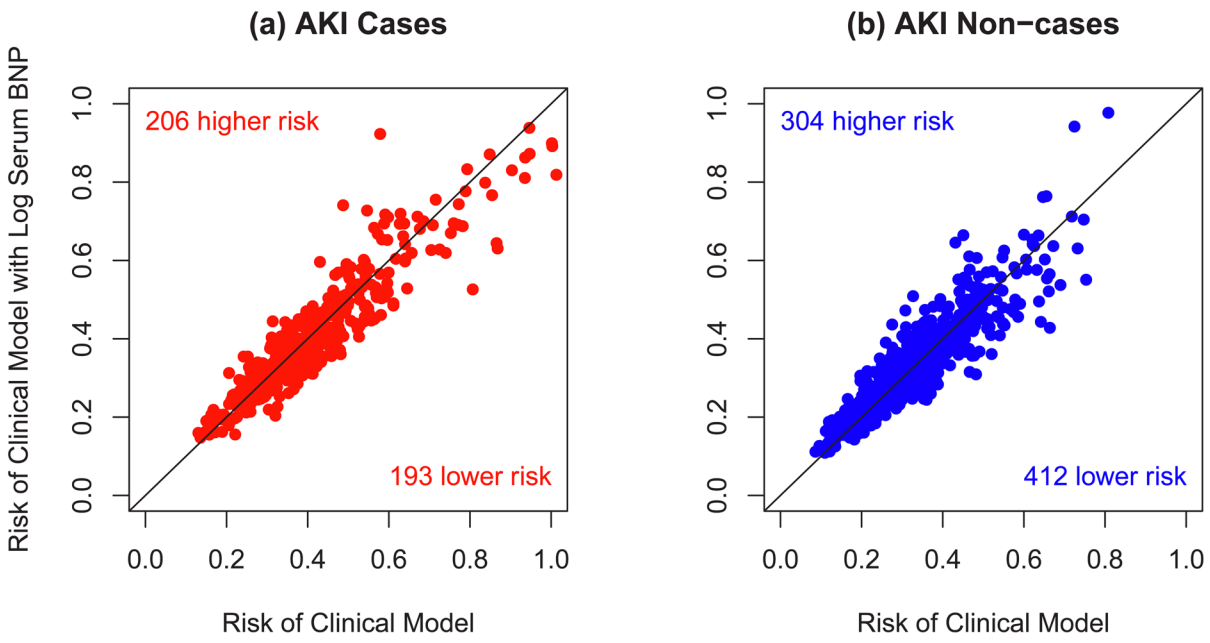

Figure 3.

Reclassification Plot of Predicted Probabilities of At Least Mild AKI Based on the Clinical Model with and without Pre-operative BNP, by AKI status. Predicted risks for at least mild AKI according to the clinical model (x-axis) and according to the clinical model with pre-op serum BNP included (y-axis) for AKI cases (panel **A**; red) and non-cases (panel **B**; blue). The diagonal line indicates a line of identity, such that for points above this line the predicted risk is higher in the new model (improved reclassification for AKI cases) and for points below this line the predicted risk is lower (improved reclassification for non-AKI cases). Abbreviations: Acute kidney injury (AKI); brain natriuretic peptide (BNP)

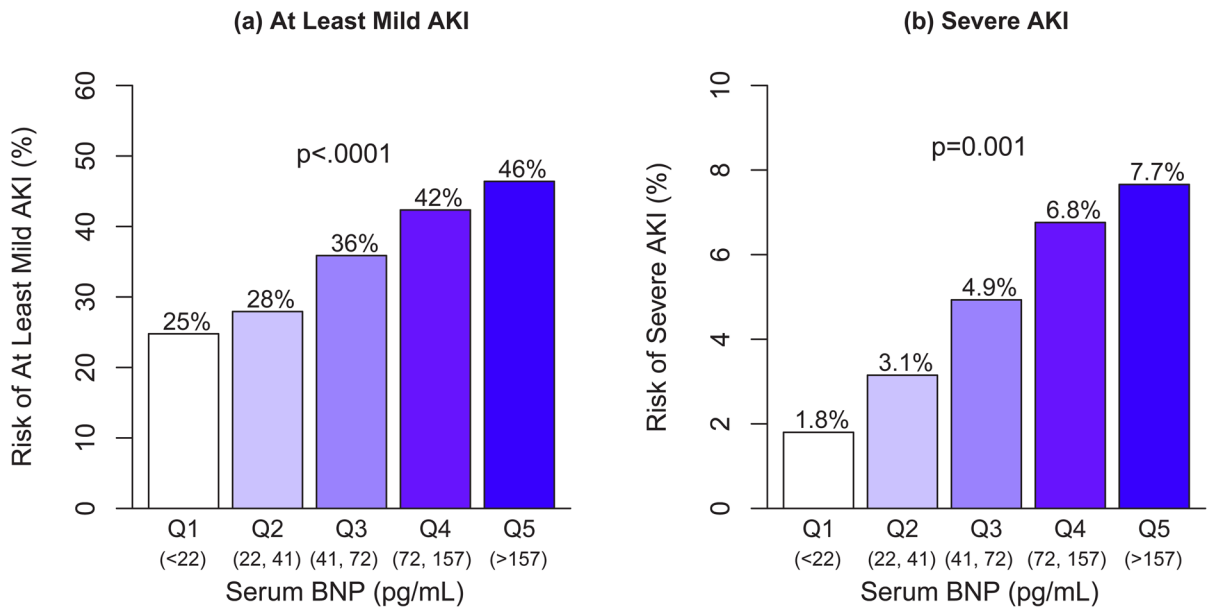

Figure 4.

Incidence of At Least Mild AKI (a) and Severe AKI (b) by Quintiles of Post-operative BNP. AKI defined as during entire hospitalization, at least mild AKI (**A**) defined as ≥50%, ≥0.3 mg/dL or dialysis; severe AKI (**B**) defined as ≥100% or dialysis. Post-operative BNP levels (pg/mL) were measured 0–6 hours following cardiac surgery (mean 0.6 h, SD1.6 h). Abbreviations: Acute kidney injury (AKI); brain natriuretic peptide (BNP)

Table 1

Baseline Characteristics by Pre-operative BNP among 1,139 Patients Undergoing Cardiac Surgery

	Quintile 1 Range [<28] N=227	**Quintile 2 Range [28, 56] N=228**	**Quintile 3 Range [56, 105] N=228**	**Quintile 4 Range [105, 241] N=228**	**Quintile 5 Range [>241] N=228**	**P-value for Trend**
Age (mean, SD)	66.6 (11.6)	71.1 (8.7)	72.8 (8.4)	72.8 (9.8)	74.5 (9.6)	<.0001
< 65 years (n, %)	86 (38%)	50 (22%)	40 (18%)	42 (18%)	28 (12%)	
65–75 years	85 (37%)	100 (44%)	90 (39%)	81 (36%)	75 (33%)	
75–85 years	53 (23%)	73 (32%)	88 (39%)	91 (40%)	101 (44%)	
>85 years	3 (1%)	5 (2%)	10 (4%)	14 (6%)	24 (11%)	
Male (n, %)	177 (78%)	156 (68%)	154 (68%)	140 (61%)	149 (65%)	0.001
White Race (n, %)	212 (93%)	212 (93%)	211 (93%)	219 (96%)	212 (93%)	0.66
Diabetes (n, %)	118 (52%)	93 (41%)	90 (39%)	87 (38%)	81 (36%)	0.0006
Hypertension (n, %)	170 (75%)	177 (78%)	188 (82%)	183 (80%)	178 (78%)	0.30
Myocardial infarction (n, %)	42 (19%)	54 (24%)	62 (27%)	65 (29%)	70 (31%)	0.0022
Heart Failure (n, %)	26 (11%)	32 (14%)	50 (22%)	76 (33%)	108 (47%)	<.0001
Ejection fraction ≤ 40% (n, %)	18 (9%)	19 (10%)	42 (21%)	43 (20%)	98 (46%)	<.0001
Operative Characteristics (n, %)						
Prior Cardiac Surgery	29 (13%)	26 (11%)	25 (11%)	29 (13%)	38 (17%)	0.19
Elective Surgery	192 (85%)	193 (85%)	180 (79%)	178 (78%)	164 (72%)	0.0002
Cardiac catheterization in last 48 hours	13 (6%)	11 (5%)	11 (5%)	10 (4%)	13 (6%)	0.92
Surgery (n, %)						<.0001
CABG	144 (63%)	132 (58%)	113 (50%)	91 (40%)	68 (30%)	
Valve	41 (18%)	57 (25%)	65 (29%)	79 (35%)	89 (39%)	
CABG and valve	42 (19%)	39 (17%)	50 (22%)	58 (25%)	71 (31%)	
Renal Function (mean, SD)						
Pre-op Serum Creatinine (mg/dL)*	1.03 (0.26)	1.01 (0.27)	1.09 (0.31)	1.09 (0.32)	1.21 (0.46)	<.0001
Pre-op eGFR (mL/min per 1.73 m2)	74.3 (19.6)	73.0 (19.5)	67.0 (18.7)	66.7 (18.6)	63.0 (24.5)	<.0001
< 30 mL/min (n, %)	1 (0%)	2 (1%)	3 (1%)	5 (2%)	15 (7%)	
≥ 30 and < 60	56 (25%)	57 (25%)	86 (38%)	76 (33%)	100 (44%)	
≥ 60 and > 90	127 (56%)	130 (57%)	119 (52%)	128 (56%)	78 (34%)	
≥ 90	43 (19%)	39 (17%)	20 (9%)	19 (8%)	35 (15%)	

	Quintile 1 Range [<28] N=227	Quintile 2 Range [28, 56] N=228	Quintile 3 Range [56, 105] N=228	Quintile 4 Range [105, 241] N=228	Quintile 5 Range [>241] N=228	P-value for Trend
Preoperative Serum BNP (median, IQR)	16.8 (10.0, 23.1)	40.8 (34.7, 48.3)	77.6 (66.2, 88.6)	151.2 (133.1, 196.7)	422.8 (322.8, 599.2)	<.0001

* To convert serum creatinine values to mmol/L, multiply by 88.4*; Abbreviations*: coronary artery bypass grafting (CABG); estimated glomerular filtration rate (eGFR); brain natriuretic peptide (BNP; in pg/mL); interquartile range (IQR)

Table 2

Association of BNP Quintiles with Risk for At Least Mild and Severe Acute Kidney Injury, and Other Post-operative Outcomes

BNP Quintile	At Least Mild AKI			Severe AKI			Other Outcomes		
(cut points, pg/mL)	% AKI cases	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	% AKI cases	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	% In-hospital Death or Dialysis	Length of stay in ICU, mean (SD)	Length of stay in hospital, mean (SD)
Q1 (<28)	24.7	1 (referent)	1 (referent)	1.8	1 (referent)	1 (referent)	1.3	2.5 (4.3)	6.6 (5.0)
Q2 (28, 56)	28.5	1.16 (0.85, 1.57)	1.24 (0.91, 1.69)	3.1	1.74 (0.52, 5.87)	1.69 (0.51, 5.62)	1.8	2.6 (6.8)	7.1 (6.8)
Q3 (56,105)	37.3	1.51 (1.14, 2.01)	1.48 (1.10, 1.97)	7.0	3.98 (1.35, 11.73)	3.38 (1.13, 10.06)	0.9	3.1 (6.2)	8.5 (9.2)
Q4 (105, 241)	39.5	1.60 (1.21, 2.11)	1.59 (1.19, 2.11)	6.1	3.48 (1.16, 10.43)	2.92 (0.96, 8.90)	1.8	3.3 (12.2)	9.0 (14.7)
Q5 (>241)	48.7	1.97 (1.52, 2.57)	1.87 (1.40, 2.49)	7.5	4.23 (1.45, 12.38)	3.17 (1.06, 9.48)	7.0	4.9 (9.0)	11.4 (12.3)
Unadjusted p for trend	<.0001			0.0017			0.0006	<.0001	<.0001
Adjusted p for trend	<.0001			0.049			0.047	0.047	0.0016

Adjusted for age (per year), gender, race, non-elective surgery, type of surgery, cardiac catheterization in the last 48 hours, diabetes, hypertension, myocardial infarction, chronic heart failure, pre-op eGFR (continuous), and site. The number of patients per quintile: Q1 n=227, Q2 n=228, Q3 n=228, Q4 n=228, Q5 n=228.

Abbreviations: Brain natriuretic peptide (BNP); acute kidney injury (AKI); relative risk (RR); confidence interval (CI); intensive care unit (ICU); standard deviation (SD)

Table 3

Areas Under the Receiver Operating Characteristic Curve and Continuous Net Reclassification Index of Pre-operative BNP and Clinical Risk Factors for AKI Risk Following Cardiac Surgery

	At Least Mild AKI	Severe AKI
Area under the ROC curve (95% CI)		
Serum BNP*	0.604 (0.569, 0.639)	0.628 (0.562, 0.695)
Clinical model†	0.667 (0.635, 0.699)	0.725 (0.659, 0.793)
Serum BNP & clinical model	0.682 (0.650, 0.714)	0.736 (0.670, 0.802)
Continuous Net Reclassification Index (95% CI)	0.183 (0.061, 0.314)	0.231 (−0.067, 0.506)

*log-transformed continuous BNP

†Clinical model includes age (per year), gender, race, non-elective surgery, type of surgery, cardiac catheterization in the last 48 hours, diabetes, hypertension, myocardial infarction, chronic heart failure, pre-op eGFR (continuous), and site

AKI defined as during entire hospitalization, at least mild AKI defined as ≥50% or ≥0.3mg/dL, severe AKI defined as ≥100% or dialysis.

Abbreviations: Acute kidney injury (AKI), brain natriuretic peptide (BNP)