B-type natriuretic peptide as a surrogate marker for survival in patients undergoing cardiac surgery

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Background: B-type natriuretic peptide (BNP) is a biomarker predicting morbidity and mortality in patients with congestive heart failure. However, the usefulness of pre- or postoperative BNP levels in patients undergoing cardiac surgery remains uncertain. We sought to determine the association of pre- or postoperative BNP levels on mortality in patients undergoing cardiac surgery under cardiopulmonary bypass (CPB).

Methods: This study retrospectively evaluated 1,642 patients undergoing cardiac surgery under CPB over 2 years. The primary outcomes were 30-day and overall mortality after cardiac surgery.

Results: The 30-day mortality rate was 3.0% (n=49), and the overall mortality occurred in 118 patients during the mean follow-up period of 24.9±8.9 months. In multivariable analyses, preoperative BNP level was not significantly associated with 30-day [odds ratio (OR), 1.03; 95% confidence interval (CI), 0.99–1.06; P=0.06] or overall [hazard ratio (HR), 1.01; 95% CI, 0.98–1.03; P=0.50] mortalities. However, the postoperative BNP level was significantly associated with 30-day (OR, 1.05; 95% CI, 1.02–1.09; P=0.001) and overall (HR, 1.03; 95% CI, 1.01–1.04; P=0.01) mortalities. As a sensitivity analysis, postoperative BNP levels were divided into quartiles. The top quartile (≥484 pg/mL) was identified as a strong predictor of overall mortality (HR, 2.18; 95% CI, 1.14–4.19; P=0.02).

Conclusions: Preoperative BNP level was not associated with mortality after cardiac surgery. However, postoperative BNP level was associated with mortality after cardiac surgery, especially in patients with high levels (≥484 pg/mL). Further studies in larger cohorts are necessary to validate these results.

Keywords: Natriuretic peptide; brain; cardiac surgical procedures; heart failure; cardiopulmonary bypass (CPB)

Introduction

B-type natriuretic peptide (BNP), secreted by myocytes in response to increased ventricular wall tension (1), is a well-known biomarker that predicts morbidity and mortality in patients with congestive heart failure (2-4) and acute coronary syndrome (5,6). Consequently, many studies on the usefulness of BNP levels in cardiac surgery are limited to patients undergoing coronary artery bypass grafting (CABG). Fox *et al.* (7,8) reported that an elevated perioperative BNP level was an independent predictor of early and late adverse outcomes in patients undergoing CABG. However, the clinical implications of perioperative BNP levels in cardiac surgeries under cardiopulmonary bypass (CPB) remain

unclear as CPB is known to induce intraoperative plasma BNP release (9,10). In addition, few studies have evaluated the usefulness of perioperative BNP levels as a prognostic marker in cardiac surgeries under CPB and are also limited by their small sample sizes (11,12). Therefore, we sought to determine the usefulness of pre- or postoperative BNP levels for the prediction of mortality in patients undergoing cardiac surgery under CPB. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-2375).

Methods

Study population

This retrospective cohort analysis was conducted at Asan Medical Center, which is a tertiary care center in Seoul, Korea. Between January 2014 and December 2015, a total of 2,845 adult patients underwent cardiac surgery under Patients who underwent heart transplantation or cardiac surgery without CPB support or those who had missing preoperative and postoperative plasma BNP level (n=52) were excluded. The remaining 1,642 patients were reviewed. Follow-up information regarding outcomes was obtained from out-patient visits, telephone interviews, and from the medical records of national health insurance. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Asan Medical Center, which waived the requirement for informed consent (IRB number: 2017-0412).

Outcomes

The primary outcomes were 30-day and overall mortality after cardiac surgery during the follow-up period. The preoperative BNP level was the most recent available value recorded within one month prior to surgery. The median interval between preoperative BNP measurement and the operation was 1 day [interquartile range (IQR), 1–3]. The postoperative BNP level was measured within two days after cardiac surgery.

Statistical analysis

Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC). Data are expressed as the median and interquartile ranges for continuous variables and as

numbers and percentages for categorical variables. Missing data in the baseline characteristics were handled by multiple imputations. P values ≤0.05 was considered statistically significant for all comparisons.

Univariable and multivariable analyses were performed for the entire patient cohort using logistic regression to determine predictors of 30-day mortality and a Cox proportional hazard model to determine overall mortality. In all Cox proportional hazards regression analyses, subjects were censored at the time of postoperative loss to follow-up in cases of loss to follow-up. For the multivariable analyses, variables assessed in univariable models were included in the final multivariable analyses based on clinical importance if their univariable significance was <0.05.

We used a logistic regression model to estimated risks of '30-day mortality' and 'death within 2-year' based on a significant predictor revealed in the multivariable model. The multicollinearity of the covariates was assessed by variance inflation factor. Pre- and postoperative BNP level data were entered separately into the final multivariable models as an independent variable to evaluate each independent effect on outcomes. Then, pre- and postoperative BNP were entered together into the final multivariable models to identify the additional interaction to the outcomes.

For sensitivity analysis, the postoperative BNP levels were divided into quartiles and entered separately into the multivariable model to provide additional clinical information. Kaplan-Meier curves were created to compare overall survival between patients in each postoperative BNP quartile. Log-rank tests were used to assess the significance of differences between the stratified curves.

To validate the best threshold value of postoperative BNP for overall mortality was obtained using receiver operating characteristic (ROC) curves.

Results

As shown in flow diagram (*Figure 1*), 1,642 patients out of the total 2,845 patients undergoing cardiac surgery during the study period were finally enrolled and reviewed. 1,151 patients undergoing cardiac surgeries without CPB, mechanical circulatory support, or heart transplantation were excluded and 52 patients with missing both pre- and postoperative BNP level were also excluded in the analysis. Among this study population, patients with preoperative BNP and with postoperative BNP were 1,452 and 1,208 patients, respectively. The baseline and operative characteristics of 1,642 patients enrolled in this
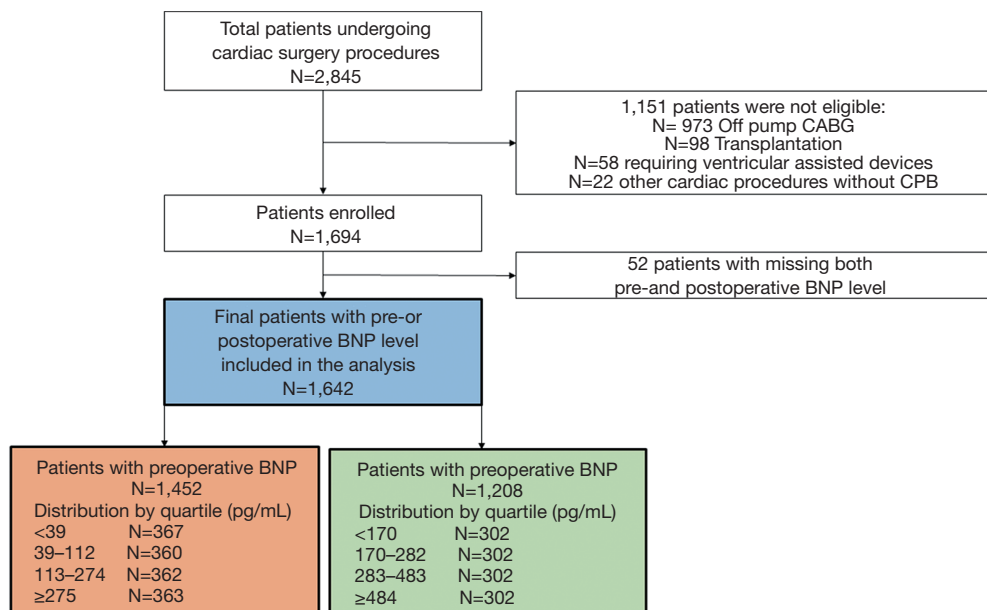
Figure 1 The study population. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; BNP, B-type natriuretic peptide.

study are summarized in *Table 1*. Median age was 60.0 (50.0–69.0) years. Most patients (64.7%) received valve surgery whereas CABG was performed in 110 patients (6.7%). Median CPB and aortic cross clamp (ACC) time was 134.0 (99.0–182.0) and 81.0 (53.0–114.0) minutes, respectively. The median pre- and postoperative BNP levels were 112.0 (38.0–275.0) pg/mL and 282.0 (170.0–483.5) pg/mL, respectively. Missing data rates for preoperative hemoglobin and creatinine level was 1.6% and 1.4%, respectively. Missing data rates for other variables were less than 1%. Follow-up was completed in all patients. 30-day mortality occurred in 49 (3.0%) patients. The overall mortality rate occurred in 118 patients during the mean follow-up period of 24.9±8.9 months.

Preoperative BNP level and mortality

A total of 1,452 patients with preoperative BNP levels were analyzed without including postoperative BNP variable. Multivariable analyses showed that preoperative BNP level was not associated with 30-day or overall mortality (P>0.05). These findings are summarized in *Tables 2,3*.

Postoperative BNP level and mortality

A total of 1,208 patients with postoperative BNP levels were analyzed without including preoperative BNP variable.

Multivariable analysis identified postoperative BNP level as risk factor for 30-day and overall mortalities (OR, 1.05; 95% CI, 1.02–1.09; P=0.001 and HR, 1.03; 95% CI, 1.01–1.04; P=0.01, respectively), as summarized in *Tables 4,5*. As postoperative BNP level was identified as a risk factor, probabilities of risks of 30-day mortality and death within 2 years according to postoperative BNP level were estimated by logistic regression models. It revealed a significant relation as shown in *Figure 2A* and *B*. According to the ROC curves, cutoff values of postoperative BNP for 30-day and overall mortality were 790 and 483 pg/mL, respectively.

Pre- and postoperative BNP levels and mortality

Both pre- and postoperative BNP levels were measured for 1,018 patients. These patients were analyzed including both pre- and postoperative BNP variables in the model. In the multivariable analysis, postoperative BNP, but not preoperative BNP was associated with 30-day and overall mortality (OR: 1.04; 95% CI: 1.01–1.08; P=0.01 and HR: 1.02; 95% CI: 1.002–1.05; P=0.03, respectively) (*Tables 6,7*).

Sensitivity analysis

Postoperative BNP levels divided into quartiles and associations with mortality

The patients were divided into quartiles based on postoperative

Table 1 Baseline characteristics

Variable	30-day mortality (n=49)	Survivors (n=1,593)	Total (n=1,642)	P value
Sex, male	23 (46.9)	881 (55.3)	904 (55.1)	0.31
Age, years	66.0 (57.0–74.0)	60.0 (50.0–69.0)	60.0 (50.0–69.0)	<0.001
DM	14 (28.6)	253 (15.9)	267 (16.3)	0.03
Hypertension	27 (55.1)	634 (39.8)	661 (40.3)	0.05
CVA	2 (4.1)	80 (5.0)	82 (5.0)	1.00
RRT	7 (14.3)	47 (3.0)	54 (3.3)	<0.001
Euro score	3.4 (1.6–7.2)	1.5 (0.8–2.8)	1.5 (0.8–2.8)	<0.001
LVEF	57.3 (48.0–64.0)	61.0 (55.3–65.3)	61.0 (55.1–65.2)	0.015
Medications				
ARB	18 (36.7)	527 (33.1)	545 (33.2)	0.70
Diuretics	21 (42.9)	652 (40.9)	673 (41.0)	0.90
Hypoglycemic agents	14 (28.6)	287 (18.0)	301 (18.3)	0.09
Statin	16 (32.7)	519 (32.6)	535 (32.6)	1.00
Antiplatelet	20 (40.8)	491 (30.8)	511 (31.1)	0.18
Laboratory findings				
Hemoglobin, g/dL	10.9 (9.6–12.7)	13.0 (11.6–14.1)	12.9 (11.5–14.1)	<0.001
Creatinine, mg/dL	1.0 (0.8–1.6)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.005
Total bilirubin, mg/dL	0.7 (0.5–1.2)	0.5 (0.4–0.8)	0.5 (0.4–0.8)	0.004
Albumin, g/dL	3.3 (2.8–3.7)	3.7 (3.5–4.0)	3.7 (3.4–4.0)	<0.001
BUN, mg/dL	19.0 (14.0–27.5)	16.0 (13.0–21.0)	16.0 (13.0–21.0)	0.005
BNP, pg/mL	187.0 (116.0–490.0)	110.0 (37.5–266.5)	112.0 (38.0–275.0)	0.001
Emergency operation	1 (2.0)	10 (0.6)	11 (0.6)	0.28
Procedures				0.18
Valve	28 (57.1)	1,035 (65.0)	1,063 (64.7)	
CABG	2 (4.1)	108 (6.8)	110 (6.7)	
Valve + CABG	4 (8.2)	58 (3.6)	62 (3.8)	
Aorta	11 (22.4)	222 (13.9)	233 (14.2)	
Others	4 (8.2)	170 (10.7)	174 (10.6)	
CPB time, min	185.0 (141.0–295.0)	133.0 (98.0–178.5)	134.0 (99.0–182.0)	<0.001
ACC time, min	104.0 (78.0–160.0)	80.0 (53.0–113.0)	81.0 (53.0–114.0)	0.002
PostBNP, pg/dL	817.0 (307.0–1866.0)	278.0 (168.5–468.5)	282.0 (170.0–483.5)	<0.001
Ventilator duration, days	3.0 (1.5–8.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	<0.001
ICU stay, days	5.0 (2.0–8.5)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	<0.001

Variables were presented as median (IQR) and frequency (percentage). DM, diabetes mellitus; CVA, cerebrovascular accident; RRT, renal replacement therapy; LVEF, left ventricular ejection fraction; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; PostBNP, postoperative BNP; ICU, intensive care unit.

Table 2 Preoperative B-type natriuretic peptide levels and 30-day mortality (n=1,452)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Outcome: 30-day mortality						
Age	1.04	1.01–1.07	0.001	–	–	–
Sex (male)	0.78	0.45–1.38	0.40	–	–	–
DM	2.02	1.08–3.81	0.02	–	–	–
Hypertension	1.69	0.97–2.96	0.12	–	–	–
CVA	0.77	0.19–3.25	0.73	–	–	–
LVEF	0.97	0.95–0.99	0.01	–	–	–
Hemoglobin	0.66	0.58–0.76	<0.001	0.81	0.70–0.96	0.02
Creatinine	1.34	1.17–1.60	<0.001	–	–	–
Preop BNP[†]	1.05	1.02–1.07	<0.001	1.03	0.99–1.06	0.06
Euro score	1.05	1.02–1.09	0.001	1.01	0.95–1.06	0.87
Procedures						
Valve	1	–	–	–	–	–
CABG	0.72	0.17–3.09	0.66	–	–	–
Valve + CABG	2.07	0.61–7.05	0.25	–	–	–
Aorta	2.49	1.17–5.26	0.02	–	–	–
Others*	0.94	0.32–2.72	0.90	–	–	–
CPB time[‡]	1.01	1.01–1.01	<0.001	1.06	1.02–1.09	0.001
ACC time[‡]	1.01	1.01–1.01	<0.001	–	–	–
Post AKI	13.25	7.15–24.59	<0.001	7.61	3.81–15.19	<0.0001

[†], BNP for 100 increase; [‡], CPB time or ACC time for 10 increase. BNP, B-type natriuretic peptide; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; AKI, acute kidney injury.

BNP level (BNP <170 pg/mL, 170≤ BNP <282 pg/mL, 282≤ BNP <484 pg/mL, and BNP ≥484 pg/mL). Of these, the top quartile (BNP ≥484 pg/mL) was associated with a higher risk of 30-day (OR 8.69, 95% CI: 1.93–39.05, P=0.005) and overall mortality (HR 2.18, 95% CI: 1.14–4.19, P=0.02) (*Tables 8,9*). Kaplan-Meier curves comparing the probability of survival in each quartile revealed that patients in the top quartile (BNP ≥484 pg/mL) had increased risk of death (log-rank P<0.001) (*Figure 3*).

Discussion

This study investigated the relationship between pre- and postoperative BNP levels and 30-day and overall mortalities

in patients who underwent cardiac surgery under CPB. The multivariable analysis revealed no significant association between the preoperative BNP level and mortality. However, the postoperative BNP level was strongly associated with 30-day and overall mortalities. Furthermore, postoperative BNP level in the top quartile (BNP ≥484 pg/mL) was identified as a significant risk factor for 30-day and overall mortalities. Therefore, high postoperative BNP was suggested as a helpful surrogate marker for mortality after cardiac surgery.

Our findings regarding preoperative BNP levels seem contradictory to those of previous reports. One meta-analysis investigating the relationship between BNP levels and adverse outcomes after cardiac surgery (13)

Table 3 Preoperative B-type natriuretic peptide levels and overall mortality

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Outcome: overall mortality						
Age	1.03	1.02–1.05	<0.001	1.02	0.99–1.04	0.11
Sex (male)	1.11	0.75–1.65	0.59	–	–	–
DM	2.27	1.49–3.46	<0.001	1.67	0.98–2.82	0.06
Hypertension	1.45	0.98–2.14	0.06	–	–	–
CVA	1.17	0.51–2.66	0.71	–	–	–
LVEF	0.97	0.96–0.99	<0.001	0.99	0.97–1.02	0.60
Hemoglobin	0.65	0.59–0.72	<0.001	0.79	0.69–0.90	<0.001
Creatinine	1.36	1.23–1.50	<0.001	1.33	1.13–1.57	0.001
Preop BNP[†]	1.04	1.03–1.05	<0.001	1.01	0.98–1.03	0.50
Euro score	1.05	1.04–1.07	<0.001	1.03	1.00–1.07	0.04
Procedures						
Valve	1			–	–	–
CABG	1.33	0.63–2.78	0.45	–	–	–
Valve + CABG	1.87	0.80–4.32	0.15	–	–	–
Aorta	2.25	1.35–3.74	0.002	–	–	–
Others	1.07	0.55–2.10	0.83	–	–	–
CPB time[‡]	1.09	1.07–1.12	<0.001	1.06	1.03–1.10	<0.001
ACC time[‡]	1.09	1.06–1.13	<0.001	–	–	–
Post AKI	9.33	6.36–13.69	<0.001	8.55	5.22–13.97	<0.001

[†], BNP for 100 increase; [‡], CPB time or ACC time for 10 increase. BNP, B-type natriuretic peptide; CI, confidence interval; DM, diabetes mellitus; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; AKI, acute kidney injury; HR, hazard ratio.

reported that higher preoperative BNP levels increased mortality after cardiac surgery. However, most studies in this meta-analysis enrolled patients who underwent CABG only or a combination of few valve surgeries and CABG. Except for the study by Fox *et al.* (8), the study populations were relatively small (<100 patients). Another review paper assessed BNP as a biomarker in common forms of valvular heart disease (14). Four of these studies (15-18) reported a relationship between higher preoperative BNP levels and adverse surgical outcomes. However, the study populations were also small (n=22–144), with limited statistical power. Our study population was relatively large (n=1,642) compared to those in previous studies and included unselected patients undergoing cardiac surgery

under CPB regardless of the specific type of operation. Contrary to the findings of these previous studies, we found that preoperative BNP level was not associated with mortality after cardiac surgery. The broad inclusion criteria may be criticized as contributing to the heterogeneity of the study population. However, our study population was homogenous in terms of undergoing cardiac surgery under CPB regardless of surgery type. Therefore, this study population could reflect the effect of CPB on postoperative BNP levels.

Few studies have evaluated the usefulness of postoperative BNP levels in patients undergoing cardiac surgery. Fox *et al.* (8) proposed that preoperative BNP levels may be better than peak postoperative BNP levels

Table 4 Postoperative BNP and 30-day mortality (n=1,208)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Outcome: 30-day mortality						
Age	1.04	1.01–1.07	0.02	–	–	–
Sex male	0.62	0.32–1.20	0.15	–	–	–
DM	1.68	0.81–3.55	0.16	–	–	–
Hypertension	2.30	1.17–4.52	0.02	–	–	–
CVA	0.24	0.01–4.05	0.32	–	–	–
LVEF	0.98	0.95–1.00	0.06	–	–	–
Hemoglobin	0.69	0.58–0.82	<0.001	0.81	0.66–0.97	0.04
Creatinine	1.25	1.04–1.51	0.02	–	–	–
Euro score	1.05	1.01–1.09	0.009	1.00	0.95–1.06	0.91
Procedures						
Valve	1			–	–	–
CABG	0.83	0.19–3.59	0.80	–	–	–
Valve + CABG	2.01	0.58–6.70	0.27	–	–	–
Aorta	1.46	0.64–3.35	0.37	–	–	–
Others	1.19	0.35–4.05	0.79	–	–	–
CPB time[‡]	1.08	1.04–1.12	<0.001	1.02	0.98–1.07	0.23
ACC time[‡]	1.07	1.01–1.12	<0.001	–	–	–
Post AKI	9.67	4.91–19.0	<0.001	6.59	3.06–14.20	<0.001
Postop BNP[†]	1.08	1.05–1.12	<0.001	1.05	1.02–1.09	0.001

[†], BNP for 100 increase; [‡], CPB time or ACC time for 10 increase. BNP, B-type natriuretic peptide; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; AKI, acute kidney injury.

at predicting prolonged hospitalization and late mortality after CABG. However, several studies on postoperative BNP level had findings consistent with ours, showing postoperative BNP level to be an independent predictor of postoperative cardiac dysfunction, prolonged hospital stay, and mortality (11,12,19). The optimal cutoff postoperative BNP value to predict 30-day mortality based on the ROC method was 790 pg/mL [area under the curve (AUC): 0.71, 59% CI: 0.61–0.82, P<0.001, sensitivity 54.1%, specificity 87.6%], which was the same as the cutoff suggested by Lurati Buse *et al.* (19). The cutoff value for overall mortality was 483 pg/mL (AUC: 0.65, 95% CI: 0.58–0.71, P<0.001, sensitivity 48.9%, specificity 77.1%), which was the same as the critical postoperative value of the top quartile in the sensitivity analysis.

Besides preoperative BNP, any serial change of BNP level between before and after cardiac surgery was not associated with mortalities. Only postoperative BNP was independently associated with mortalities. This may be due to the contributions of other intraoperative or immediate postoperative factors to the increased postoperative BNP level as well as the patient's preoperative condition. Postoperative volume status or inotropic support may be potential factors contributing to postoperative BNP levels even though they were not considered in our study. Among the factors included in our study, longer CPB time was identified as the most significant factor associated with elevated postoperative BNP level in the multiple linear

Table 5 Postoperative BNP and overall mortality

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Outcome: overall mortality						
Age	1.02	1.00–1.04	0.02	1.01	0.99–1.03	0.43
Sex male	1.16	0.78–1.73	0.46			
DM	1.84	1.19–2.85	0.006	1.43	0.88–2.33	0.15
Hypertension	1.49	1.01–2.21	0.05	1.18	0.75–1.85	0.47
CVA	0.80	0.29–2.17	0.66			
LVEF	0.98	0.96–0.99	0.008	1.00	0.98–1.01	0.68
Hemoglobin	0.68	0.62–0.76	<0.001	0.81	0.72–0.90	<0.001
Creatinine	1.30	1.17–1.44	<0.001	1.20	1.05–1.36	0.008
Euro Score	1.05	1.03–1.07	<0.001	1.01	0.98–1.04	0.49
Procedures						
Valve	1			1		
CABG	1.42	0.67–2.98	0.36	1.44	0.60–3.47	0.42
Valve + CABG	1.40	0.56–3.50	0.48	0.84	0.32–2.19	0.72
Aorta	2.08	1.30–3.31	0.002	1.42	0.84–2.42	0.19
Others	1.51	0.74–3.06	0.26	2.89	1.34–6.25	0.01
CPB time‡	1.08	1.05–1.10	<0.001	1.03	0.99–1.07	0.14
ACC time‡	1.07	1.04–1.11	<0.001			
Post AKI	7.07	4.82–10.37	<0.001	4.76	3.00–7.57	<0.001
Postop BNP†	1.03	1.04–1.07	<0.001	1.03	1.01–1.04	0.01

†, BNP for 100 increase; ‡, CPB time or ACC time for 10 increase; BNP, B-type natriuretic peptide; CI, confidence interval; DM, diabetes mellitus; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; AKI, acute kidney injury; HR, hazard ratio.
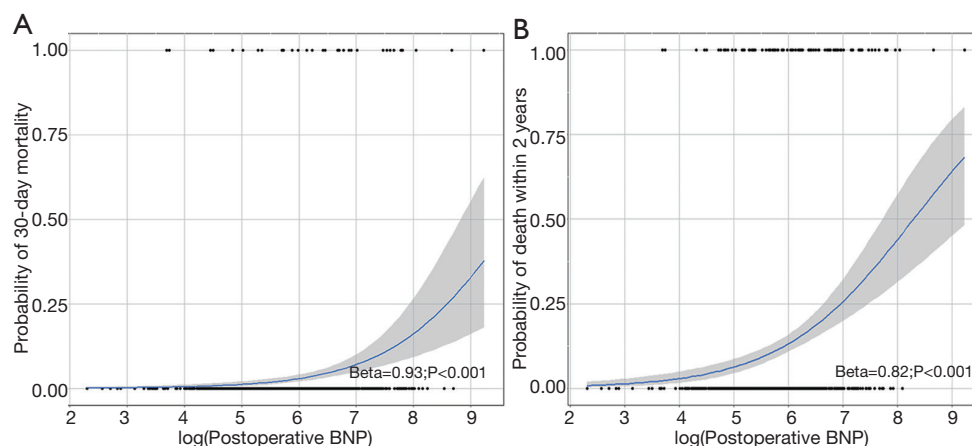
Figure 2 Association between postoperative BNP level and mortalities. (A) Probability of 30-day mortality according to the (log) postoperative BNP level; (B) probability of death within 2-year according to the (log) postoperative BNP level estimated by logistic regression models. BNP, B-type natriuretic peptide.

Table 6 Both preoperative and postoperative BNP and 30-day mortality (n=1,018)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Outcome: 30-day mortality						
Age	1.04	1.01–1.07	0.02	–	–	–
Sex male	0.62	0.32–1.20	0.15	–	–	–
DM	1.68	0.81–3.55	0.16	–	–	–
Hypertension	2.30	1.17–4.52	0.02	–	–	–
CVA	0.24	0.01–4.05	0.32	–	–	–
LVEF	0.98	0.95–1.00	0.06	–	–	–
Hemoglobin	0.69	0.58–0.82	<0.001	–	–	–
Creatinine	1.25	1.04–1.51	0.02	–	–	–
Euro score	1.05	1.01–1.09	0.009	1.02	0.96–1.07	0.45
Pre BNP	1.05	1.02–1.07	<0.001	1.01	0.97–1.06	0.46
Procedures						
Valve	1			–	–	–
CABG	0.83	0.19–3.59	0.80	–	–	–
Valve + CABG	2.01	0.58–6.70	0.27	–	–	–
Aorta	1.46	0.64–3.35	0.37	–	–	–
Others	1.19	0.35–4.05	0.79	–	–	–
CPB time[‡]	1.08	1.04–1.12	<0.001	1.03	0.99–1.08	0.13
ACC time[‡]	1.07	1.01–1.12	<0.001	–	–	–
Post AKI	9.67	4.91–19.0	<0.001	8.24	3.93–20.23	<0.001
Postop BNP[†]	1.08	1.05–1.12	<0.001	1.04	1.01–1.08	0.01

[†], BNP for 100 increase; [‡], CPB time or ACC time for 10 increase. BNP, B-type natriuretic peptide; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; AKI, acute kidney injury. bypass grafting; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; AKI, acute kidney injury.

regression analysis. Ischemic reperfusion injury occurs during CPB and CPB induces BNP release during cardiac surgery. According to earlier reports (11,12), CPB increases BNP release in the initial stages of reperfusion following global ischemia. These reported that BNP levels returned to baseline within hours or days of reperfusion initiation. Therefore, the postoperative BNP level measured on the first day after surgery may reflect the combined effects of ischemic/reperfusion injury during CPB support. Also, postoperative alterations in renal function might affect the increased postoperative BNP level because one of the BNP clearance mechanisms is urinary excretion (20). However, postoperative creatinine level did not show significant correlation with postoperative BNP level in our study (r=0.18).

Other possible mechanisms contributing to the elevation of postoperative BNP level are acute changes in systolic or diastolic function after cardiac surgery and neurohormonal compensation for cardiac dysfunction. As BNP is more sensitive, specific and accurate than an echocardiography in detecting myocardial dysfunction, those patients with high postoperative BNP could have diastole dysfunction or possibly high levels of vasoconstrictor neurohormonal factors such as norepinephrine, angiotensin II or tumor

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Table 7 Both preoperative and postoperative BNP and overall mortality

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Outcome: overall mortality						
Age	1.02	1.00–1.04	0.02	1.01	0.99–1.03	0.26
Sex male	1.16	0.78–1.73	0.46	–	–	–
DM	1.84	1.19–2.85	0.006	1.46	0.87–2.46	0.15
Hypertension	1.49	1.01–2.21	0.05	1.13	0.69–1.85	0.64
CVA	0.80	0.29–2.17	0.66	–	–	–
LVEF	0.98	0.96–0.99	0.008	1.00	0.98–1.02	0.95
Hemoglobin	0.68	0.62–0.76	<0.001	0.81	0.71–0.91	0.001
Creatinine	1.30	1.17–1.44	<0.001	1.20	1.04–1.39	0.01
preBNP	1.04	1.03–1.05	<0.001	1.00	0.98–1.03	0.77
Euro score	1.05	1.03–1.06	<0.001	1.02	0.99–1.05	0.23
Procedures						
Valve	1	–	–	1	–	–
CABG	1.42	0.67–2.98	0.36	1.20	0.47–3.09	0.70
Valve + CABG	1.40	0.56–3.50	0.48	0.66	0.23–1.92	0.44
Aorta	2.08	1.30–3.31	0.002	1.47	0.82–2.65	0.20
Others	1.51	0.74–3.06	0.26	3.30	1.53–7.10	0.002
CPB time[‡]	1.08	1.05–1.10	<0.001	1.04	1.00–1.07	0.053
ACC time[‡]	1.07	1.04–1.11	<0.001	0.99	0.94–1.04	0.59
Post AKI	7.07	4.82–10.37	<0.001	5.38	3.25–8.91	<0.001
Postop BNP[†]	1.03	1.04–1.07	<0.001	1.02	1.002–1.05	0.03

[†], BNP for 100 increase; [‡], CPB time or ACC time for 10 increase. BNP, B-type natriuretic peptide; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; AKI, acute kidney injury; HR, hazard ratio.

Table 8 Postoperative BNP levels divided into quartiles and associations with 30-day mortality

Variables	OR	95% CI	P value
Outcome: 30-day mortality			
Postoperative BNP (pg/mL)			
<170	4.10	0.80–21.08	0.09
170–282	1[†]		
283–483	2.50	0.47–13.29	0.28
≥484	8.69	1.93–39.05	0.005

[†], the quartile with lowest mortalities in each outcome was used as a reference. BNP, B-type natriuretic peptide.

Table 9 Postoperative BNP levels divided into quartiles and associations with overall mortality

Variables	HR	95% CI	P value
Outcome: overall mortality			
Postoperative BNP (pg/mL)			
<170	1[†]		
170–282	1.03	0.49–2.15	0.94
283–483	1.03	0.50–2.15	0.93
≥484	2.18	1.14–4.19	0.02

[†], the quartile with lowest mortalities in each outcome was used as a reference. BNP, B-type natriuretic peptide.
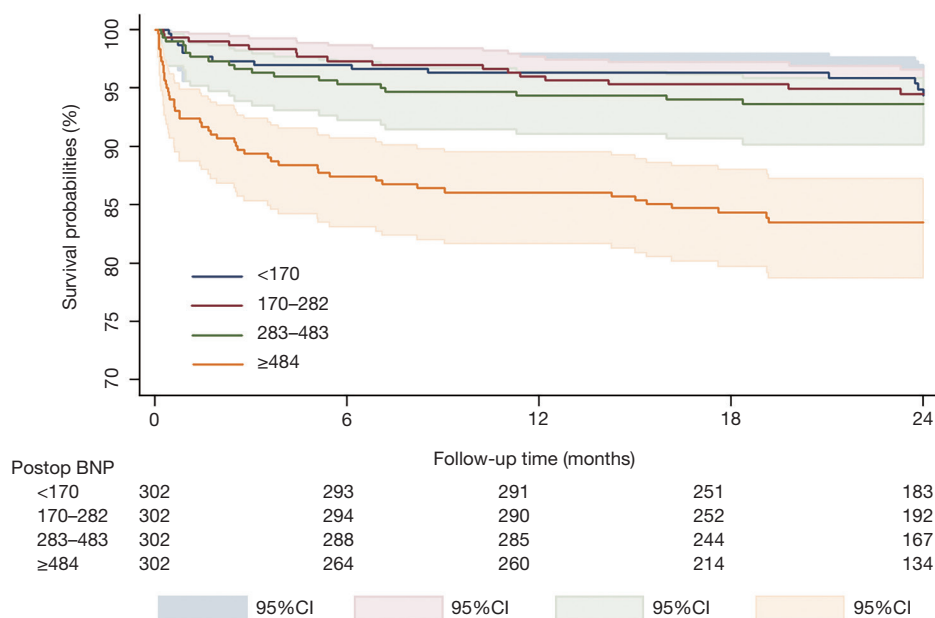
Figure 3 The probability of overall survival of the postoperative BNP level according to quartiles during the follow-up period. Increased risk of mortality in the top quartile (BNP ≥484 pg/mL) (orange line) compared to the bottom three quartiles (green, red, and blue line) (P<0.001). BNP, B-type natriuretic peptide.

necrosis factor. These suboptimal conditions, which were not managed properly during admission, could lead to chronic heart failure during the follow-up period. In addition, a non-cardiac event, such as infection or pneumonia, could contribute to decompensated heart failure in the long term.

While postoperative BNP level is a useful surrogate marker allowing primary physicians to flag patients at risk of death after cardiac surgery, our results could not suggest any practical guideline to optimize the care and management of these patients. The possible recommendations include closer monitoring during hospital stays with frequent checkups such as echocardiography and frequent outpatient clinic follow-up with optimal medical management of underlying medical problems.

This study has several limitations. First, this was a retrospective observational study. While multivariable adjustment analysis and were performed to reduce bias, many potentially important confounders remained. Especially, preoperative or postoperative BNP level was measured without a standardized study protocol. This diverse timing of BNP measurement might induce bias to the study results. Also, postoperative factors such as right ventricular function, volume status, inotropic support and newly developed arrhythmia that might affect the elevation of postoperative BNP levels were not validated

in this study. Second, in the risk factor analysis for 30-day mortality, variables with a statistical significance in univariable analysis were selected as candidates for the final multivariable models based on the clinical relevance and importance to avoid overfitting the model, which could be another bias. Third, even though this study included a relatively large cohort compared to those in previous studies, the patient population included the various types of cardiac surgery under CPB. In addition, this study excluded 995 patients who underwent cardiac surgery without CPB; therefore, the results may not be generalizable to those patients. Finally, some patients were excluded for a lack of available perioperative BNP values, which may raise an issue of selection bias. However, relatively few patients were excluded for this reason (n=52, 3.1%); therefore, the impact of this exclusion on the overall study results may be limited.

Conclusions

Preoperative BNP level was not significantly associated with mortality following cardiac surgery under CPB. However, postoperative BNP level was identified as a useful surrogate marker for predicting postoperative mortality. High postoperative BNP level (≥484 pg/mL) was strongly associated with mortality. Further prospective studies in

larger cohorts are necessary to verify the predictive values of postoperative BNP levels on cardiac surgical outcomes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-2375

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-2375). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Asan Medical Center, which waived the requirement for informed consent (IRB number: 2017-0412).

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