Clinical Correlates and Prognostic Value of B-Type Natriuretic Peptide in Left Ventricular Assist Device Recipients With Cardiogenic Shock: Insights from INTERMACS

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B-type natriuretic peptide (BNP) is a cardiac-derived hormone used for diagnosing, prognosticating, and risk stratification of heart failure.[1] Though BNP levels differ by sex, obesity, and race/ethnicity, the prognostic value of BNP for heart failure remains intact in these subgroups.[2,3] However, data characterizing BNP levels in end-stage heart failure patients with cardiogenic shock is limited. This nationwide Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) study characterized BNP levels and tested the association of BNP levels with clinical outcomes in stage D heart failure patients with cardiogenic shock.

Patients receiving a continuous-flow LVAD between 2005 and 2017 with cardiogenic shock (INTERMACS profiles 1-3) and BNP data were included. BNP levels were assessed at the time of LVAD implantation. The cohort was divided into quartiles based on BNP values. The primary outcome was long-term mortality post-LVAD implantation. Long-term mortality was assessed in LVAD recipients alive at 1-month post-implantation. Secondary outcomes of the study included post-LVAD implantation peri-operative mortality (within 30 days of LVAD implantation), cardiovascular mortality, arrhythmias, and right heart failure.

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All analyses were conducted on SAS 9.4 (Cary, NC). Continuous and categorical variables were compared using the Wilcoxon rank sum and Chi-square tests, respectively. Cox regression models were used to assess the association of BNP levels with the study outcomes after accounting for age, sex, race/ethnicity, BMI, INTERMACS profile, estimated glomerular filtration rate, implantation year, device strategy, employment status, education level, and implantation center volume.[4,5] The model assessing peri-operative mortality was additionally adjusted for temporary circulatory support in the past 48 hours (extra-corporeal membrane oxygenation or intra-aortic balloon pump), intravenous inotrope use, right atrial pressure, and pulmonary capillary wedge pressure. For the primary outcome, a Fine and Gray sub-distribution model was used to account for the competing risk of heart transplantation. A two-sided $p < 0.05$ was considered statistically significant.

Among 7,290 LVAD recipients with cardiogenic shock, the median value of BNP was 859 (427, 1,614) pg/mL. Upon stratification by factors known to influence BNP, the pre-implantation BNP levels were lower in males, non-Hispanic Blacks, and obese patients compared with their respective counterparts. (Table 1) Compared with the first quartile of BNP, the risk for long-term mortality in the second quartile was 1.06 (95%CI: 0.94-1.20), the third quartile was 0.97 (95%CI: 0.85-1.10), and the fourth quartile was 1.04 (95%CI: 0.91-1.18). The risk of peri-operative mortality was 1.06 (95%CI: 0.67-1.70) in the second quartile of BNP, 1.30 (95%CI: 0.83-2.02) in the third quartile of BNP, and 1.27 (95%CI: 0.81-1.98) in the fourth quartile of BNP compared with the first quartile of BNP. Taking the lowest quartile of BNP as the reference group, the risk for cardiovascular mortality for the second quartile was 0.76 (95%CI: 0.55-1.05), the third quartile was 0.98 (95%CI: 0.73-1.32), and the fourth quartile was 0.89 (95%CI: 0.65-1.23). With the lowest quartile of BNP as the reference group, the risk for arrhythmias in the second quartile was 0.98 (95%CI: 0.87-1.11), the third quartile was 0.94 (95%CI: 0.83-1.06), and the fourth quartile was 1.04 (95%CI: 0.92-1.17). With the lowest quartile of BNP as the reference group, the risk for right heart failure was similar in the second [HR_{adj}: 1.01 (95%CI: 0.88-1.15)], third [HR_{adj}: 0.97 (95%CI: 0.84-1.11)], and fourth [HR_{adj}: 1.04 (95%CI: 0.91-1.20)] quartiles of BNP. The risk of long-term mortality [HR_{adj}: 1.01 (95%CI: 0.97-1.06)], peri-operative mortality [HR_{adj}: 1.11 (95%CI: 0.94-1.30)], cardiovascular mortality [HR_{adj}: 1.00 (95%CI: 0.90-1.11)], arrhythmias [HR_{adj}: 1.03 (95%CI: 0.98-1.07)], right heart failure [HR_{adj}: 1.01 (95%CI: 0.97-1.06)] was not associated with a log-unit increase in BNP levels. Figure 1 summarizes the association of BNP levels with study outcomes.

A sensitivity analysis of 3,390 LVAD recipients assessing the prognostic value of NT-proBNP for mortality was performed. Compared with the first quartile of NT-proBNP, the risk of long-term mortality was similar in the second [0.88 (95%CI: 0.71-1.09)], third [0.88 (95%CI: 0.71-1.09)], and fourth [1.14 (95%CI: 0.92-1.42)] quartiles of NT-proBNP. Similarly, the risk of peri-operative mortality in the second [0.85 (95%CI: 0.46-1.57)], third [1.01 (95%CI: 0.55-1.84)], and fourth [0.69 (95%CI: 0.36-1.34)] quartiles of NT-proBNP was comparable to the first quartile of NT-proBNP. There was no association of per unit increase in log NT-proBNP with the risk of long-term mortality [HR_{adj}: 1.07 (95%CI: 0.99-1.15)] or peri-operative mortality [HR_{adj}: 0.96 (95%CI: 0.79-1.17)].

This nationwide study of >7,000 LVAD recipients characterized and assessed the prognostic value of BNP in stage D heart failure patients with cardiogenic shock. BNP levels were lower in males, non-Hispanic Blacks, and obese individuals compared with their respective counterparts suggesting that factors affecting BNP levels in healthy individuals[2,3,6,7] persist throughout the clinical spectrum of heart failure. Additionally, BNP levels were not associated with mortality or any adverse events such as right heart failure and arrhythmias.

BNP levels in end-stage heart failure are not used to guide therapeutic decisions. The current study informs the broader cardiology audience about the futility of measuring BNP in a protocolized manner in patients with end-stage heart failure due to the lack of prognostic value for mortality or other adverse outcomes. Considering the shift of device strategy to destination therapy in the contemporary era[8], biomarkers with intact prognostic ability may improve patient selection and promote judicious utilization of limited healthcare resources.

Given the lack of prognostic value of a single biomarker in LVAD recipients, a multi-biomarker approach representing different pathophysiological pathways may have prognostic value in this patient population.[9] Considering that the offloading of the left ventricle by an LVAD increases the circulatory burden of the right ventricle, about 35% of LVAD recipients develop right ventricular failure.[10] Therefore, a marker that can help predict right heart failure in LVAD recipients can be of great clinical significance. These markers may be combined with other variables to develop a prognostic score for end-stage heart failure patients. Machine-learning models may be employed to develop a comprehensive score incorporating a large number of variables that accurately estimate the risk of post-LVAD adverse events. These scores may guide clinical decision-making by allowing weighing the risk of adverse outcomes after LVAD implantation against the potential years of life gained.

Limitations of this study include the use of self-reported race/ethnicity, exclusion of patients without BNP measurements, and the timing of the BNP measurements before LVAD implantation was not standardized.

In summary, BNP levels in patients with Stage D heart failure varied by sex, race/ethnicity, and BMI, with lower levels noted in males, non-Hispanic Blacks, and obese patients. BNP values did not predict mortality or other adverse events post-LVAD implantation. The role of routine measurement of pre-implantation BNP in LVAD recipients for prognostication requires further investigation.

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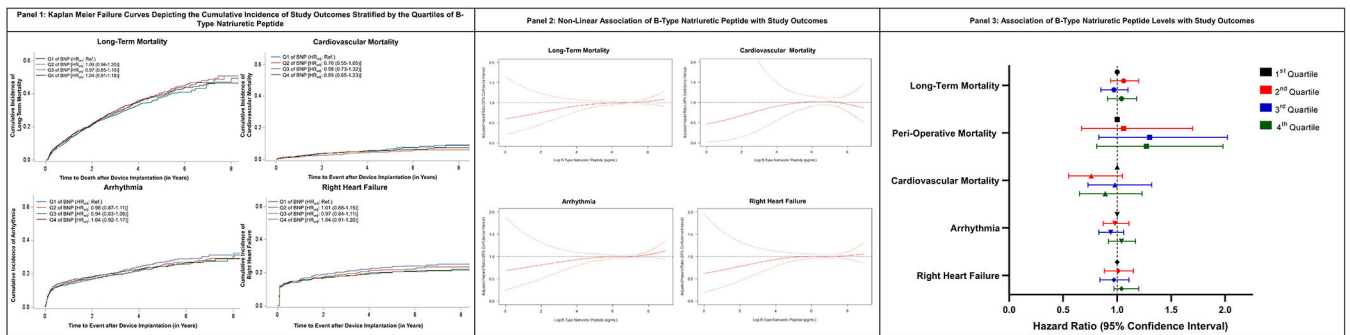
Figure 1: Association of B-Type Natriuretic Peptide with Study Outcomes in Continuous Flow Left Ventricular Assist Device Recipients

Panel 1: Kaplan Meier Failure Curves Depicting the Cumulative Incidence of Study Outcomes Stratified by the Quartiles of B-Type Natriuretic Peptide

The cumulative incidence curves for long-term mortality, cardiovascular mortality, right heart failure, and arrhythmia stratified by the quartiles of B-type natriuretic peptide (BNP) have been depicted. Quartiles 1, 2, 3, and 4 of BNP have been presented in blue, red, green, and brown, respectively.

Panel 2: Non-Linear Association of B-Type Natriuretic Peptide with Study Outcomes

The figure represents the non-linear association of B-type natriuretic peptide (BNP) with long-term mortality, cardiovascular mortality, arrhythmia, and right heart failure. Restricted cubic spline modeling adjusted for age, sex, race/ethnicity, body mass index, INTERMACS profile, estimated glomerular filtration rate (2021 CKD-EPI creatinine equation), implantation year, device strategy, employment status, education level, and volume of the center at which the device was implanted was used to demonstrate the non-linear association of BNP and study outcomes.

Panel 3: Association of B-Type Natriuretic Peptide Levels with Study Outcomes

Multivariable-adjusted Cox proportional hazard regression models were used to assess the risk of the study outcomes which accounted for age, sex, race/ethnicity, body mass index, INTERMACS profile, estimated glomerular filtration rate (2021 CKD-EPI creatinine equation), implantation year, device strategy, employment status, education level, and volume of the center at which the device was implanted. The Cox model for peri-operative mortality was additionally adjusted for extra-corporeal membrane oxygenation use in the past 48 hours, intra-aortic balloon pump use in the past 48 hours, intravenous inotrope use, right atrial pressure, and pulmonary capillary wedge pressure. The first, second, third, and fourth quartiles of BNP are presented in black, red, blue, and green, respectively.

Table 1:

Median Absolute and Log-Transformed Values of B-Type Natriuretic Peptide Stratified by Race/Ethnicity, Gender, and Body Mass Index

	Absolute value	Log Transformed Value	p-values	
			Unadjusted	Adjusted*
Race/Ethnicity				
Non-Hispanic White (n=4,532)	870 (438, 1,639)	6.77 (6.08, 7.40)	<0.001	0.002
Non-Hispanic Black (n=1,836)	777 (362, 1,514)	6.66 (5.89, 7.32)		
Sex				
Male (n=5,670)	851 (429, 1,577)	6.75 (6.06, 7.36)	0.07	0.27
Female (n=1,620)	893 (404, 1,765)	6.79 (6.00, 7.48)		
Body Mass Index				
<25 kg/m² (n=2,389)	1,186 (630,2,170)	7.09 (6.45, 7.68)	<0.001	<0.001
25-30 kg/m² (n=2,289)	873 (438, 1,632)	6.77 (6.08, 7.40)		
30 kg/m² (n=2,612)	642 (311, 1,170)	6.46 (5.74, 7.06)		

Median (interquartile range) of BNP values depicted in pg/mL.

*
Adjusted for age, sex, body mass index, and race/ethnicity