

## BNP, CRP and D-Dimer: A Robust Biomarker Panel for Heart Failure Diagnosis?

Nandini Nair<sup>1,3\*</sup>, Daniel Jupiter<sup>2,5</sup>, Sheba John<sup>1</sup> and Enrique Gongora<sup>2,4</sup>

<sup>1</sup>Division of Cardiology, Scott and White Memorial Hospital, Temple, TX, USA

<sup>2</sup>Division of Cardiothoracic Surgery, Scott and White Memorial Hospital, Temple, TX, USA

<sup>3</sup>Division of Cardiology, Texas Tech Health Sciences Center, Lubbock, TX, USA

<sup>4</sup>Memorial Cardiac and Vascular Institute, Hollywood, FL, USA

<sup>5</sup>Preventive and Community Medicine, UTMB, Galveston, TX, USA

\*Corresponding Author: Nandini Nair, Division of Cardiology, Texas Tech Health Sciences Center, Lubbock, TX, USA.

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### Abstract

Inflammatory and procoagulant pathways are activated in heart failure. This study tests the utility of addition of CRP and D-dimer to BNP for diagnosing acute heart failure. For each variable we determined area under a ROC curve (AUC) using variable level as cutoff for discriminating acute heart failure. For prediction logistic regression (LR) model and support vector machine (SVM) models were built. The AUCs using LR and SVM for the three variable models were .89 and .98. Addition of CRP and D-dimer to BNP has potential to create a powerful diagnostic biomarker panel.

**Keywords:** BNP; CRP; D-Dimer; Biomarker Panel

### Abbreviations

BNP: Brain Natriuretic Peptide; CRP: C-Reactive Protein; LR: Logistic Regression; SVM: Support Vector Machine; AUC: Area Under the Curve; ROC: Receiver Operating Characteristic

### Introduction

Dilated cardiomyopathy (DCM) is the most common type of cardiomyopathy encountered with a prevalence of approximately 1 in 2500 [1]. Ten year mortality is greater than 40% despite present day therapies [2]. Heart failure is a syndrome affecting many pathways including inflammation and coagulation. Increased levels of D-dimer and c-reactive protein (CRP) in dilated cardiomyopathy have been noted [3]. This study investigates if utilization of these biomarkers in addition to brain natriuretic peptide (BNP) could enhance the diagnostic predictive value for congestive heart failure (CHF) in patients with dilated cardiomyopathy. CRP has been correlated with progression, prognostication and response to therapeutic interventions in heart failure patients [3-5]. CRP appears to be involved in heart and vascular remodeling via up regulation of the renin-angiotensin activating system (RAAS), activation of matrix metalloproteinases (MMP) and suppression of tissue MMP inhibitors. Complement activation and the prothrombotic state may be enhanced by CRP as it stimulates plasminogen activator inhibitor-1 (PAI-1). CRP may increase oxidative stress by increasing the production of reactive oxygen species in vascular vessel walls. The complex role of CRP in heart and vascular remodeling may be explained by its biochemical actions at the cellular level [6]. A pro-thrombotic state and dysfunction of the coagulation system is known to exist in heart failure [7]. Increased levels of d-dimer have been shown to significantly correlate with left atrial size, left ventricular internal dimension in diastole (LVlDd) and ejection

fraction (EF) in heart failure with reduced ejection fraction. D-dimer levels were used to predict cardiovascular mortality and were found to be associated with poor prognosis [8]. Pathology of the vascular system, increased coagulability, neurohormonal up regulation and impaired flow have all been implicated in the hypercoagulability noted in heart failure [7,8]. This study tests the use if any of adding CRP and D-dimer to BNP for diagnosing heart failure.

**Materials and Methods**

BNP, CRP and D-dimer were assayed in 9 control subjects, 9 DCM patients who were compensated (DCM) and 10 decompensated DCM patients (DCM-CHF). All DCM subjects underwent a coronary angiogram which excluded any coronary artery disease. Inclusion criteria included age > 18 years of age, able to consent and no diagnosis of any other comorbidities in the control group. For the DCM group, subjects were included in the study only if they had no angiographically detectable coronary artery disease. Subjects less than 18 years of age, unable to consent and with known comorbidities were excluded. Blood samples were collected from all subjects in the first 48 hours of hospitalization. All the three biomarkers were measured in the core laboratory of Scott and White Hospital, Temple, TX using standard hospital derived protocols. The project protocol was approved by Scott and White Hospital institutional board review. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee. None of the patients had a history of hypercoagulability or use of any anticoagulation therapy.

A logistic regression (LR) and a support vector machine (SVM) model, using BNP, CRP, and D-Dimer were created for prediction. AUC (the area under curve) was determined using receiver operating curves (ROC) for each variable with cutoff levels for discriminating acute heart failure.

**Results**

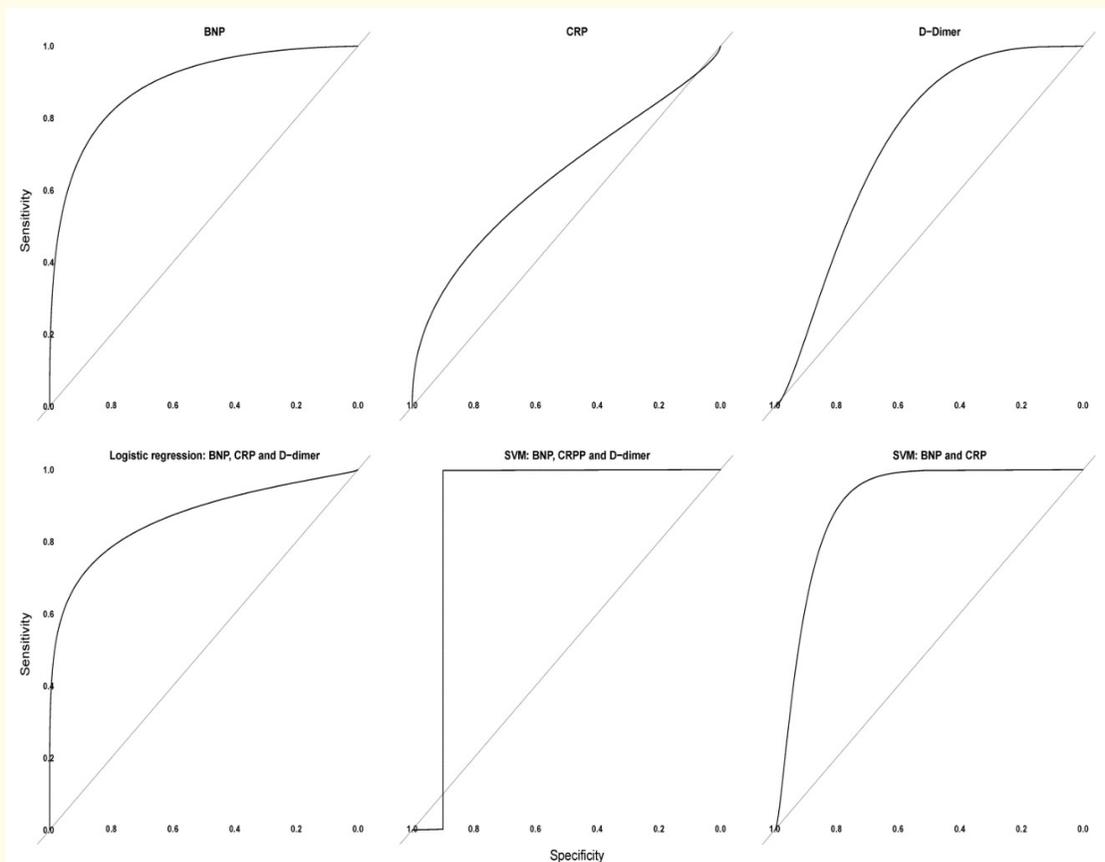
Table 1 shows the characteristics of the 3 study groups. The p-value denotes the significance between control subjects versus the dilated cardiomyopathy patients. Table 1 shows significant changes in BNP, LVIDd and LVEF between the control and DCM and DCM-CHF groups.

Baseline characteristic	Control (n = 9)	DCM (n = 9)	DCM-CHF(n = 10)
Age (years)	58 +/- 10	48 +/- 9	54 +/- 17
Gender			
Males	56%	88%	80%
Females	44%	12%	20%
BNP (pg/ml)	45+/-35	248+/-156*	2808+/-1355*
LVIDd (cm)	4.5+/-0.3	6.6+/-0.8*	6.4+/-1.0*
EF %	63.1+/-7.4	22+/-5.7*	21+/-7*
Creatinine (mg/dl)	0.87+/-0.12	1.2+/-0.3*	1.1+/-0.2

**Table 1:** Shows baseline characteristics between the control and DCM and DCM-CHF groups.

The difference in biomarker levels were estimated by the t-test. Figure 1 shows the ROC curves. The area under the curves (AUCs) for BNP, CRP and D-dimer were 0.81, 0.76, and 0.86 respectively. The AUCs determined using the two models LR and SVM for BNP and CRP were 0.9 and 0.96, and for the three variable models were .89 and .98 respectively. The BNP and CRP levels per patient had a Pearson correlation of 0.54 (p = 0.04), suggesting that subjects with high BNP tend to have high CRP. When adjusted per patient and when inter-

patient variation was eliminated using a multivariable regression system, BNP and CRP had a high correlation coefficient of 0.95 ( $p = 0.004$ ) demonstrating that BNP and CRP tend to increase with each other within every patient tested.



**Figure 1:** Figure shows the logistic regression (LR) and a support vector machine (SVM) models created for prediction of acute heart failure using BNP, CRP, and D-Dimer to generate AUC (the area under curve) with receiver operating curves (ROC) for each variable.

### Discussion

Considering the rising cost of health care for treatment of heart failure it is relevant to increase the diagnostic accuracy for early detection. The efficient management of heart failure requires cost effective biomarkers to guide therapy. Hence a panel of biomarkers may be more useful to increase the specificity and sensitivity of the test rather than any one biomarker alone. For diagnosis BNP remains a class I indication in the latest ACC/AHA guidelines [9]. However it remains still a class IIb for guiding therapy [9]. CRP has been previously shown to increase with increasing severity of heart failure and associated with mortality and morbidity in an independent fashion [3]. Stasis and endothelial dysfunction are the hallmarks of chronic systolic dysfunction with heart failure influencing formation and resolution of thrombi in the setting of upregulation of prothrombotic factors which in turn contribute to the morbidity and mortality of heart failure [7,8]. It is therefore an exciting concept to include markers of inflammation and thrombosis to BNP for enhancing the diagnostic accuracy of heart failure [9].

Limitations include size and the observational/cross sectional design of the study. Due to the cross sectional nature of the study the exact percentages of diabetes and hypertension in the DCM subjects were not elucidated. The control study subjects were free of a diagnosis of diabetes or hypertension. The creatinine was within normal limits and not significantly different in the control and DCM-CHF groups.

This is a small single center observational study and has the limitation of being influenced by confounding factors. Confounding is reduced by age matching and also by using logistic regression model for analyses though these strategies may not completely eliminate the confounding factors in such small observational studies. These results need validation in larger populations.

### **Conclusion**

The addition of CRP and d-dimer to BNP appears to enhance the predictive value of BNP. The study needs to be validated in a larger and longitudinal cohort. The utility of such a biomarker panel also needs to be further tested and validated for prognostication and risk stratification. This investigation opens new avenues for the combination of BNP, CRP and D-dimer to be explored and standardized in larger populations and possibly extended to patients with preserved ejection fraction.

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### **Conflict of Interest**

The authors Drs. Nandini Nair, Daniel Jupiter, Sheba John and Enrique Gongora have no conflicts of interest to disclose with respect to this study.

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