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Full length research paper

B-type Natriuretic Peptide (BNP) Cutpoint for Assessing Heart Failure (HF) Patients' Readmission Within 6 months from an Index Hospitalization

Yao A. Djilan,[1,2] Robert G. Zoble,[1,3] Adam G. Zoble,[1] Britta I. Neugaard*[1,2,3]

[1] Department of Veterans Affairs (VA) Medical Center, Tampa, FL,
[2] College of Public Health, University of South Florida, Tampa, FL,
[3] College of Medicine, University of South Florida, Tampa, FL

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The objective of this research was to determine the optimum BNP cutpoint to assess the risk of readmission of HF patients within 6 months from an index HF hospitalization. Heart Failure (HF) is a major cause of morbidity and mortality, with a global prevalence estimated at 16 million people. Understanding its risk factors and predictors will help identify patients at high risk of re-hospitalization and death. We identified 1,255 HF patients with IDC-9 codes 428.X for HF admitted to a Veterans' hospital between January 2004 and December 2009. Those with at least 2 HF-specific admissions were assessed using C-statistic to determine the optimum BNP cutpoint. Cox proportional hazards and logistic regression analyses were conducted to assess the risk of readmission of the patients. C-statistic value of 0.56 shows an optimum BNP cutpoint at 500 with a p -value of 0.006. Logistic regression and Cox proportional hazards significantly shows that BNP cutpoint value at 500 can predict the risk of readmission of HF patients while adjusting for patients' age at the first admission. For our population, cut point at 500pg per millimeter is the optimum cutpoint to dichotomize BNP and this cutpoint shows that patients with a BNP value greater than 500 are 1.7 times likely to be readmitted with 6 months post discharge compared to patients with a BNP value less than 500. These results could help clinicians to identify patients at high-risk for re-admission based on their BNP level and provide more intense treatment of their HF.

Keywords: heart failure; BNP; hospital readmissions; cardiovascular disease

INTRODUCTION

Cardiovascular diseases (CVD) are on rise and have become an important public health concern not only in the United States but throughout the world (Koglin *et al.* ,2001). Furthermore, heart failure (HF) is a major cause of morbidity and mortality (Krum and Gilbert, 2003; Kannel, 2000) with a global prevalence estimated at 16 million (Sebern and Riegel, 2009). Nearly 5 million people in the United States have HF with 550,000 incident cases each year (Hunt 2005; Weintraub *et al.,* 2002; McCullough *et al.,* 2002a). Half of HF patients above 65 years old are re-admitted within 6 months of hospitalization (Phillips *et al.,* 2004; Krumholz *et al.,* 2002).

Even though mortality rates have decreased among CVD patients, the rate of HF patients has increased in the past two decades (Kannel, 2000; Stewart, 2001). Despite medical treatment, 1 in 2 patients with HF die within five years of diagnosis (Sundin, 2010). Thus, understanding HF's prognosis and manifestation will improve the process of reducing its incidence and prevalence. Many risk factors such as age, smoking, diabetes and other CVD comorbidities have been shown to be significantly associated with HF. However, other factors less studied could also be potential risk factors for HF. Plasma concentration of B-type natriuretic peptide (BNP), which is a HF biomarker, can be used to diagnose and predict HF (Paulus, 2007). It is a cardiac neuro-

*CorrespondingAuthorEmail: britta.neugaard1@va.gov

hormone specifically secreted from the ventricles as a response to ventricular volume expansion, pressure overload, and resultant increased wall tension (Nakagawa *et a*l., 1995; Maeda, 1998). BNP is measured as a continuous variable ranging from 1 to 1400pg per millimeter. Many studies have shown that elevated BNP is positively associated with high risk of HF (Haugen, 2008; Jourdain, 2007; Troughton, 2000; Miller, 2009) even though others did not find significant associations (Pfisterer, 2009). In order to diagnose and treat HF patients, health care providers generally rely on dichotomized values for BNP instead of the continuous measure. Various cutpoints have been used by different clinicians and scientists to dichotomize BNP and investigate its correlation with CVD (Koglin, 2001; Jourdain, 2007; Troughton, 2000; Miller, 2009; Pfisterer, 2009; Maisel et al., 2002a; McCullough, 2002b). Some researchers choose to use the median of the continuous BNP data as their cutpoint (Bettencourt et al. 2000), while 100pg per millimeter has been recommended by others as a cutoff level with a high negative predictive value (Maisel *et al.,* 2002a). Cutoff values less than 400pg per millimeter have less robust positive predictive values and do not assist clinicians in excluding other causes of elevated BNP in their diagnosis (Maisel *et al.,* 2002b, Maisel *et al.,* 2002c). Thus a need for further investigation and understanding of the “gray zone” (defined as range from 100 to 500 mg/mL), which contains the best BNP cutpoint) is clinically important (Brenden *et al.,* 2006;Strunk, 2006) and would also be helpful for epidemiologic studies. Concordance statistics (C statistics), which is related to Receiving Operating Characteristics (ROC), can be used to determine the best possible cutpoint with the most valid prognosis (Paulus *et al.,* 2007; Strunk *et al.,* 2005; Kamath *et al.,*2001; Dunn *et al.,* 2005). C statistics are one of the statistical methods used to evaluate the accuracy of models (Angermayr *et al.,* 2003; Morrow *et al.,* 2000). They are also used to describe and compare the performance of diagnostic algorithms based on patients’ characteristics (Hanley *et al.,* 1982; Hanley *et al.,* 1983).

In the present study we have determined the optimum BNP cutpoint using C-statistics and assessed how this cutpoint is related to the risk of readmission of HF patients within 6 months from an index HF hospitalization.

MATERIALS AND METHODS

Study Design and Sample

This study is based on a retrospective medical record review to investigate the effects of using an optimum cutpoint for BNP for predicting readmission of HF patients at a large Veterans’ hospital. The study population consisted of patients admitted to the acute care center with a primary diagnosis of HF (using ICD codes 428.X for HF) from January 2004 to December 2009. The main independent variable in the study was the dichotomized BNP variable at the optimum cutpoint. The BNP value was obtained during the patient’s index hospitalization at the time of admission. In order to minimize the effects of possible attrition bias, the inclusion criteria required each patient to at least have 2 HF specific admissions. Hence, patients with only 1 HF specific admission, loss of follow-up or second admission to other hospitals were excluded. The outcome variable was a HF specific readmission within 6 months from a HF discharge.

Procedure

Data were abstracted electronically from the patients’ medical records. Information was collected on outpatient clinic visits, admissions, vital signs, outpatient prescriptions, co-morbid diagnoses, patient demographics, and laboratory tests through the Veterans Health Information Systems and Technology Architecture (VistA) and the Computerized Patient Record System (CPRS) database. Specific data sources included assessment records of physicians, interdisciplinary outpatient assessments, patient admission assessment, as well as progress notes from ambulatory care, emergency department notes and enrollment group clinic notes. These sources were cross analyzed to capture the most valid information about each patient, and then used to assess the eligibility of the patient for the study. Patients re-hospitalized for HF within 6 months post discharge were coded as “yes” for readmission status and the rest were coded “no”.

Statistical Analysis

Data from Microsoft Excel were exported to SAS (Statistical Analysis Software, SAS 9.2 Inc. Cary, NC) for analysis. Descriptive statistics were calculated for the study sample at baseline; mean and standard deviation were used for continuous variables, while frequency and percentage were used for categorical variables. The baseline characteristics for the continuous variables were determined with the Univariate procedure in SAS. Chi-square analysis was done to assess differences in proportions of the categorical variables and their respective levels of significance. Concordance (C) statistics derived from logistic regression analysis were computed with 10 different cutpoints (100 – 1000) and graphed on an Excel spreadsheet for visual presentation. For each chosen cutpoint, a logistic regression model with forward stepwise selection was used to estimate the risk of HF readmission for patients who had a BNP value greater than that selected cutpoint. In addition, the Kaplan Meier method was used to assess the proportion

Table1: Baseline characteristics of the study sample.

Covariates	Mean / Count
Age, Mean (SD)	71.7 (11.4)
Diabetes, N (%)	267 (52.7)
Tobacco, N (%)	47 (9.31)
Alcohol, N (%)	9 (1.78)
Discharged on Beta-Blocker	407 (81.2)
Discharged on ACE/ARB	384 (76.8)
Discharged on Diurectics	420 (83.8)
BNP	
< 100 pg/ml, N (%)	11 (2.19)
< 200 pg/ml, N (%)	49 (9.74)
< 300 pg/ml, N (%)	102 (20.2)
< 400 pg/ml, N (%)	146 (29.0)
< 500 pg/ml, N (%)	184 (36.6)
< 600 pg/ml, N (%)	212 (42.2)
< 700 pg/ml, N (%)	238 (47.3)
< 800 pg/ml, N (%)	278 (55.3)
< 900 pg/ml, N (%)	309 (61.4)
< 1000 pg/ml, N (%)	324 (64.4)

of patients re-hospitalized over time from the index hospitalization. Finally, a Cox proportional hazards regression indexed by the time elapsed from the discharge date was conducted to verify the consistency of the results from the logistic regression model. Alpha of 0.05 was used to determine the statistical significance of all analysis.

RESULTS

Demographics and Clinical Values

Among the 1,255 patients identified, only 511 met the inclusion criteria. Ninety-eight percent were males (N = 499) with an average age of 71.7 (SD: 11.4). 2%) had a history of diabetes, 47 (9.31%) were tobacco users and 9 (1.78%) had some alcohol abuse history. At their previous hospitalization, 407 (81.2 %) were discharged on beta-blockers, 384 (76.8 %) on ACE/ARB and 420 (83.8 %) on diuretics. The mean BNP values was 1018.88pg per millimeter, with a standard deviation of 969.26. The median BNP value was 742.11pg per millimeter. Table 1 shows all these characteristics in addition to the numbers of patients and proportions for different BNP cutpoints.

Concordance statistics

Figure 1 and Table 2 display the outcomes from the concordance statistics analysis for the different BNP cutpoints that were analyzed. The cutpoint at 500pg per millimeter seemed to be the best cutpoint in predicting HF specific readmission within 6 months. The C statistic of 0.56 at that cutpoint led to the best separation of those readmitted and those not readmitted for HF within 6 months. This estimate corresponded to an odds ratio of 1.67 (p=0.006). In Figure 1 the bar graph shows the different C statistics obtained and the embedded line graph the odds ratio associated with these statistics at the corresponding BNP cutpoint.

Table 2: Concordance statistics and measure of associations

BNP cutpoints	C-Statistics	OR	P values
100	0.505	1.638	0.4201
200	0.509	1.218	0.5131
300	0.539	1.612	0.032
400	0.552	1.657	0.0108
500	0.56	1.672	0.006
600	0.548	1.482	0.0314
700	0.548	1.468	0.0342
800	0.552	1.525	0.0213
900	0.547	1.492	0.0329
1000	0.549	1.549	0.0224

HF Readmission

Table 3 below showed the characteristics of patients with a readmission status “yes”versus“no”. The patients readmitted within 6 months post discharge (N=289) had a mean age of 41.9 (SD=11.0). Among them, 198 (68.5 %) had recorded a BNP greater than 500pg per millimeter compared to 121 (56.5 %) in the group not readmitted within 6 months. In addition there were higher proportions of patients discharged on HF medications(81.8 %on beta-blockers, 79.9% on ACE/ARB and 85.6% on diuretics) in the latter group compared to the one readmitted within the first 6 months post discharge. The Kaplan Meier plot in Figure 2 shows the survival curves depicting the percentage of patients readmitted to hospital over time based on their BNP strata at the cutpoint 500pg per millimeter. There was a clear difference, with those with a BNP value above 500pg per millimeter readmitted earlier to the hospital compared to the ones whose BNP values were below 500.

Measures of association

As predicted, a BNP cutpoint of 500pg per millimeter can significantly predict HF patients’ readmission to a hospital within 6 months post discharge from a HF specific hospitalization (Table 4). The crude odds ratio (OR) from

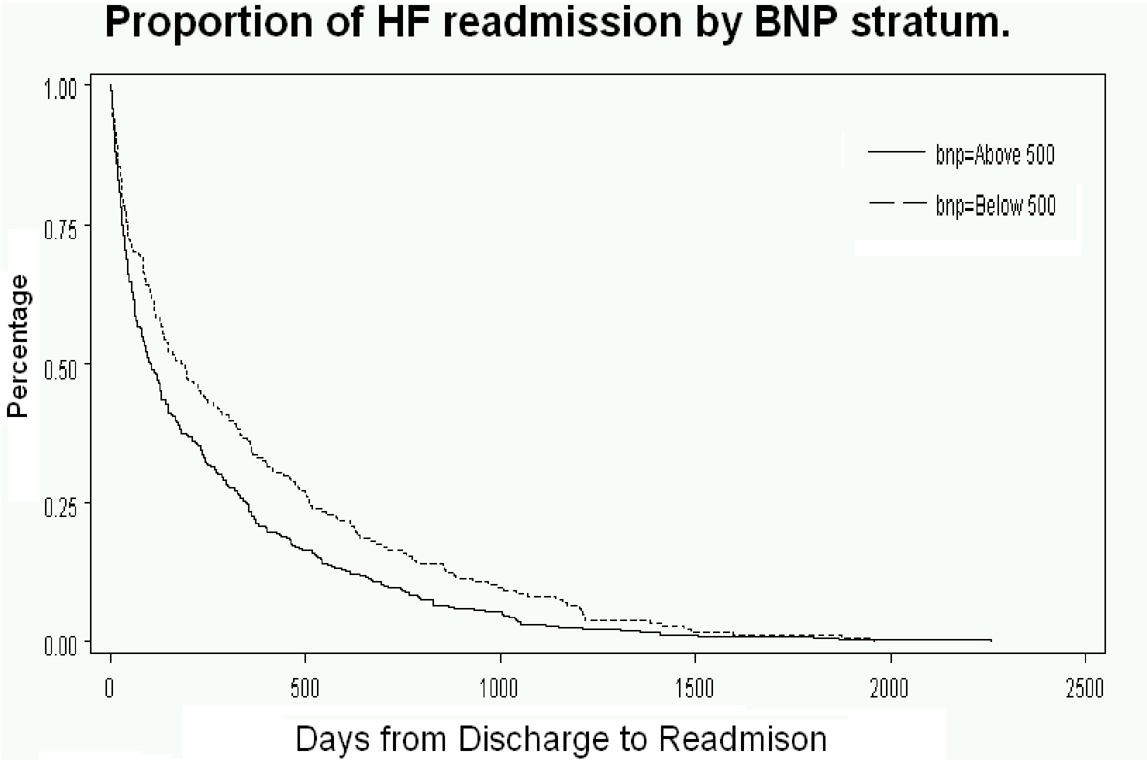

Figure 2: Kaplan Meier survival curve.

Table 3: Patients characteristics based on their readmission status

Readmitted within 6 months	No (N = 214)	Yes (N = 289)	P values
Age, Mean (SD)	41.3 (11.8)	41.9 (11.0)	0.025
Diabetes, N (%)	111 (51.4)	156 (53.6)	0.0059
Tobacco, N (%)	21 (9.72)	26 (9.0)	0.4658
Alcohol, N (%)	5 (2.31)	4 (1.38)	0.7389
Discharged on Beta-Blocker	176 (81.9)	231 (80.8)	0.0064
Discharged on ACE/ARB	171 (79.9)	213 (74.5)	0.0321
Discharged on Diurectics	184 (85.6)	236 (82.5)	0.0112
BNP > 500 pg/ml, N (%)	121 (56.5)	198 (68.5)	<.0001

Table 4: Measures of association estimates

	Estimate	95% Confidence Interval	P value
Unadjusted Odd Ratio	1.67	(1.16 - 2.41)	0.006
Adjusted Odd Ratio*	1.66	(1.14 - 2.42)	0.008
Unadjusted Hazard Ratio	1.32	(1.14 - 1.5)	0.003
Adjusted Hazard Ratio*	1.3	(1.12 - 1.48)	0.005

*Adjusted for only age at baseline as a result from the stepwise selection

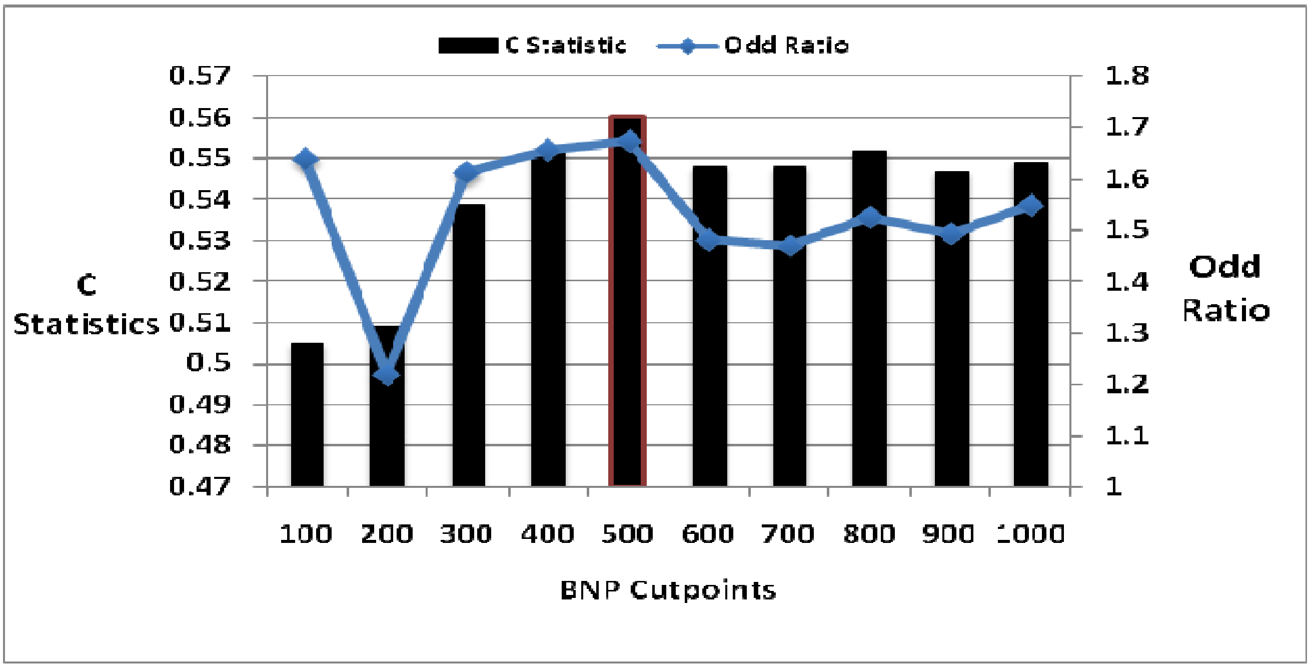

Figure 1: Plots showing the different C-statistics and Odds Ratios at different BNP cutpoints

the univariate logistic regression was estimated at 1.67 with a 95% confidence interval of (1.16 - 2.41) and a p value of 0.006. A multivariate logistic regression with stepwise selection adjusted only for the patients' age at baseline yielded an OR of 1.66 with a 95% confidence interval of (1.14 - 2.42) and a p value of 0.008. The univariate Cox proportional hazard regression yielded a crude Hazard Ratio (HR) of 1.32 with a 95% confidence interval of (1.14 - 1.5) and a p value of 0.003; while the bivariate model with age at baseline estimated the HR to 1.3 with a 95% confidence interval of (1.12 - 1.48) and a p-value of 0.005.

DISCUSSION

As demonstrated in previous studies, we found that BNP was a predictive factor for HF. The results show that a cutpoint around 500pg per millimeter is optimum. The concordance statistics (Figure 1) show that the most accurate model was obtained with the cutpoint at 500 with least error probability ($p = 0.006$). Even though most clinicians prefer using smaller BNP values such as 100 or 200pg per millimeter as a cutpoint in order to increase their negative predicted values, these cutpoints are less accurate in diagnosing HF, due to their less robust positive predicted values; hence the need for an increased cutpoint value is critical. Both logistic regression and Cox proportional hazards regression show that patients with BNP higher than 500pg per millimeter are at significantly higher risk to be readmitted to a hospital within 6 months from an index HF specific hospitalization. The logistic regression with stepwise selection estimated a final model that included age at baseline as the only covariate. Thus patients with BNP value greater than 500 were 1.66 times likely to be readmitted to a hospital within 6 months from an index hospitalization compared to those with a BNP value less than 500. Cox proportional hazard regression showed that the hazard of patients with more than 500 as a BNP value was 1.3 times the one for those with BNP less than 500. The Kaplan Meier plot depicts this relation graphically. Age at baseline is the only variable adjusted for in our final model. Studies showed that age is a strong predictor for CVD; consequently an assessment of interaction between age at baseline and BNP may be useful in evaluating HF readmissions in future studies.

This study has a several limitations; a main one is the lack of external validity, because the results cannot be very well generalized to the U.S. population because 98% of the study sample is composed of male Veterans. Selection bias may also be present because half of the identified patients were not included in the study sample since they did not have at least two HF specific admissions.

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ABREVIATION

HF: Heart Failure
ICD: International Classification of Disease
BNP: B-type Natriuretic Peptide
CVD: Cardiovascular Disease

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