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Research Article

Evaluation of the Efficacy of ST2 and NT-proBNP in the Diagnosis and Prediction of Short- Term Prognosis in Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Purpose: i) To determine the relationship between the cardiac biomarkers ST2 and NT-proBNP with ejection fraction (EF) in heart failure (HF) patients. ii) Assess whether a superiority existed between the aforementioned cardiac markers in diagnosing the HF with reduced EF. iii) Determine the efficacy of both biomarkers in predicting a 30-day cardiovascular event and rehospitalization in patients with HF with reduced EF iv) To assess the influence of age, gender, BMI, anaemia and renal failure on the ST2 and NT-proBNP levels. Design and Methods: A prospective double-blind study was conducted to obtain data from a sample of 64 cardiology patients. A blood sample was collected to test for ST2 and NT-proBNP. An echocardiogram (to obtain EF value), electrocardiogram and questionnaire were also obtained. Results: Of the 64 patients enrolled, 59.4% of the population had an EF less than 40%. At the end of the 30- day period, 7 patients were warded, 37 were not warded, one died and 17 were non respondent. Both biomarkers were efficacious at diagnosing HF with a reduced EF. However, neither of them were efficacious in predicting 30-day rehospitalization. The mean NT-proBNP values being: not rehospitalized (2114.7486) and 30 day rehospitalization (1008.42860) and the mean ST2 values being: not rehospitalized (336.1975), and 30-day rehospitalization. (281.9657). Conclusion: Neither ST2 or NT-proBNP was efficacious in predicting the short- term prognosis in HF with reduced EF. Both however were successful at confirming the diagnosis of HF in HF patients with reduced EF.

Keywords: NT-Pro BNP, ST2 marker, Ejection fraction.

INTRODUCTION

Heart failure (HF) is prevalent worldwide, thus making it a major public health issue. It is also a major contributor to morbidity and mortality rates[1]. In Trinidad and Tobago (T&T), heart disease is the number one cause of death. Thirty seven out of every 100 persons who die each year in T&T result from heart disease[2].

Several biomarkers are used for the prognosis, diagnosis and monitoring HF. Currently, Natriuretic Peptides (NP) are the gold standards used in T&T. However, there are limitations. In addition to HF several other conditions alter BNP and NT-proBNP levels, which prevents either from being considered perfect tools for prognostication. Thus, other biomarkers are required to complement BNP and NT-proBNP to better understand the pathophysiology of HF.

Consequently, ST2 is a biomarker that shows high specificity to cardiac tissue, thus accounting for its use in risk stratification and prognosis of HF patients. ST2 a soluble protein is released by the heart due to myocardial damage. Unlike many other cardiac biomarkers, ST2 is highly sensitive to variation of the patient's condition. This advantage of ST2 enables physicians to accurately monitor a patient's condition and/or recovery to quickly adjust treatment or course of action[3]. The levels of ST2 within the blood is not altered by confounding factors thereby eliminating the limitations encountered with BNP and NT-proBNP. In Trinidad, ST2 is unavailable in clinics and no studies in the Caribbean has been done on it.

METHODOLOGY

Ethical approval was obtained from The University of the West Indies (UWI) and The North Central Regional Health Authority (NCRHA), Trinidad and Tobago. A prospective double-blind study was done and a quantitative method was employed to collect data. The target population consisted of multi-ethnic HF patients, all with a reduced ejection fraction (EF) between the ages of 18-70 years. Patients under the age of 18 and over the age of 70 with HF with no reduced EF were excluded. The sample size consisted of 64 subjects.

After obtaining written consent, a blood sample, demographic data via self-administered questionnaires, an ECG and echocardiogram indicating reduced EF were collected from each patient after they gave written consent. Cardiology clinics at the NCRHA were the chosen

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research sites. Blood sample of 5.0 ml was collected from the patients. The blood samples were then sent to the Biochemistry Lab at the Eric Williams Medical Sciences Complex to be centrifuged to obtain serum samples. The serum samples were stored in a -70 degree centigrade freezer and were utilized to evaluate ST2 and NT-proBNP levels. The ST2 levels were assessed via The Critical Diagnostics Presage® ST2 Assay kit which was supplied by Critical Diagnostics. The NT-ProBNP was analysed using the ELISA kit. Follow up of the patient was done after a 30 day- period and no samples were collected during the second visit. The Statistical Package for the Social Sciences (SPSS) was used to analyse the data. Categorical data were reported as frequencies and percentages while continuous data were reported as means and standard deviations or standard errors. Student t-tests, and bivariate correlation were done. Overall, a p value of <0.05 was deemed significant.

RESULTS

The study encompassed 64 patients recruited from the cardiology clinics at the EWMSC, all of whom were on heart failure medication such as Coreg. Of the 64 participants, 57.8% were males while 42.2% were female. Among the participants 1.6% were between the ages of 18-24, 3.1% were 25-34 years, 3.1% were 35-44 years and 20.3% were 45-54 years old. Age groups 55-64 years old, made up the largest percentage of 35.9%. Around 23.4% of participants were 65-74 years old and 12.5% were in the 75-84 years old age bracket. Among the participants 26.6% were of African descent, 68.8% Indian and 4.7% were mixed. The study noted that 18.8% were anaemic, 55.9 % were diabetic, 15.6% had kidney failure, 5.2 % were asthmatic and 42.1% had dyslipidaemia. The population's stress levels were determined on a scale of 0-10 and 65.7 % of participants reported stress levels of 0-5 and 34.3 % indicated that their stress levels were within the 6-10 range.Using the standard BMI ranges 3.2% of the population were underweight, 24.2% were of normal weight, 37.1 % were overweight and 35.5% were obese. Our study also collected data for their level of exercise we found that 18.8% exercised regularly (once daily), 7.8% exercised once or twice a week, 28.1% rarely exercised whilst 45.4% never exercised. Participants of 6.3 % were diagnosed with HF for less than 1 year, 62.5 % between 1-5 years, 9.4% between 6-10 years, 12.5 % between 11-15 years and 9.4 % of the population had heart failure for over 15 years. The majority of patients in the study were previously hospitalized (79.7%), with 59.4% of the population having an EF less than 40%. Using the NYHA Functional Classification the population was divided as follows; Class 1 - 42.2%, Class 2- 35.9 %, Class 3 - 28.8 %, Class 4 - 3.1 %. At the 30 day period after collection of the sample, 7 patients were admitted to ward, 37 were not warded, one died and 17 were non respondent. However, beyond the 30 day period, 2 patients had been warded and one died. Both ST2 and NT-proBNP were efficient at confirming the diagnosis of HF patients. All ST2 values were above 35ng/ml which signified increased hospitalization or death. The mean ST2 value was found to be 347.5865 Also, NT-proBNP values (mean value of NT-proBNP = 3218.0194) of HF patients, considering age groupings confirmed HF.

DISCUSSION

The p- value for ST2 in relation to ejection fraction was *p* = 0.348. Also, a mean comparison was done between the ST2 values and patients who had either lower-(<40%) or higher EF's (40<EF>50). The means comparison revealed a significance of 0.207 (n=64). This signifies that there is a very weak correlation between ST2 and ejection fraction. NT-proBNP is significantly correlated with the severity of left ventricular ejection fraction (LVEF)[4]. An increased concentration of the natriuretic peptide is indicative of impaired LVEF. A comparison of the raw mean values of NT –pro BNP for EF's <40 (3858.3919) and 40<EF>50 (2270.2680) revealed that there was an increase in the concentration of NT-proBNP with decreasing EF.

The study revealed that all ST2 levels obtained were above a mark of 35 ng/ml. The mean ST2 value was 347.5865. According to published data[3,] our findings confirm the ability of ST2 in the diagnosis of heart failure. NT proBNP also confirmed the diagnosis of HF in the patients who participated in our study with a mean value of 3218.0194. With reference to previous studies[5,] our values were within the diagnostic ranges.

The results showed significant inconsistencies in mean ST2 concentrations among patients who were not warded (336.1975), and warded (281.9657). Based on these findings, ST2 was ineffective in predicting a short term cardiovascular event and rehospitalisation rate in patients with HF with reduced EF. However, multiple studies have found ST2 to be an effective predictor of short term prognosis in patients with cardiovascular disease. To account for this, patients enrolled in the study were on a regimen of cardiac medication thus leading to inconsistencies.

The results revealed a great variation in the mean NT proBNP levels among the patients who were not warded (2114.7486) and warded after 30 days (1008.4286). Thus there was no relationship between the NT pro BNP levels of patients and rate of rehospitalisation, rendering NT proBNP as an ineffective prognostic marker contrary to previous studies[6-8]. To account for this, patients enrolled in the study were on a regimen of cardiac medication thus leading to inconsistencies.

ST2 levels are not adversely affected by confounding factors. Our study supported this claim. According to the p-values there is no significant correlation between the measured variables and ST2 values, giving ST2 an advantage over other cardiac biomarkers.

According to a study published by Critical Diagnostics in 2014 they found that there was no correlation between ST2, gender, anaemia and renal dysfunction.[9] The results verified this as there were little to no correlation between ST2 levels and gender (r = -.186). In addition, it was also seen that ST2 and renal failure were independent of one another (Pearson correlation was -.032). An article entitled Role of Soluble ST2 as a Prognostic Marker in Patients with Acute Heart Failure and Renal Insufficiency (2015)

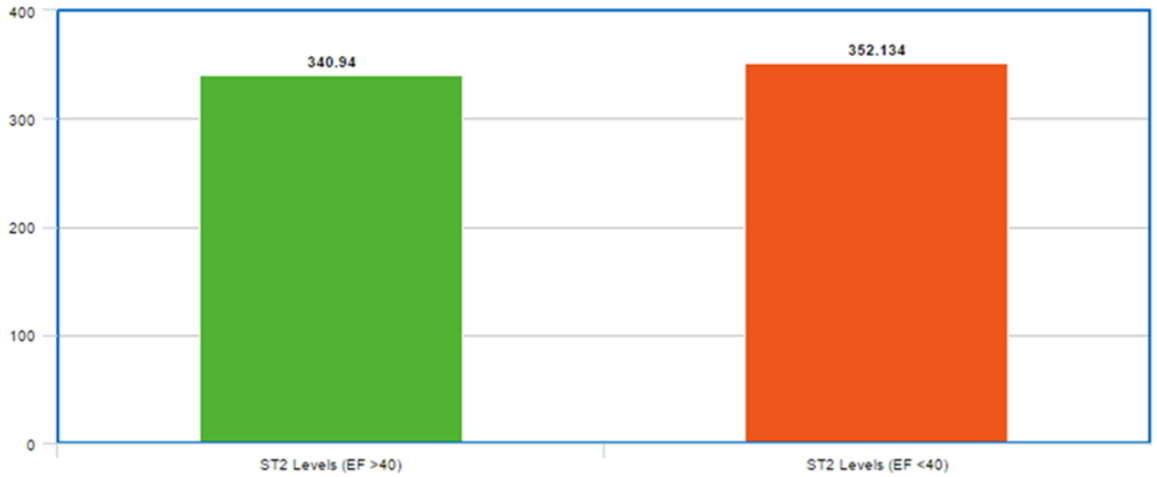

Figure 1: Mean ST2 levels vs Ejection fraction values.

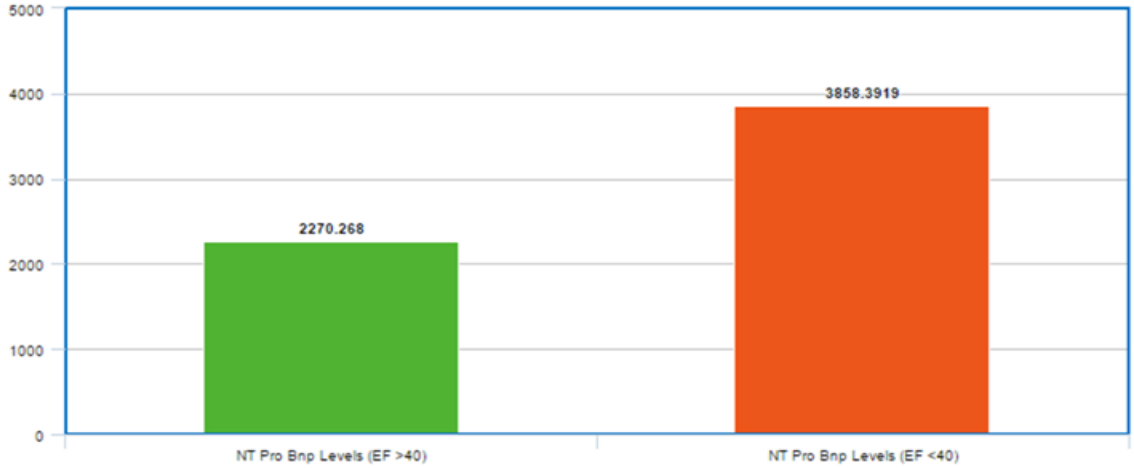

Figure 2: ProBNP levels vs Ejection fraction values.

concluded that there was no change to ST2 levels with the degree of renal function [10]. -Therefore, our results positively corresponded with previously published data.

In comparison to this, the study revealed that NT-proBNP was not related to renal failure (Pearson correlation was -.218). This did not conform to previous research which stated that the biomarker was in fact affected by the degree of renal failure. Also, there was a correlation between gender and NT-proBNP as reflected in our results. (p = .033)

Results from the study concluded that there is no significant correlation between ST2 values and the age of the participants (p = 0.86). Karolina Wojtczak-Soska study titled Soluble ST2 protein in chronic heart failure is independent of traditional factors also concluded that there was no relationship between sST2 levels and age (p = 0.67)[11].

Published data stated that NT-proBNP levels fluctuate depending on various factors, including age[12, 13], however, the value of NT-proBNP shows no significant correlation (-.178). The Pearson correlation value for ST2 (-.023) is compared to that of NT-proBNP (-.178)

As it pertains to BMI and ST2, no significant statistical correlation in our study was seen, (Pearson's correlation, p = .049). This finding corresponds with results obtained in previous HF studies (acute and chronic)[14,15] as ST2 interleukins are observed to be produced by stretched cardiomyocytes, independently of factors such as BMI. There was also no significant statistical correlation between BMI and NT-proBNP (p=0.472)

Patients' ST2 levels were unaffected by anemia (P-0.930). It was also concluded that no relationship existed between anemia and NT pro-BNP levels in the participants. Contrary to previous studies[16].

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