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Comparison of high sensitivity troponin I and NT pro BNP as prognostic markers of major adverse cardiac events across spectrum of ischemic heart disease

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***Abstract*---**Background: In an era of a cardiovascular epidemic an imminent search for highly sensitive and specific markers for prognostication in ischemic heart disease have been sought. This study attempted to assess how high sensitive troponin I and NT pro BNP fare as prognostic markers for major adverse cardiac events across the spectrum of ischemic heart disease and hence estimate cardiovascular risk.Objective: To compare high sensitivity Troponin I and NT pro BNP as prognostic markers of major adverse cardiac events across the spectrum of ischemic heart diseases including SIHD, USA/NSTEMI and STEMI. Methods:112 subjects were chosen across the spectrum of ischemic heart disease with equal number of STEMI, USA/NSTEMI AND SIHD. Patients were recruited after satisfying the inclusion criteria and standard definitions as per recommendations and guidelines. Hs trop I and NT pro BNP values were obtained for all patients apart from other parameters. The patients in the study underwent treatment as per standard recommendations.. RESULTS: Hs Troponin I was a poor prognostic marker of overall/ cardiovascular mortality if the entire study

population was taken into context with a P value=0.954 and 0.765 respectively for baseline and third hour values. The results for overall 30 days or 6- month mortality did not reach statistical significance; P=0.732,0.462 and P=0.217,0.183 respectively for baseline and third hour positive troponin values. However, a subgroup analysis across the spectrum of ischemic heart disease revealed that the results were more promising, especially for patients falling under the category of stable coronary artery disease and unstable angina. NT pro BNP was a good prognostic marker for overall cardiovascular mortality P value=0.029; sensitivity and specificity being 100% and 54% respectively. The P value for 30-day and 6-month mortality were 0.017 and 0.022 respectively which were all statistically significant Conclusion: When compared to Hs Trop I, NT pro BNP proved to be a better prognostic marker for cardiovascular mortality and major adverse cardiac events across the spectrum of ischemic heart disease. Over and above it provided additional negative predictive value in troponin positive patients and better sensitivity in troponin negative patients advocating the fact that NT pro BNP may be used as an independent prognostic indicator and hence should be implemented into routine clinical practice

***Keywords*---**atherosclerotic cardiovascular disease, coronary artery bypass grafting, chromic stable angina, high sensitivity Troponin I.

Introduction

The burden of cardiovascular diseases is ever increasing especially in the adult Indian population[1]. Hence it is of paramount importance that such patients are prognosticated and risk stratified to decide on the approach and course of treatment, predict future outcomes, and decide on duration of hospital stay and discharge and the periodicity of follow-up [2]. Hs troponin I and NT pro-BNP are markers which can be used as prognostic tools. Cardiac troponin I is a regulatory subunit of the troponin complex. Troponin I in conjunction with Troponin C and Troponin T plays an integral role in the regulation of muscle contraction.[3,4,5] Circulating levels of NT-Pro BNP are normally very low in healthy individuals. In response to increased myocardial wall stress states NT pro-BNP is released. It is also essential to evaluate whether NT pro BNP gives incremental prognostic information as it is an easily available biomarker. In the setting of acute coronary syndromes, Hs troponin I elevation provides information concerning the risk for subsequent adverse cardiovascular events, as well as the benefit of therapeutic intervention .[1,6]

Using a highly sensitive assay for Troponin I, a study group demonstrated the presence of detectable levels in a large proportion of patients with stable coronary artery disease (CAD).[7] It has been shown that NT-pro BNP, levels obtained in the first few days after ACS provide independent, predictive information on mortality. Regardless of the presence or absence of baseline risk indicators, elevation of NT-pro BNP is an independent, strong predictor of short- and long-term mortality, with a continuous increase in mortality at 1 year in relation to these levels. The

combination of NTpro BNP with creatinine clearance rate, heart rate, or levels of troponins provides an even better risk stratification concerning mortality in ACS patients.[8,9] Among patients with suspected ACS considered to be at low risk because of normal troponin I values, NT- Pro BNP is able to discriminate individuals at higher risk. Because of its incremental prognostic value, NT-pro BNP assessment should be considered in clinical routine for risk stratification of patients with normal troponins.

Objectives

to compare high sensitivity Troponin I and NT pro BNP as prognostic markers of major adverse cardiac events across the spectrum of ischemic heart diseases including SIHD, USA/NSTEMI and STEMI.

Materials and Methods

The present longitudinal study was carried out by the department of Cardiology at M S Rammaiah Medical College and Hospital Bengaluru among the patients presenting to the emergency department , Out patient and In patient in the Department of Cardiology and Medicine from January 2016 to November 2017. Sample size was estimated by the study done by Louise Cullen et al and Michael Weber et al respectively it was observed that the specificity of predicting major adverse cardiac events for Hs Troponin I was 91.9% and for NT Pro BNP it was 83%[1,2] In the present study expecting to get similar results with 7% relative precision and 95% confidence interval the sample size was estimated to be a minimum of 112.

Inclusion criteria

Patients age > 18 years, Patients who have symptoms suggestive of angina pectoris and angina equivalents, Patients satisfying the third universal definition of myocardial infarction as per the Joint ESC/ACCF/AHA/WHF Task Force , Stress test positive for SIHD patients, TIMI risk score >2 for patients with unstable angina

Exclusion criteria

Cardio- Pulmonary Resuscitation, Cardiac arrhythmias before estimation, Positive rheumatoid factor, Sepsis, Anemia, Renal insufficiency, Increased alkaline phosphatase levels 24, Pulmonary embolism and pulmonary arterial hypertension, Valvular heart disease, pre-existing heart failure, Drugs – cefoxitin, ibuprofen, adrenaline, nifedipine, verapamil. Data was be collected by pretested semi structured questionnaire, clinical examination and investigations. An estimation of Hs troponin I and NT Pro BNP by serum and blood samples was done for all the patients satisfying the inclusion and exclusion criteria at admission. Serial estimation of Hs Troponin I was done at 3 hours for initial negative or intermediate values since it is also used as a diagnostic tool in NSTEMI patients as per departmental protocol. The two biomarkers were be compared as prognostic markers to predict outcomes and major adverse cardiac events across the spectrum of ischemic heart disease to fulfill the study objective.

The spectrum of ischemic heart disease includes stable ischemic heart disease (SIHD), unstable angina (USA), non- ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI). The patients were grouped into their respective cohorts for the purpose of group-wise analysis. The primary study end point was major adverse cardiac events (MACE) till six months. The patient were followed up during the hospital stay, at 1 month and at 6 months for major adverse cardiac events with repeat investigations, imaging and interventions as required.

Statistical Analysis

The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. Chi square test was used to test the significance.

Results

A total of 112 study subjects were selected for the purpose of the study and analysed .

Table 1: Distribution of the spectrum of ischemic heart disease

Diagnosis	No. of patients	%
STEMI	35	31.3
CSA	30	26.8
NSTEMI	28	25.0
USA	19	17.0
Total	112	100.0

In the present study 31% of the patients had STEMI, 27% had chronic stable angina/stable ischemic heart disease, 25% had NSTEMI and 17% had unstable angina

Table 2 : Comparison of demographic/clinical variables with respect to diagnosis of patients studied

variables	Diagnosis				Total (n=112)	P value
	STEMI (n=35)	NSTEMI (n=28)	USA (n=19)	CSA (n=30)		
Gender						
• Female	13(37.1%)	12(42.9%)	7(36.8%)	15(50%)	47(42%)	0.719
• Male	22(62.9%)	16(57.1%)	12(63.2%)	15(50%)	65(58%)	
Age in years						
• <40	0(0%)	1(3.6%)	2(10.5%)	4(13.3%)	7(6.3%)	0.234
• 40-50	8(22.9%)	3(10.7%)	3(15.8%)	3(10%)	17(15.2%)	
• 51-60	12(34.3%)	13(46.4%)	4(21.1%)	11(36.7%)	40(35.7%)	
• 61-70	12(34.3%)	7(25%)	8(42.1%)	11(36.7%)	38(33.9%)	
• 71-80	2(5.7%)	4(14.3%)	2(10.5%)	0(0%)	8(7.1%)	

• >80	1(2.9%)	0(0%)	0(0%)	1(3.3%)	2(1.8%)	
BMI (kg/m2)						
• <18.5	1(2.9%)	0(0%)	1(5.3%)	1(3.3%)	3(2.7%)	0.577
• 18.5-25	22(62.9%)	15(53.6%)	7(36.8%)	14(46.7%)	58(51.8%)	
• 25-30	11(31.4%)	10(35.7%)	8(42.1%)	13(43.3%)	42(37.5%)	
• >30	1(2.9%)	3(10.7%)	3(15.8%)	2(6.7%)	9(8%)	

The above tables represents the distribution of age group and gender and BMI among the study subjects with reference to the differential diagnosis and the association between age group , gender and BMI with the diagnosis was found to be statistically insignificant .

Table 3: Major Adverse cardiac events

	No. of patients (n=112)	%
Shock	28	25.0
IABP	18	16.1
Heart failure at Admission	21	18.8
Recurrent Hospitalizations	17	15.2
Heart failure post procedure or prior to discharge	14	12.5
Heart Failure on follow up	11	9.8
Stent thrombosis/target vessel revascularization	6	5.4
Cardiogenic shock	13	11.4

In terms of major adverse cardiac events in the STEMI group; 34% of patients had cardiogenic shock at presentation, 20% had an IABP inserted, 29% had heart failure at admission, 14% had heart failure post procedure or prior to discharge, 17% had recurrent hospitalizations, 8.6% had heart failure on follow up till 6 months, 5.7% had stent thrombosis/ target vessel revascularization and 11.4% had cardiogenic shock on follow up till 6 months

Table 4: Overall incidence of Troponin I and NT Pro BNP in the study population

		No. of patients	%
Troponin I	Negative	49	43.8
	Positive	63	56.3
NT pro BNP	Negative	52	46.4
	Positive	60	53.6

Table 5 : Comparison of overall Mortality in relation to positivity of Troponin I

		Troponin I		
		Negative	Positive	Total
Mortality	No	46(93.9%)	60(95.2%)	106(94.6%)
	Yes	3(6.1%)	3(4.8%)	6(5.4%)

Table 6 : Comparison of overall Mortality in relation to positivity of NT PRO BNP in patients studied

		NT PRO BNP		
		Negative	Positive	Total
Mortality	No	52(100%)	54(90%)	106(94.6%)
	Yes	0(0%)	6(10%)	6(5.4%)

56% and 54% of the entire study population had a positive Hs Trop I and NT pro BNP value respectively; this includes either the baseline or third hour value for Trop I and the baseline or 72-hour value for NT pro BNP. While inferring from this study it is very essential to take a note of the fact that the biomarkers have been evaluated as prognostic tools and not as diagnostic markers because patients have been randomly chosen with a diagnosis across the spectrum of ischemic heart disease and followed up for six months

Figure 1 : a, b: ROC for Hs Trop I at a) 0 hours (P value=0.954) and b) at 3 hours (P value=0.765) for overall mortality

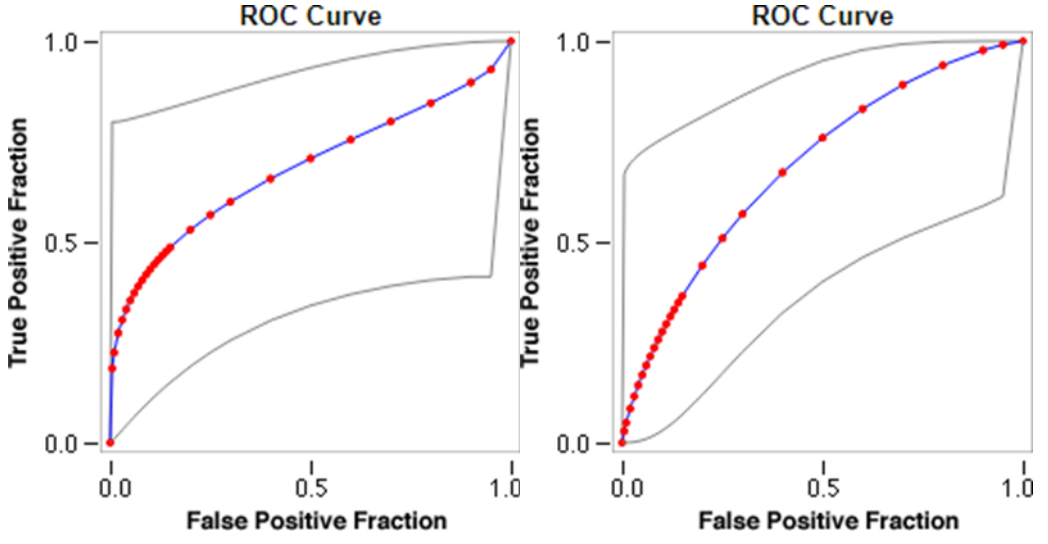
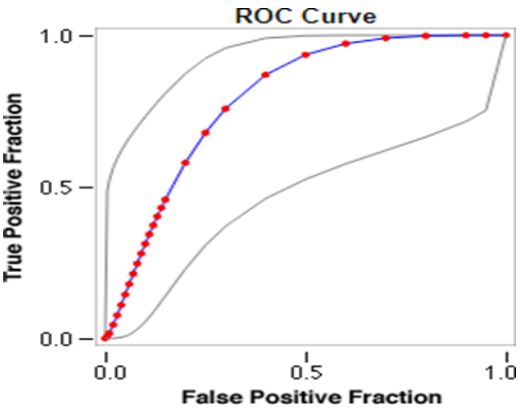


Figure 7: ROC for baseline NT pro BNP (P value=0.029) for overall mortality



Discussion

The epidemic of cardiovascular diseases in the adult Indian population has raised a serious concern regarding the risk stratification of patients with ischemic heart disease. Hence it is of paramount importance that such patients are prognosticated and risk stratified to decide on the approach and course of treatment, predict future outcomes, and decide on duration of hospital stay and discharge and the periodicity of follow-up. The roles of high sensitivity Troponin I and NT pro BNP as prognostic markers have been critically evaluated in this prospective observational study.

In our study, 112 subjects were recruited over the last two years across the spectrum of ischemic heart disease who satisfied the inclusion criteria. Cases with a diagnosis of STEMI, NSTEMI, Unstable Angina and stable ischemic heart disease; that is comprising the spectrum of ischemic heart disease were included. The mean age in the study group was 58.13±10.79 years. Patients in the study were found to be clustered in the sixth and seventh decade of life with 36% and 34% cases belonging to these categories respectively. There were 58% males and 42% females in the study. In similar studies done by Louise Cullen et al.[1] and Michael Weber et al. [2] the mean age and the gender distribution showed similar results. This may suggest a higher incidence of at risk population in the sixth and seventh decades who need to be carefully followed up for major adverse cardiac events.

In our study, the mean BMI was 26.9±2.5 kg/m2 with 37.5% of the study population being overweight and 8% falling under the category of obesity with a P value of 0.033 (fisher exact test). 31% of the patients had STEMI, 27% had chronic stable angina/stable ischemic heart disease, 25% had NSTEMI and 17% had unstable angina. 5% patients had non-obstructive coronary artery disease, 37% had single vessel disease, 42% had double vessel disease and 16% had triple vessel disease. 78.6% patients underwent PCI as a mode of revascularization, 12.5% underwent CABG while 7% patients were managed medically and two patients underwent cardiac transplant.

The patients in the NSTEMI group differed from the STEMI group in that the mean age was higher, more patients were overweight or obese in this group, lesser number of patients had classical symptoms, increasing numbers were found to have double and triple vessel coronary artery involvement. The number of patients referred for CABG were significantly more. The MACE events were less in this group and one patient underwent cardiac transplant who is doing extremely well on follow up. The patients in the unstable angina group had more males, greater number in the seventh decade and 58% falling under the category of either obese or overweight. Mean age and BMI was similar to other groups.

56% and 54% of the entire study population had a positive Hs Trop I and NT pro BNP value respectively; this includes either the baseline or third hour value for Trop I and the baseline or 72-hour value for NT pro BNP. While inferring from this study it is very essential to take a note of the fact that the biomarkers have been evaluated as prognostic tools and not as diagnostic markers because patients have been randomly chosen with a diagnosis across the spectrum of ischemic heart disease and followed up for six months

In terms of major adverse cardiac events; 25% of patients had cardiogenic shock at presentation, 16% had an IABP inserted, 19% had heart failure at admission, 12.5% had heart failure post procedure or prior to discharge, 15% had recurrent hospitalizations, 10% had heart failure on follow up till 6 months, 5.4% had stent thrombosis/ target vessel revascularization and 11.6% had cardiogenic shock on follow up till 6 months. 5.4% of the study population had all-cause mortality over a follow up period of 6 months.

All the patients with cardiovascular mortality in this study had an elevated NT pro BNP value either at baseline(n=4) or at 72 hours(n=2). NT pro BNP was a good prognostic marker for overall cardiovascular mortality P value=0.029; sensitivity and specificity being 100% and 54% respectively. The P value for 30-day and 6-month mortality were 0.017 and 0.022 respectively which were all statistically significant. The above results imply that NT pro BNP might be used a highly sensitive prognostic marker for overall cardiovascular mortality.

Conclusion

This study has critically evaluated the utility of high sensitivity Troponin I and NT pro BNP as prognostic markers across the spectrum of ischemic heart disease, with promising results. The importance of Hs Trop I as a diagnostic marker has been well established but its ability as a prognostic maker to predict mortality and future major adverse cardiac events has been recognized in this study of the adult Indian population, especially in the setting of stable ischemic heart disease and unstable angina where even higher normal values of troponin I were found to be effectively prognostic for overall, 30-day and 6-month cardiovascular mortality, although less effective with respect to MACE events. The above results however prompt a need to consider values even in higher normal ranges equally important and implement such results into institutional protocols and routine clinical practice. In the setting of STEMI/NSTEMI the results were less robust with Hs Trop I.

NT pro BNP proved to be a very robust and effective prognostic indicator of all major adverse cardiac events except stent thrombosis/target vessel revascularization. It also strongly predicted overall, 30-day and 6-month cardiovascular mortality in all patients especially in stable coronary artery disease and unstable angina, although less specific it was better even in NSTEMI/STEMI compared to Hs Trop I.

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