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ST-2 as a Prognostic Biomarker in Acute Heart Failure

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Abstract

Background: Heart failure (HF) is an important and common cardiovascular health problem seen in day today practice with significant mortality and morbidity. HF patients require timely evaluation, emergent and appropriate therapyas they usually present with acute onset of dyspnea to emergency department. Proper risk-stratification is a prerequisite to identify high risk group for adverse outcomes which directs us in proper management and plan timely follow up of the patients.

Methods: This was a prospective,single centre study involving 102 consecutive AHF patients in NYHA class III/IV who were enrolled over a period of 6 months from October 2013 to march 2014. Patients with acute coronary syndrome, significant renal, hepatic or valvular heart disease, sepsis and pulmonary embolism were excluded. ST-2, hs-TropT, hs-CRP and Uric acid were evaluated at admission.

Results: The mean admission values of ST-2 were 100.2±66.6ng/ml. ST-2 values found significantly raised in Group 1 (HFrREF) compared to Group 2 (HFpEF) (108.7±66.6 Vs 63.9±39.7) which is statistically significant (p=0.001). ST-2 is raised in group with events compared to non-event group but statistically insignificant (p=0.078).

Conclusions: Although ST-2, hsTropT, hsCRP and UA were all elevated in the vast majority of patients, None of them were independent predictor of adverse outcomes on follow-up. But Several important relations of biomarkers with various outcomes were derived in this study.

Keywords: ST-2; Prognostic Biomarker; Acute Heart Failure.

Introduction

Heart failure (HF) is a burgeoning worldwide epidemic and a major public health problem, with an increasing incidence and prevalence.[1] HF is a common condition with prevalence ofmore than 10% within the 70-years-or-older agegroup and is the result of a wide range of cardiovascular disorders that influence negatively the heart's property to fill or to pump blood Episodes of acute decompensated HF (ADHF) are associated with a rise in hospital admissions, high morbidity and mortality, and escalating health care costs.[2,3,4] The care of patients with acutely decompensated heart failure (ADHF) is complex, involving clinical assessment and risk prediction as integral parts of daily clinical practice. Indeed, Clinical risk stratification after hospitalization for ADHF remains a relevant challenge, in order to best identify those patients likely to encounter serious complications, and to potentially better allocate resources in order to mitigate this considerable risk. Several demographic and clinical factors, co-morbidities, and biochemical variables are associated with shortor mid-term mortality in ADHF, including measures of renal function and blood pressure as well as other relevant predictors.[5–10] Primary hospitalization is not the only issue with HF as it is also the most common cause of hospital readmissions, with approximately 30% of patients

readmitted to the hospital within 60–90 days of discharge from their index hospitalization, the hospitalization immediately prior to readmission.[11] Despite successful treatment achievements in recent decades, the mortality of patients with HF continues to be high. Theuse of established mortality risk factors including physician-assessed New York Heart Association (NYHA) functional class, specific medication use, laboratory values, and left ventricular ejection fraction (LVEF) does not fully explain the risk of death in HF patients.[12,13,14] A more refined approach to risk assessment might include the use of biological markers of pathophysiological processes not directly reflected by these established mortality risk factors, such as myocardial fibrosis and stretch, conditions that are associated with an increased risk of death in patients with HF.[15,16] An enhanced risk assessment would be of great clinical value if it could more accurately identify HF patients at increased risk of death and who could then be targeted for more intensive treatment and monitoring.[17] Among a variety of proposed heart failure treatment modalities, cardiac biomarkers have emerged as powerful adjuncts to standardised clinical care in the diagnosis, prognosis, and treatment of acute heart failure (AHF).[18] An array of biomarkers is now available for the evaluation of patients with acute HF (AHF). N-terminal pro B-type Natriuretic peptide (NT-proBNP), cardiac-specific troponin (cTn) and C-reactive protein (CRP) are the more common biomarkers which are widely available with several studies on their relation to both short- and long-term outcomes being published. The natriuretic peptides, brain natriuretic peptide (BNP) and its amino-terminal fragment (NT-proBNP), are the most studied HF biomarkers. Currently, they are the "gold standard" biomarkers for HF. They can be used in diagnosis/exclusion, prognosis and management of HF. All the major societies such as the European Society of Cardiology, the American College of Cardiology and the American Heart Association recommend their clinical use in their Guidelines.[2,19–21] N-terminal pro brain natriuretic peptide (NTproBNP), which indicates myocardial stretch, is currently recognized as a robust prognostic marker at all stages of HF, and for all related clinical outcomes.[22,23] cTns have revolutionised the evaluation and management of patients with acute coronary syndromes (ACS) but their role in AHF is far from clear. Limited data exists on the relation between hs-CRP and adverse outcomes in AHF. ST2 is an inflammatory cytokine, member of the interleukin (IL-1) receptor family. ST2 is thought to be involved in modifying immunologic processes through its soluble (sST2) andmembrane-bound (ST2L) forms, produced duringmyocardial strain.[24] ST2, a biomarker reflective of myocardial fibrosis and remodelling, was able to predict mortality in acutely decompensated HF patients, and may identify HF patients at higher risk of sudden cardiac death.[25–27] Soluble ST2 is considered a decoy receptor of IL 33 (a member of IL-1 receptor family of cytokines) that blocks the protective effects of the cytokine in atherosclerosis, obesity and cardiac remodeling.[27,18] Together with natriuretic peptides and highly sensitive troponins, ST2 has a powerful prognostic value.[28] In patients with heart failure, an increase of ST2 during a 2-week period was an independent predictor of subsequent death or the need for cardiac transplantation.[24,29,30] Previous data suggest for ST2 measurement in the prognosis of acutely destabilized HF. With these considerations, the present study was undertaken to describe the association between these biomarkers and adverse cardiovascular outcomes in patients hospitalized for AHF and to specifically evaluate the prognostic significance of a ST-2 level in a cohort of AHF patients.

Methods

Study design and patient population

This was a prospective, single centre study involving 102 consecutive AHF patients in NYHA class III/IV who were enrolled over a period of 6 months from October 2013 to march 2014. 102 consecutive patients with AHF in New York Heart Association (NYHA) class III/IV were enrolled for the present study over a period of 6. For this study purpose, AHF was defined as a sudden or recent onset of symptoms of HF (breathlessness, orthopnea, paroxysmal nocturnal dyspnoea or evidence of systemic venous congestion) that represented either a de novo presentation or decompensation of an established chronic heart failure (ADHF) and sufficiently severe to warrant hospitalization. After a rapid clinical evaluation in the ED, patients were admitted to the intensive care unit (ICU) for further management. All patients received optimal HF treatment as per current guidelines[32–34] which included diuretics, vasodilators and/or inotropes. Detailed history and physical examination were followed by laboratory tests which included a complete blood count, hemogram, blood glucose, renal, liver and thyroid function tests, Electrocardiography (ECG), chest X-ray and urinalysis. An etiology was established on the basis of these clinical and laboratory parameters. Ischemic etiology was classifiedbased

on the evidence of an old infarction (historically or presence of Q or non-Q myocardial infarction (MI) on ECG), ischemia on functionaltesting, chronic stable angina or documented coronary artery disease (CAD) (>50% stenosis in at least one major coronary artery) or revascularization (percutaneous or bypass surgery). Patients with significant renal (serum creatinine>2mg/dl), hepatic, pulmonary or valvular heart disease and sepsis were excluded from the study as were patients who presented with ACS (new-onset angina, ST segment depression ≥1mm on ECG, recent or acute Q or non-Q ST segment elevation MI) within the past one month. Informed consent was obtained from all patients before participation in the study, and the protocol was approved by the Ethical Committee of our institution.

Echocardiography

A detailed Echocardiographic examination was performed on all patients; all echocardiograms were performed by the same author (PS) on the PHILIPS En Visor C HD machine (PHILIPS ULTRASOUND, Bothell, WA, USA). Left ventricular (LV) and left atrial (LA) dimensions and LV ejection fraction (EF) were quantified as per American Society of Echocardiography (ASE) recommendations on chamber quantification (2005).[36] LV diastolic function was assessed as per the recommendations of ASE (2009)[37] using the following parameters of mitral inflow (E/A- mitral early/late diastolic velocities, DT-deceleration time of the mitral E wave, IVRT-Isovolumetric relaxation time) and LA volume Index (LAVI). Based on the LV EF, patients were divided into two groups: those with heart failure with reduced EF (HFrEF) (EF<50%) and those with preserved EF (HFpEF) (EF≥50%).

Results

The baseline characteristics of the 102 study patients are presented in Table 1.

(BMI=Body mass index, EF=LV ejection fraction, LDL=Low-density lipoprotein cholesterol, LVID= Left ventricular internal dimension in d (diastole) or s (systole)).

The mean age of the patients was 56.3±15.7 years, with roughly more than half of patients being males. Hyponatremia (Sodium level <135mEq/L) was seen in more than half of the patients (51%) with a mean sodium of 133.9±5.8mEq/L with a range of 121.4–146.8 mEq/L. The average duration of stay in the hospital was 5.8±2.9 days. Mean ST-2 level at baseline is 100.2±66.6ng/ml. Statistically significant difference was noted for baseline characters such as Age, ST-2,LVIDd, LVIDs, Diastolic stage, EF and fractional shortening between group 1 and 2 (Table 2).

Table 1: Baseline characteristics of the patients.

Baseline Characteristics	Values*
Age (in years)	56.3±15.7
% of males	52.9
Duration of hospital stay (in days)	5.8±2.9
Diabetes mellitus (%)	39.4
Hypertension (%)	35.5
BMI (in kg/m^2)	24.5±4.6
Smoking History (%)	39.2
% of Ischemic heart failure	30.8
Blood Glucose (mg/dl)	158.9±106.5
Hemoglobin (gm/dl)	12.4±2.5
Total blood count (per cumm)	9906±2463
Blood Urea (mg/dl)	51.3±33.9
Serum Creatinine (mg/dl)	1.4±1.0
Uric Acid (mg/dl)	7.9±2.7
Sodium (mEq/L)	133.9±5.8
Potassium (mEq/L)	4.0±0.8
Follow up duration(Days)	37.3±12
ST-2(ng/ml)	100.2±66.6
hsTropT (ng/ml)	0.34±0.92
LDL (mg/dl)	87.8±39.5
hsCRP (mg/dl)	4.2±3.3
LVIDd (mm)	5.4±0.9
LVIDs (mm)	4.4±1.0
% fractional shortening (FS)	22.7±8.4
EF (%)	38.5±9.3
% of patients with EF≥50%	17.6
Diastolic Stage	2.3±1.3

*Values expressed as mean± standard deviation (SD) and percentages.

Etiology of heart failure

The underlying substrate for HF was determined after the preliminary clinical examination and relevant biochemical and imaging evaluation. Neary half of the patients had dilated cardiomyopathy (44.1%), followed by ischemic heart failure (33.7%), hypertensive heart disease (18.3%), peripartum cardiomyopathy (3.9%) Thus, more than two-thirds (69.2%) of cases were of non-ischemic etiology (p=0.002) of which idiopathic dilated cardiomyopathy was the dominant form.

ST-2

The mean admission value was 100.2±66.6 and ng/ml. ST-2 values found significantly raised in Group1 compared to Group 2 (108.7±66.6 Vs 63.9±39.7) which is statistically significant (p=0.001). ST-2

is raised in group with events compared to non-event group but statistically insignificant (p=0.078) Table 2 and 3. A Receiver operating characteristic (ROC) curve analysis of admission ST-2 was performed (Fig. 1). At admission, an optimal cut-point of 185.5ng/ml predicted adverse outcomes with a sensitivity and specificity of 32.4% and 83.8% respectively (AUC=0.578, p=0.198) with a relative risk of adverse events of 1.0 (95% CI=0.99–1.0, p=0.407). ST-2 showedcorrelation with serum creatinine (r=0.29, p=0.002).

Table 2: Comparison of HFrEF and HFpEF.

Baseline Characteristics	HFrEF (n=84)	HFpEF (n=18)	p value
Age (in years)	50.0±15.5	66.5±13.5	0.0001*
% of males	53.5	51.5	0.850
Diabetes (%)	34.5	41.5	0.777
Hypertension (%)	27.2	47.5	0.233
BMI (in kg/m2)	24.7±4.4	24.3±4.2	0.725
% of Ischemic heart failure	38.5	50	0.469
Uric Acid (mg/dl)	8.1±2.7	6.8±3.1	0.074
Sodium (mEq/L)	134.5±5.6	133.5±7.0	0.512
ST-2(ng/ml)	108.7±66.6	63.9±39.7	0.001*
hsTropT (ng/ml)	0.36±1.0	0.06±0.11	0.220
hsCRP (mg/dl)	4.4±3.3	4.1±3.3	0.698
LVIDd (mm)	5.7±0.8	4.2±0.3	<0.0001*
LVIDs (mm)	4.5±0.8	2.9±0.4	<0.0001*
LV ejection fraction (%)	35.1±5.5	55.6±3.9	<0.0001*
Diastolic Stage	2.6±1.3	1.1±0.3	<0.0001*
Adverse Events (%)	37.1	18.5	0.177
Mortality (%)	10.5	5.0	0.525

(BMI = Body mass index, LVID = Left ventricular internal dimension in d (diastole) or s (systole)).

Table 3: Comparison of patients with or without an adverse event on follow-up.

Baseline Characteristic	Adverse event	No adverse event	p value
Age (in years)	56.7±15.1	56.1±16.1	0.856
% of males	62.5	49.8	0.445
Duration of hospital stay (days)	6.5±3.4	5.5±2.5	0.094
Diabetes Mellitus (%)	44.1	29.2	0.232
Hypertension (%)	41.1	24.1	0.121
Body mass index (kg/m^2)	24.8±4.6	24.25±3.6	0.492
Blood Glucose (mg/dl)	178.9±107.1	148.9±105.6	0.181
Hemoglobin (gm/dl)	11.6±2.6	12.8±2.4	0.018*
Total blood count (per cumm)	10267±2446	9545±2480	0.167
Serum Creatinine (mg/dl)	1.9±2.4	1.2±0.6	0.155
Uric Acid (mg/dl)	7.8±2.5	7.9±2.8	0.948
Sodium (mEq/L)	134.5±7.0	135.0±6.0	0.708
ST-2(ng/ml)	113.5±69.6	93.6±61.6	0.144
hsTropT (ng/ml)	0.25±0.47	0.23±0.6	0.865
hsCRP (mg/dl)	4.9±3.3	4.1±3.3	0.264
LVIDd (mm)	5.4±0.8	5.4±0.99	0.817
LVIDs (mm)	4.2±0.9	4.3±1.0	0.795
EF (%)	36.2±7.9	39.6±9.8	0.079
Follow-up duration (in days)	31.4±10.4	40.2±11.7	0.0003*

(EF=LV ejection fraction, LVID= Left ventricular internal dimension in d (diastole) or s (systole)).

hsTropT

Elevated Troponin (>0.014ng/ml) was seen in the majority of patients (98/102) (96.5%). Specifically, patients with heart failure of ischemic etiology had higher troponin compared with patients of non-ischemic etiology (0.45±1.0 versus 0.22±0.7ng/ml, p=0.188).hsTropT correlated with serum creatinine (r=0.53, p=<0.0001), and UA (r=0.49, p<0.0001). it was seen that no significant difference in non eventand events groupwereobserved. No statistically significant value of TNT between Group 1 and 2.

hsCRP

Elevated hsCRP (≥ 1.0 mg/dl) was seen in 79 out of 102patients (77.4%). CRP values between group1 and group 2 were found statistically insignificant (4.4±3.3 Vs 4.2±3.3, p=0.698). Between event and non event group (4.9±3.3 Vs 4.1±3.3,p=0.264) were not found statistically significant. Hs CRP was not correlated with creatinine (r=–0.06,p=0.507). ROC for admission TNT and CRP are depicted in Fig. 2 and 3.

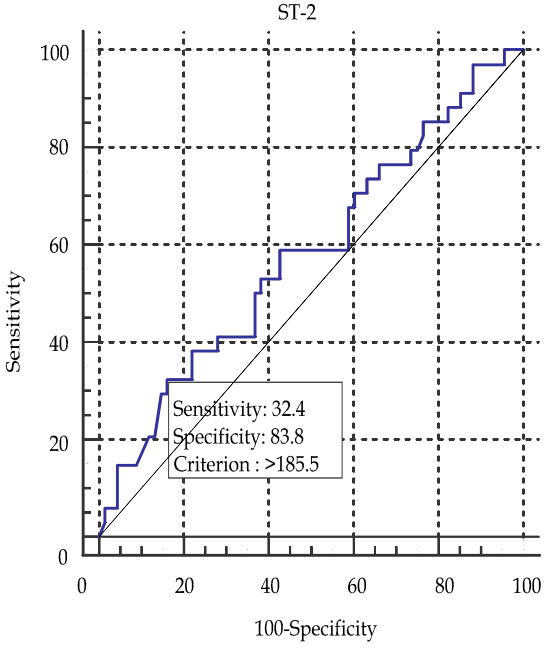

Fig. 1: Receiver operating characteristic curves for admission ST-2.

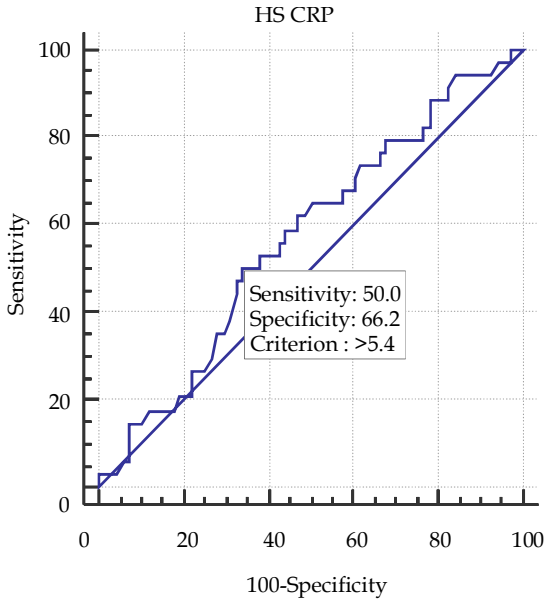

Fig. 2: Receiver operating characteristic curves for admission hS CRP.

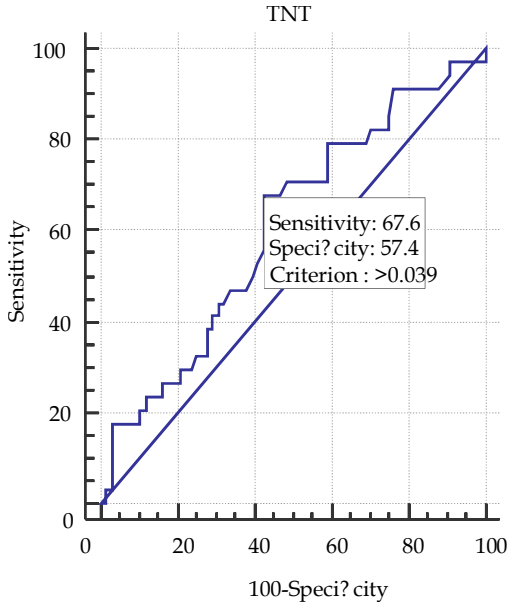

Fig. 3: Receiver operating characteristic curves for admission TROPONIN-T .

Echocardiography

The LV EF had a strong inverse relation to LV diastolic dimension (r=–0.78, p<0.0001). The average diastolic stage was 2.3±1.3. The average EF was 38.5±9.3%; majority of the patients thus had HFrEF (82.3%), the remainder (17.7%) having HFpEF. A comparison of these two groups with respect to baseline characteristics can be seen in Table 2.

Follow-up

Follow-up duration: Median follow-up of 37.3±12 (range 2 days to 68 days).

Adverse Events

A total of 34 patients (33.3%) had an end point on follow-up which included 9 deaths (8.82%) overall mortality, including 1.9% in-hospital mortality), 12 rehospitalisation forworsening HF symptoms and 21 patients in refractory HF (NYHA class III or IV). The remaining patients (66.7%) were in NYHA class I or II on follow-up with no revisits or rehospitalisation for worsening HF symptoms. Table 3 shows the comparison between the patients with or without an adverse event on follow-up. ST-2 is raised in group with events compared to non-event group but statistically insignificant(p=0.078) (Table 4). The other 3 biomarkers (hsTropT, hsCRP and UA) were not significantly different between the two groups. A regression analysis was done using the Cox proportional-hazards regression model (Table 5) with the variables of age, serum creatinine, serum sodium, ST-2, LV dimension in diastole, hsTropT, UA, hsCRP and LVEF. None were found to be an independent predictor of adverse outcomes in this study.

Table 4: Parameters in relation to events.

Parameter		Event (n=34)		No Event (n=68)		χ2	P-Value
		n	%	n	%		
HS TNT	Normal	1	3%	3	4%	0.130	0.718
	Increased	33	97%	65	96%		
HS CRP	Normal	7	21%	16	24%	0.112	0.738
	Increased	27	79%	52	76%		
ST-2	Normal	24	71%	58	85%	3.110	0.078
	Increased	10	29%	10	15%		

The biomarkers showed significant correlation with serum creatinine as shown in Table 6.

Table 5: Cox proportional-hazards regression analysis.

Variable	HR (95% CI)	p value
Age	1.01 (0.99–1.04)	0.168
Serum Creatinine	0.93 (0.77–1.13)	0.479
Sodium	0.96 (0.90–1.01)	0.189
LVIDd	0.99 (0.68–1.44)	0.974
ST-2	1.00(0.99–1.00)	0.407
Uric Acid	1.01 (0.89–1.15)	0.824
Troponin	1.27 (0.93–1.72)	0.186
HsCRP	0.98 (0.89–1.09)	0.814
EF (%)	0.96 (0.92–1.00)	0.107

Table 6: Spearman Correlation of biomarkers with baseline creatinine.

Biomarker	Spearman r	p value
ST-2	0.29	0.002
HsTropT	0.53	<0.0001
HsCRP	–0.06	0.507
Uric Acid	0.49	<0.0001

Discussion

ST2, an inflammatory cytokine and member of the interleukin (IL–1) receptor family, appears to predict mortality and heart failure and may play a vital role in cardiac pathophysiology.[38–42] ST2 is thought to be involved in modifying immunologic processes, specifically mediated by T-helper 2 lymphocytes.[38] Interleukin-33, a hormone which may protect against LVH and myocardial fibrosis[39] has recently been identified as the ligand for ST2. [38] The interaction between IL-33 and ST2L is necessary for the protective effect of IL-33 making it counterintuitive that high levels of sST2 have a deleterious effect. Because sST2 lacks both the transmembrane and the intracellular domains of its membrane-bound counterpart ST2, excess levels of sST2 bind and neutralize IL-33 without subsequently activating the beneficial signalling cascade. In this way, sST2 acts as a decoy receptor, limiting the availability of IL-33 to bind and activate the protective effects of ST2.[41,42]

Patients with acute HF often have ischemic events as the predominant cause.[43] In our study 69.2% of patients were of non-ischemic HF.

Presage® ST2 Assay is a quantitative sandwich monoclonal ELISA in a 96-well microtiter plate format for measurement of soluble ST2 in serum, EDTA plasma, or heparin plasma.The assay had lower control concentration of 23ng/ml with control range 19–27ng/ml and high control concentration of 81ng/ml with 63–99ng/ml control range. Less than 35ng/ml was used as normal value for all patients.

Higher median concentrations of ST2 were seen in patients with ADHF plus impaired left ventricular systolic function than those with non-systolic HF. Patients with elevated levels of both ST2 and BNP are at a considerably high risk of death compared with patients with none or with only one marker elevated.[25,26] In our study,we have not involved BNP as a biomarker and concentrations of ST-2 found high in patients with ADHF plus impaired LV function compared to preserved LV function group.

As shown by Shimpoet al,[29] baseline levels of ST2 were significantly higher in those patients who died or developed new congestive heart failure by 30 days. Moreover, in an analysis by quartiles of ST2, the risk of death and the composite of death or congestive heart failure increased in a graded stepwise fashion with higher levels of ST2. Overall, serum ST2 may be of prognostic value in assessing risk for heart failure and death.[29] Weinberg et al's concluded in his study from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE)-2 trial, which showed that change in ST2 levels, but not the baseline ST2, was predictive of 30-day mortality in patients with chronic NYHAClass III-IV HF.[24,25]

Some studiesshows that during HF decompensation, baselines ST2 concentrations correlate with clinical indicesof severity, such as NYHA functional class.[22,24] For ambulatory patients with HF, the only relevant data about s ST2 comefrom a sub-analysis of the PRAISE-2 Trial (Prospective Randomized Amlodipine Survival Evaluation–2). This study showed that change in sST2 level was an independent predictor ofmortality in a cohort of patients with established HF of non-ischemic origin.[22,24] In our study although there was high ST-2 levels found in events group compared to non-event group, there was no statistical significance (p=0.078).

In a larger pooled analysis of patients with acutelydecompensated HF, using the Presage ST2 assay, Rehmanetal[28] further examined the association between sST2 concentrations and clinical characteristics and prognosis. Unlikenatriuretic peptides, sST2 levels were not related to age, priordiagnosis of HF, body-mass index, or etiology (ischemic versus non-ischemic).[28] Same observation noted in our study but correlated with serum creatinine levels (r=0.293 andp=0.0028). In our study, patients with HFpEFhad lower values of ST-2 compared to those with HFrEF and found to be statistically significant (p=0.001). ST-2 correlated with serum creatinine for events (r=0.29 and p=0.002).

cTn is a heterotrimeric complex consisting of TnC (a 18kDa calcium-binding subunit), TnI (a 23 kDa unit that inhibits actin-myosin interaction and shuttles between binding actin and TnC in response to intracellular calcium), and TnT (an asymmetric 37kDa protein that binds Tn to tropomyosin); all being present in a 1:1:1 stoichiometric ratio.[44,45] TnT is released both as a Tn T:I:C complex (77kDa) and free TnT (37kDa). A persistently low level elevation or gradual decline is characteristic of cTn kinetics in AHF.[44]

Conclusions

We have prospectively evaluated the prognostic significance of ST-2 and other 3 serum biomarkers in this small cohort of acute heart failure patients.

Although ST-2, hsTropT, hsCRP and UA were all elevated in the vast majority of patients, None of them were independent predictor of adverse outcomes on follow-up. But Several important relations of biomarkers with various outcomes were derived in this study.

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