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Serum soluble ST2 as a potential mediator in prediction of heart failure after acute ST elevation myocardial infarction and primary percutaneous coronary intervention

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Abstract

Background: Serum soluble ST2 levels are elevated early after acute myocardial infarction (AMI) and are associated with lower pre-discharge left ventricular (LV) ejection fraction and adverse cardiovascular outcomes. **Objectives:** This study aimed to evaluate the efficacy of measuring serum soluble ST2 level in prediction of development of heart failure in patients with acute ST elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PPCI). **Methods and Results:** This study included 24 STEMI patients, with their age ranged from 34 to 72 years with a mean age of 56.71±9.59 years. All of cases underwent successful PPCI. Serum soluble ST2 level was measured at index presentation and at follow up after 30 days, and assessed the cases clinically. Echocardiography are used for assessment of development of cardiac muscle dysfunction. Patients diagnosed as having HF had statistically significant higher levels of ST2 than other patients at 30 days follow up. A highly significant positive correlation was shown between ST2 level and LVMI. Serum soluble ST2 level revealed significant positive correlation with degree of diastolic dysfunction at time of presentation. **Conclusions:** Measurement of serum soluble ST2 level, after acute STEMI managed with primary PCI can help prediction of both early and delayed onset heart failure development.

Keywords: Serum soluble ST2, Heart failure, Left ventricular mass index.

INTRODUCTION

Development of heart failure (HF) after acute ST elevation myocardial infarction (STEMI) is a major cause of morbidity and mortality [1]. Left ventricular remodeling is a key factor of the development of overt heart failure and is an important predictor of worse prognosis after STEMI [2]. Prediction of LV remodeling and dysfunction after acute myocardial infarction treated with primary PCI not only depends on angiographic data involving either epicardial blood flow, by TIMI grade, or myocardial perfusion , by myocardial blush grade (MBG). Furthermore, it involves a variety of clinical, echocardiographic, and laboratory indicators. One of promising biomarkers of left ventricular and infarct remodeling after acute myocardial infarction is Serum soluble ST2 [3].

Some biomarkers considered as a valuable tool that can help physicians to address more efficiently the management of the different stages of the heart failure, from early detection and diagnosis to risk prediction and also guiding therapy [4,5].

Although ST2 effect is strongly belonged to IL-33 mechanism, its action in cardiac muscle is complicated and not enough clarified**.** IL-33 produce an anti-hypertrophic action by blocking the mechanism of angiotesin II or phenylephrine on myocardium. sST2, by acting as a decoy receptor, reduces the positive actions of IL-33 [6]. Thus, an increase in sST2 could reduce the cardioprotective action of IL-33 on cardiomyocytes and could induce a negative prognostic effect on the overall cardiovascular risk profile [7-9].

Recent studies have demonstrated soluble ST2 as a cardiovascular biomarker to be a strong predictor of cardiovascular outcomes in both chronic and acute heart failure through elevation in cases with acute MI [6,10-12].

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Serum soluble ST2 predicts cardiac mortality in patients with non-ischemic heart failure and could be useful especially in patients with inflammatory background [13]. Elevated sST2 concentration may involve in the progression of atrial fibrillation (AF) as sST2 is probably an objective biomarker that can predict AF patients' risk of heart failure [14]. Increased sST2 levels were closely related to the risk of adverse clinical problems in acute HF, but prognostic value of baseline sST2 decreased after control of clinical covariates and amino-terminal pro–B-type natriuretic peptide. In those with elevated baseline sST2 levels, maintained high sST2 levels at follow-up were associated with increased deaths [15].

This study was conducted to evaluate the efficacy of measuring serum soluble ST2 level in prediction of development of heart failure in patients with acute ST elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PPCI)

MATERIAL AND METHODS

Patients and Methods

This study was carried out at Cardiology department, Specialized Medical Hospital (SMH), Mansoura, Egypt, in the period from June 2016 to June 2017 after approval of the local ethical committee of Faculty of Medicine, Mansoura University. This study included 24 STEMI patients all managed via invasive mechanical reperfusion, 15 with anterior STEMI; 5 with inferior STEMI and 4 with inferolaterl STEMI, with age ranging from 34-72 years old, with a median age of 56.71±9.59 years. Patients gave their signed written consents after detailed explanation of the protocol of the study.

All patients were subjected to the following; I) History taking and clinical examination, II) serial electrocardiographic recordings, III) echocardiographic evaluation including LVEF, EVEDD, LVESD, LVMI, RSWMAs, D.D and presence of mechanical complications, IV) Measurement of serum soluble ST2 level within 24 hours of index presentation and after 30 days at follow up visit.

Ethical statement

Study protocol approved by Medical Ethics research Committee of the faculty of medicine, Mansoura University, Egypt and from the mangers of the hospital in which the study conducted. Informed written consent obtained from each participant in the study. Confidentiality and personal privacy respected in all levels of the study. Collected data will not be used for any other purpose.

RESULT

The result of this study showed that the males are significantly higher (79.2%) than females (20.8%) in the studied group. Smoking was the most prevalent risk factor, followed by hypertension, diabetes mellitus and obesity. Of the investigated patients, 37.5% had two risk factors, while 45.8% had three or more risk factors. 54.2% of studied population had an abnormally high LVMI, with a mean value of 122.46 gm/kg/m^2, higher than upper normal limits defined as 115 gm/kg/m^2 for males and 95 gm/kg/m^2 for females (Table 1).

Table 1: Comparison of demographic data of studied groups

Criteria		Study group (n=24)	
		No.	%
Age	Mean ± SD	56.71±9.59	
	Min-Max	34-72	
Sex	Male	19	79.2
	Female	5	20.8
Number of risk factors	1	4	16.7
	2	9	37.5
	3	5	20.8
	>3	6	25.0
Left ventricular internal dimensions	Normal	20	83.3
	Dilated	4	16.7
Left ventricular mass index (LVMI)		122.64±29.85	
LVMI interpretation	Normal	11	45.8
	Mild	1	4.2
	Moderate	6	25.0
	Sever	6	25.0
Mitral Regurgitation	No	14	58.3
	Mild	7	29.2
	Sever	1	4.2
	Moderate	2	8.3
HF	No	6	25.0
	Yes	18	75.0
HF class	HFpEF	8	44.4
	HFmrEF	7	38.9
	HFrEF	3	16.7

Data expressed as mean ± SD or no (%)
n : number, SD : standard deviation.

Table 2: Comparison of Serum Soluble ST2 Level at 1st day and at 30 days Follow Up

		1st	2nd	P value
ST2	Median	25.75	26.2	0.830
	Min-Max	12.5-117.9	14-74.8	

There was no statistically significant difference between ST2 levels at first contact and at follow up after 30 days (Table 2).

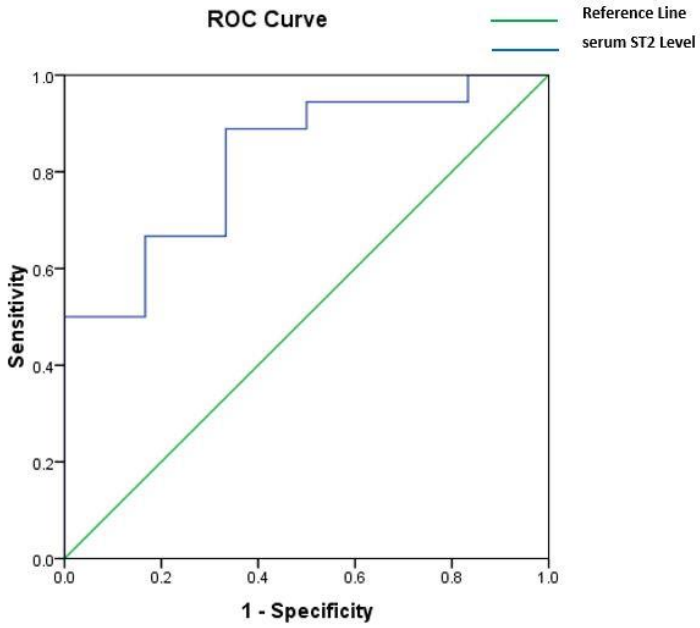
Serum soluble ST2 level revealed significant positive correlation with degree of diastolic dysfunction at time of presentation (Table 3).

This study proved negative correlation between serum soluble ST2 level after 30 days of PPCI and all of EF, MBG and STR; only the latest had a statistical significance. A highly significant positive correlation was shown between ST2 level and LVMI (Table 3). Patients diagnosed as having HF had statistically significant higher levels of ST2 than other patients at 30 days follow up (Table 4).

Roc Curve for Prediction of HF by ST 2 Level showed adequate reliability of test results with an area under the curve (AUC) of 0.824 (Figure 1). The test shows an initially accepted profile with an AUC of 0.82 and accuracy of 70-75%. Kruskal-Wallis was used. No significant difference was noted in serum soluble ST 2 level among HF subgroups (Table 4).

Table 3: Correlation between serum sST2 level in first 24 hours and at 30 days follow up visit after STEMI onset and other parameters

Item	ST2 in 1st 24 hours		ST2 at Follow up visit	
	R	P	R	P
Killip	0.040	0.851		
Ejection fraction in 1st 24 hours	0.265	0.211		
Ejection fraction at 30 days follow up	0.060	0.780		
GRACE score	-0.113	0.599		
Diastolic dysfunction at 1st 24 hours	0.422	0.04*		
maximum CPK	0.124	0.563		
NYHA class at F.U			0.494	0.014*
Ejection fracionat follow up			-0.067	0.757
Diastolic dysfunction at follow up			0.410	0.047*
ST segment resolution			-0.453	0.026*
MBG			-0.224	0.293
Left ventricular mass index			0.874	<0.001**



AUC*	95% CI		Cut off ng/ml	Sensitivity	Specificity	PPV#	NPV§	Accuracy
	Lower	Upper						
0.824	0.640	1.008	18.95	94.4%	16.7%	77%	50%	75%
			25.85	66.7%	83.3%	92%	45%	70%

Figure 1: Roc Curve for Prediction of HF by serum ST 2 Level

Table 4: Relation between serum ST2 levels at 30 days follow up assessment and HF Class

		No HF (n =6)	HF (n=18)	p-value	HFpEF (n=8)	HFmrEF (n=7)	HFrEF (n=3)	p-value
ST2	Median	22.1	27.35	0.02*	27.05	26.6	28.1	0.955
	Min-Max	14-27.1	18.9-74.8		21.6-74.8	18.9-37.1	25.1-32	

DISCUSSION

In this study, the incidence of HF within 30 days of onset of STEMI was 75% of cases, which is higher than previous studies showing 28-46% [16] and 31-39% [17]. The higher incidence of HF in our work can be explained by dominance of anterior MI making up 63% of cases, integrated diagnosis of HF in the context of clinical, echocardiographic and biochemical parameters, and comprehensive approach to HF in the form of HFrEF, HFmrEF and HFpEF [18].

In this study, we tried to establish clear correlation between LV function and serum soluble ST 2 level. Patients diagnosed as having HF had statistically significant higher levels of serum sST2 than other patients at 30 days follow up. We identified a cut off level of 25.8 ng/ml in human serum with an initially accepted sensitivity of 66.7%, a sufficient specificity of 83.3%, AUC of 0.824 and an overall test accuracy of 70%. A lower cut off value of 18.95 ng/ml revealed a higher sensitivity of 94.4% but on the expense of lower specificity. sST 2 level could be a valuable prognostic marker in risk stratification of patients with MI, HF and dyspnea. Involvement of serum soluble ST2 in a multi-marker approach with NT-pro BNP and cardiac Tn can yield a higher prognostic value.

In contrast to previous studies which illustrated a cost effective benefit of serial measurement of sST2 level after MI [19]. This study revealed no specific pattern of change in ST2 level after reperfusion. This is mostly due to limited number of cases in our study plus obtaining only two measurements at 0 and 30 days in contrast to 4 measurements in 0, 12, 30 and 180 days after STEMI onset

However, there was no significant difference between the three classes of HF. This can be explained by involvement of IL 33 / ST 2 pathway in multiple pathophysiological mechanisms in regulating myocardial dysfunction after MI. In accordance with previous trials [20-22], we failed to prove direct significant relation between sST 2 level and LVEF. A significant relation was found between ST 2 level and degree of D.D and LVMI. This goes with the findings that a decrease in serum sST 2 level with progressive functional recovery and reverse remodeling [23].

CONCLUSION

Measurement of serum soluble ST2 level, after acute STEMI managed with primary PCI can help prediction of both early and delayed onset heart failure development. This can aid risk stratification of STEMI patients for development of heart failure, thus guide early administration of adjuvant therapy in peri-procedural period and starting anti-remodelling pharmacological treatment on first admission and on discharge.

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Author Contributions

A.H.E.; A.R.E., T.E.S., E.M.A.D.: research plan design, data collection and manuscript writing; A.R.E., T.E.S., E.M.A.D.: acquisition, analysis, and interpretation of data; A.H.E.; A.R.E., T.E.S., E.M.A.D.: participated in manuscript revision. All authors have read and approved the manuscript and the full disclosure of any relationship with industry is declared.

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Disclosure

The authors have no conflict of interest to declare.

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