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Assessment of Serum Soluble Suppression of Tumourgenicity-2 level in Patients with Acute Myocardial Infarction

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ABSTRACT

Background: The "gold standard" approach for diagnosing myocardial infarction (MI) in patients with a high risk of the condition is cardiac troponins T or I (cTnT or cTnI), which are more accurate than CK-MB for myocardial damage. In addition to these well-known biomarkers, several intriguing biomarkers have gained attention in MI over the past few years. Soluble suppression of tumorigenicity-2 (sST-2), also known as Interleukin-1 receptor-like 1 (IL-1RL-1) is one of such biomarkers.

Aim: this study aimed to assess the association of sST-2 with acute MI among Egyptian population.

Patients and methods: A total of 72 individuals were enrolled in the study, including thirty-six patients with MI and thirty-six healthy normal controls. sST-2 was measured by ELISA in both groups. sST-2 was measured in patients with MI at two occasions: during first 24 hours of chest pain and 30 days after.

Results: sST-2 level was higher in MI patients compared to normal controls. The level of sST-2 declined after 30 days after attack compared to day one. A positive correlation was found between serum level of sST-2 and cardiac marker of necrosis: serum CK ($r = 0.65$, $p < 0.001$), CK-MB ($r = 0.51$, $p = 0.001$), and LDH ($r = 057$, $p < 0.001$). Soluble ST-2 was negatively correlated with ventricular ejection fraction ($r = -0.40$, $p=0.015$). We found that a cut-off value of 150 pg/ml for sST-2 denoted the presence of MI with 86.11% sensitivity and 80.56% specificity ($p<0.001$). ROC curve was plotted for serum sST-2 to indicate the development of complications after MI sets a threshold value of 3100 pg/ml with 90% sensitivity and 96.15% specificity ($p<0.001$).

Conclusions: sST-2 is a potential biomarker for acute myocardial infarction (AMI) and possible predictors for the risk of myocardial damage in the Egyptian population.

Keywords: sST-2 biomarker- Acute myocardial infarction- IL-33.

INTRODUCTION

Worldwide, heart disease is one of the main causes of death. The most common causes of ischemic heart disease (IHD) include fixed stenosis, acute rupture or dissection of an atherosclerotic coronary artery, coronary artery spasm, embolism, or vasculitis. IHD is caused due to inadequate oxygen delivery to meet the metabolic demands of heart muscle [(1)]. Early pericarditis, post-MI syndrome, left right ventricular infarction, ventricular mural thrombus and cardiogenic shock are some of the complications of myocardial infarction [(2)].

Clinicians commonly perform testing for biomarkers of myocardial injury such as the cardiac troponins T or I (cTnT or cTnI) or creatine kinase-MB (CK-MB) for patients with a moderate to high risk of MI. A perfect serum biomarker for myocardial injury had to be specific, sensitive, and quantitative with a rapide increase in serum levels for early detection. Since troponins are more specific than CK-MB for myocardial injury, they are now considered as a 'gold standard' method for diagnosis of myocardial infarction [(3).]

Along with these well-established biomarkers, a number of promising biomarkers for MI have attained interest in the past few years such as N-terminal pro-B-type natriuretic peptide, heart-type fatty acid binding protein, copeptin, mid-regional pro-atrial natriuretic peptide, growth differentiation factor-15, choline, placental growth factor, soluble CD40 ligand, C-terminal pro-endothelin 1 and mid-regional pro-adrenomedullin [(4)]. All provide additional data to predict death and heart failure following MI. Some markers such as myeloperoxidase and high-sensitivity C-reactive protein (hs-CRP) in healthy normal people predict risk of coronary disease and allow physicians to begin early preventive treatment [(3)]. Soluble suppression of tumorigenicity-2 (sST-2), also known as interleukin-1 receptor-like 1 (IL-1RL-1), is one of such biomarkers [(4)].

sST-2 is one of the members of the toll-like/Interleukin-1 receptor superfamily. It was known in 1989. In 2002, it was found that cardiac cells might express it in response to myocardial stress, bringing attention to its potential role in the cardiovascular system. sST-2 has two major isoforms: soluble or circulating (sST-2) and transmembrane or cellular (ST-2L) [(5)].

ST-2 is the receptor for interleukin-33 (IL-33), which is an IL-1-like cytokine, released by living cells in response to cell injury, and by cultured myocytes encountered mechanical stress. By binding to the transmembrane receptor ST-2L isoform, IL-33 makes its action. In experimental models, it has been proved that the

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interaction of IL-33 and ST-2L improves myocardial function by reducing myocardial fibrosis, cardiomyocyte hypertrophy, and apoptosis. This cardioprotective action occurs through the ST-2L receptor only. The IL-33/ST-2 system is activated in cardiomyocytes and fibroblasts in response to cardiac damage. When soluble ST-2 binds to IL-33, it competes with ST-2L, blocking the IL-33/ST-2L pathway, which reduces the previously mentioned cardioprotective effects. So, sST-2 is thought to be a negative regulator of IL-33/ST-2 signaling pathway [(2)].

The major role of ST-2, which activates IL-33, is to inhibit hypertrophy and fibrosis of cardiomyocytes that are stretched biomechanically [(6,7)]. However, an increase in the ST-2 level has been noticed when damage is accompanied by IL-33 inhibition and its beneficial antihypertrophic function. Therefore, the ST-2 system functions as both an inhibitor of IL-33 through its soluble sST-2 isoform as well as a mediator of IL-33 function through its ST-2L transmembrane isoform [(8,9,10)].

Some studies showed that ST-2 is an early marker of myocardial remodeling and that it is expressed on microvascular endothelial cells and macrovascular (aortic and coronary artery) in the heart in humans [(11)] as well as on cardiomyocytes in rats and mice [(9)] when underwent biomechanical strain [(12)]. Thus, it is a promising marker. Experimental models showed that reduced expression of ST-2 gene resulted in increased myocardial fibrosis and hypertrophy. Moreover, ST-2 gene was significantly increased during myocyte stretch, and mice deficient in ST-2 gene developed dilated and hypertrophied left ventricles, poor ejection fractions and shorter life [(13)].

PATIENTS AND METHODS

Thirty-six patients with acute MI were included in the study within 24 hours of the onset of chest pain and 30 days after the event. All patients were followed-up for the occurrence of serious adverse cardiovascular events over the course of the 30 days, including cardiomyopathy, arrhythmia, recurrent infarction, heart failure, and death. The research was conducted at Suez Canal University Hospital from May 2017 to February 2019.

Inclusion criteria: Patients who met the following criteria for an acute MI diagnosis (typical chest pain lasting longer than 20 minutes, laboratory findings (elevated CK, CK-MB, and troponin T levels [> 0.1 ng/mL], and ST-segment elevation of 0.1 mW in two or more contiguous leads and appearance of a complete left bundle branch block on an ECG).

Exclusion criteria: Patients who currently had a serious infection or inflammatory disease, organ failure, an autoimmune disease, a malignancy, long-term corticosteroid treatment, pregnant or nursing, or unwilling to provide informed consent were all excluded from the trial.

Full history was taken including age, sex, education, material status, employment, any existing medical conditions, such as hypertension, hyperlipidemia, diabetes and current acute MI symptoms. A healthy control group with the same age and sex visiting the hospital for routine check-up or blood donors.

Two mL of whole blood were withdrawn from each individual and evacuated into plain blood collection tubes. Blood was left to clot at room temperature then centrifuged at 1000 X g for 15 minutes at room temperature, and serum was stored in aliquots at −20°C until analyzed. The results of the following investigations were obtained from the patients' records: CK, CK-MB, LDH, and Troponin, HbA1c, LDL, HDL, Triglycerides & cholesterol. Assessment of serum sST-2 concentrations were done for both groups by Human IL1RL1/ST-2 PicoKine™ ELISA Kit (Boster Biological Technology Catalog Number: EK1116).

Ethical approval: A written consents were taken from all patients to take part in the current research. They were informed about research, aim and benefits of this study. A consent for using the data of the patients' files in the study was taken from Suez Canal University Hospital and Patients. To ensure data confidentiality a code number for linking the data from each subject was used. All data obtained from everyone were strictly confidential and were not used outside this study. The study was conducted with approval from The Scientific Research Ethical Committee of Suez Canal University. This research was conducted in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for human studies.

Statistical analysis: Data were analyzed using ANOVA to determine the statistical significant differences between groups. Statistical significance was at $P \leq 0.05$. The statistical software used was SPSS 24.0.

RESULTS

The study involved a total of 72 individuals including thirty-six patients with MI and thirty-six normal controls. Patients with MI were tested at two-time points; during first 24 hours of chest pain and 30 days after the attack. Patients aged between 52-64 years were found to be more susceptible of having acute MI. Male gender were more likely than females to develop MI. Regarding age and gender, there were no statistically significant differences between the studied groups (p=0.117, 1 respectively) (Table 1).

Table (1): Demographic characteristics of the study population

	Control (n = 36)	Patients (n = 36)	P-value
Gender			
Male n (%)	29 (80.6%)	29 (80.6%)	1.000
Female n (%)	7 (17.4%)	7 (14.4%)	
Age (years)			
Mean ± SD.	56.22 ± 3.86	58.11 ± 6.0	0.117

Quantitative data are represented by Mean/SD, range and tested by student t-test (age), Qualitative data represented by chi-Square (gender), *p ≤ 0.05: statistically significant

Baseline characteristics and risk factors of MI patient group:

Cholesterol indices were near or above optimal level. While cardiac markers of necrosis (CK, CK-MB and LDH) were elevated. Diabetic patients showed poor glycemic control **(Table 2)**. Patients with Diabetes Mellitus (DM), hypertension, and active smokers were more prone to develop MI. Twenty patients of the study group were active smokers representing 55.6% of patients. Nineteen patients (52.8%) were diabetic, and seventeen patients (47.2%) were hypertensive. Dyslipidemic patients were 13 (36.1%). Patients with previous history of MI were 12 (33.3%). Only 3 of patients (8.3%) gave family history of cardiac disease **(Table 3)**.

Table (2): Baseline characteristics of patient group (n = 36)

		Mean ± SD
LDL	(mg/dl)	128.8 ± 4.44
HDL	(mg/dl)	36.36 ± 3.04
Triglycerides	(mg/dl)	170.3 ± 10.4
Cholesterol	(mg/dl)	201.3 ± 4.15
LDH	(U/L)	804.9 ± 81.0
CK-MB	(U/L)	173.2 ± 6.9
HbA_1c	%	7.17 ± 1.49
CK	(U/L)	2011.7 ± 87.6
EF	(%)	53.19 ± 10.22

Quantitative data are represented by Mean/SD and range. LDL stands for Low density lipoprotein. HDL stands for high density lipoprotein. LDH stands for lactate dehydrogenase. CK stands for Creatine kinase. HbA_1c stands for hemoglobin A_1c. EF stands for ejection fraction

Table (3): Distribution of MI risk factors in patient group (n = 36)

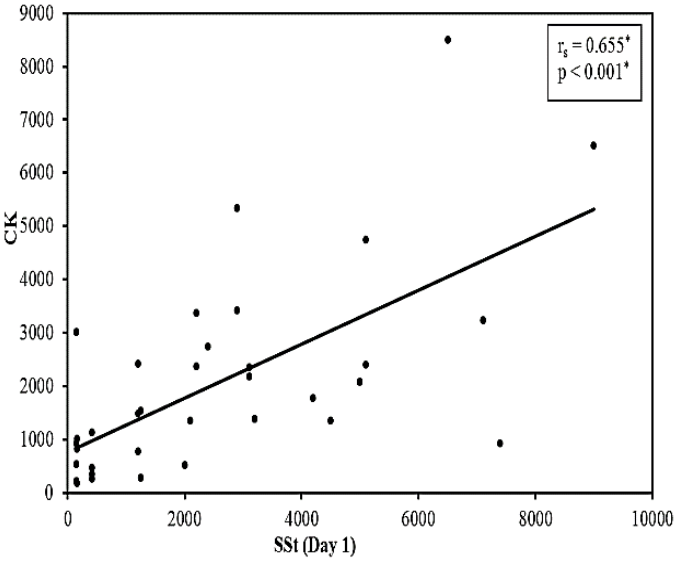
Risk factor	N (%)
IHD	12 (33.3%)
Family history	3 (8.3%)
Active Smoking	20 (55.6%)
Diabetes mellitus	19 (52.8%)
Dyslipidemia	13 (36.1%)
Hypertension	17 (47.2%)

Qualitative data represented by chi-Square Test, IHD: Ischemic heart disease.

Correlation between serum sST-2 level and different parameters in MI patients:

Serum level of sST-2 and cardiac markers of necrosis were positively correlated: serum CK (r = 0.65, p <0.001), CK-MB (r= 0.51, p= 0.001), and LDH (r= 057, p< 0.001) (Figure 1). Ventricle ejection fraction and soluble ST-2 were found to be negatively correlated (r= -0.40, p=0.015) (Figure 2). There was no correlation observed between sST-2 and cholesterol indices or HBA1c (Table 4).

Figure (1): Correlation of serum soluble ST-2 concentration Vs cardiac enzymes in MI patients.



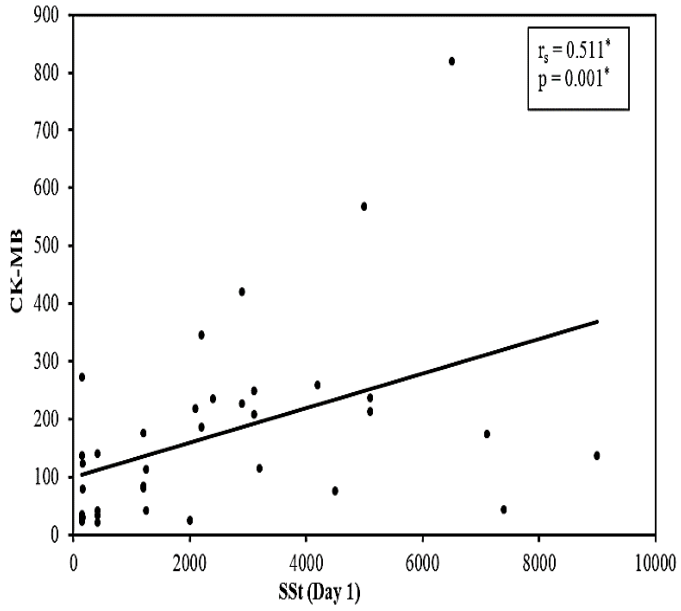


Figure (2): Correlation of serum soluble ST-2 level concentration and left ventricular ejection fraction in MI patients.

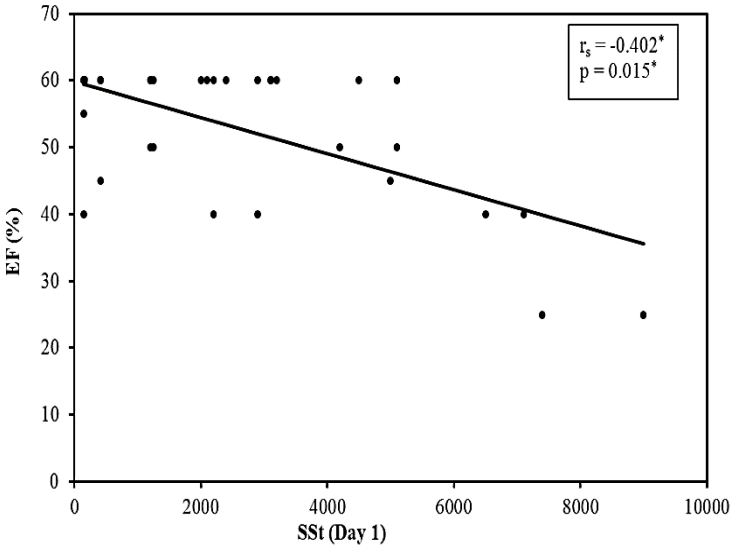


Table (4): Correlation between serum sST-2 levels and MI patients' parameters

Characteristic	sST-2 (Day 1)	
	R	P-value
HDL	0.249	0.144
LDL	-0.006	0.972
TG	0.085	0.623
Cholesterol	0.040	0.817
LDH	0.573	**<0.001***
CK-MB	0.511	**0.001***
HBA_1C	-0.095	0.583
CK	0.655	**<0.001***
Ejection fraction (%)	-0.402	**0.015***

Coefficient of correlation (R) was calculated using Pearson and Spearman tests, *Statistically significant at $p \leq 0.05$

Relation between serum soluble ST-2 concentrations and MI risk factors:

Serum sST-2 concentrations did not differ between patients with classical MI risk factors as DM, dyslipidemia, IHD, smoking or family history and those without. Meanwhile, serum sST-2 concentration was significantly higher among patients suffering from hypertension than those not suffering (3565.88 ± 272.94 vs 1490.95 ± 157.86 respectively, P=0.01) (Table 5).

Table (5): Relation between serum sST-2 (Day1) and MI risk factors in study group (n = 36)

Risk factor	N	sST-2 (pg/ml) Day1 Mean ± SD	P-value
IHD			
No	**24**	2420.13 ± 242.82	0.814
Yes	**12**	2572.08 ± 246.22	
Family history			
No	**33**	2598.24 ± 244.06	0.229
Yes	**3**	1068.67 ± 158.98	
Smoking			
No	**16**	2242.38 ± 213.14	0.936
Yes	**20**	2653.50 ± 263.11	
DM			
No	**17**	2095.94 ± 208.12	0.579
Yes	**19**	2806.16 ± 266.53	
Dyslipidemia			
No	**23**	2107.65 ± 205.50	0.306
Yes	**13**	3113.23 ± 290.16	
Hypertension			
No	**19**	1490.95 ± 157.86	**0.010***
Yes	**17**	3565.88 ± 272.94	

Mann Whitney T. to compare between sST-2 levels in those with and without MI risk factors. Quantitative data are represented by Mean/SD, range and tested by t test, Qualitative data represented by chi-Square T, *p≤0.05: statistically significant

Concentrations of serum soluble ST-2 in patients on day 1 and day 30 after acute MI vs controls:

On the first day of hospital admission for MI, the levels of sST-2 were 16.6-fold higher compared to healthy normal controls (2470.8 ± 240.3 vs. 148.39 ± 89.26, P <0.001). By day 30, the levels of serum sST2 significantly decreased by 20.6-fold (119.6 ± 18.6 vs. 2470.8 ± 240.3, P <0.001). Serum sST-2 concentrations did not differ between day 30 and control group (119.6 ± 18.6 vs. 148.39 ± 89.26, P=0.93) (Table 6 and figure 3).

Table (6): Concentrations of serum sST-2 on day 1 and day 30 after acute MI vs controls

sST-2 (pg/ml)	Control (n = 36)	MI patients (n = 36)	
		Day 1	Day 30
Mean ± SD	148.39 ± 89.26	2470.8 ± 240.3*	119.6 ± 18.6†

Quantitative data are represented by Mean/SD, range and tested by T- test Mann Whitney t. to compare between control and day1, and between control and day30 Wilcoxon signed ranks used for comparing between day1 and day30 *Compared with the control group (P <0.05); † Differences between day 1 and day 30 (P <0.05): statistically significant

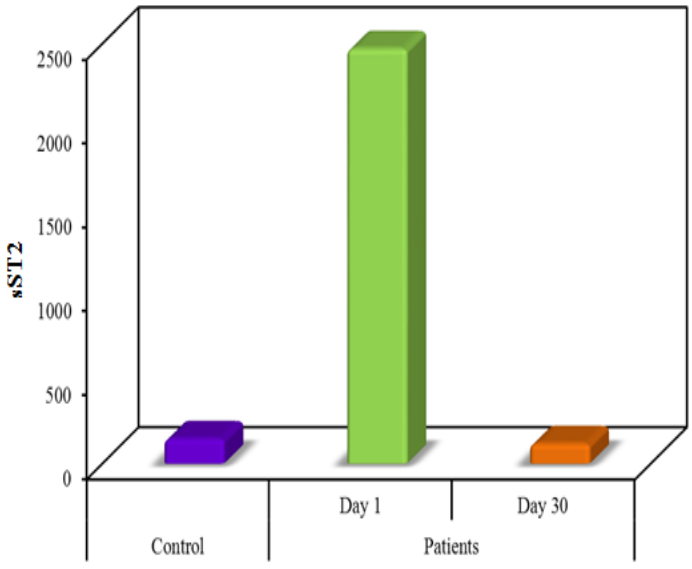


Figure (3): Concentrations of serum sST-2 on day 1 and day 30 after acute MI vs controls.

Development of complications among MI patients:

Thirty days after acute MI, patients were followed-up and were divided into two groups depending on the development of complications, patients' group with favorable outcome (n=26) and group with unfavorable outcome (n=10). Twenty-six patients (72.2%) did not develop any complications, while ten patients (27.7%) developed unfavorable outcome. Four patients (11.1%) developed heart failure, three patients (8.3%) developed arrhythmia, three (8.3%) developed another MI attack, and only one case (2.8%) developed cardiomyopathy (Table 7).

Table (7): Distribution of complications in patients' group (n = 36)

Complications	N (%)
No	26 (72.2%)
Yes	**10 (27.7%)**
Arrhythmia	3 (8.3%)
Heart failure	4 (11.1%)
Cardiomyopathy#	1 (2.8%)
Recurrent infarction	3 (8.3%)

#: A case developed both cardiomyopathy and heart failure.

Association between serum sST-2 level on day 1 after acute MI and development of complications in patients' group:

The level of serum sST-2 in the group with unfavorable outcome on day 1 was 4.6-fold more than in the favorable group (n=26) (5700.0 ± 1765.09 Vs 1228.77 ± 108.44 respectively, P<0.001), while its level did not differ among both groups on day 30 after MI. On day 1, serum concentration of sST-2 in the group with unfavorable outcome was 38.4-fold greater than in control group (5700.0 ± 1765.09 Vs 148.39 ± 89.26 respectively, P<0.001) **(Figure 4 and table 8)**. Patients suffered from heart failure showed the highest sST-2 level among the unfavorable outcome group **(Table 9)**.

Figure (4): Concentration of serum sST-2 among the groups with favorable and unfavorable outcome

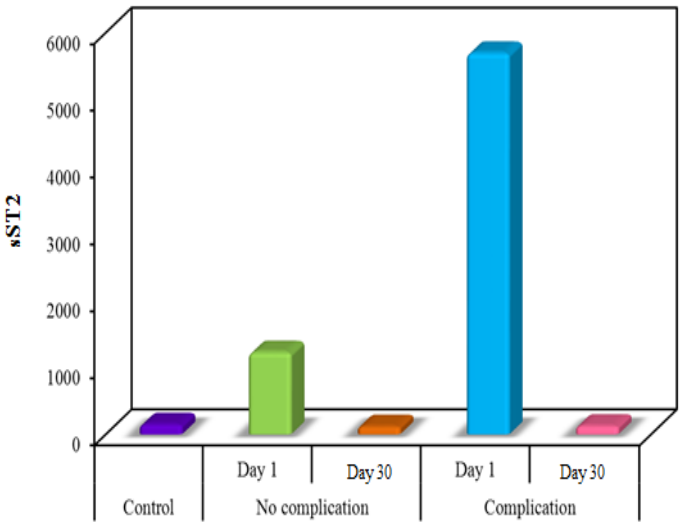


Table (8): Serum sST-2 concentration among groups with favorable and unfavorable outcome

sST-2 (pg/ml)	Control (n = 36)	Favorable outcome group (n = 26)		Unfavorable outcome group (n = 10)	
		Day 1	Day 30	Day 1	Day 30
Mean ± SD	148.39 ± 9.26	1228.77±18.44	117.69 ± 8.61	5700.0 ± 1765.09	124.50 ± 18.63
P_1		<0.001*	0.601	<0.001*	0.470
P_2		<0.001*		<0.001*	

Mann Whitney T for comparing between control and each other groups. Wilcoxon signed ranks for comparing between day 1 and day 30. * P ≤ 0.05: statistically significant.

Table (9): Concentration of serum sST-2 (Day1) among complicated MI patients

Complications	N	sST-2 (pg/ml) Day1 Mean ± SD	P-value
Arrhythmia	**3**	4766.67±493.29	0.049*
Heart failure	**4**	7500.0±1067.71	<0.001*
Cardiomyopathy	**1**#	7100.0	-
Recurrent MI	**3**	4233.33±1026.32	0.088

Quantitative data are represented by Mean/SD, range and tested by T test, Mann Whitney T: to compare between complicated cases. #: only one case was complicated with cardiomyopathy, so it has no range or SD. * p ≤ 0.05 statistically significant.

Assessment of serum sST-2 levels as a potential indicator of MI:

The optimal cut-off value of 150 pg/ml for serum sST-2, which indicated the existence of MI with 86.11% sensitivity and 80.56% specificity (p<0.001), was investigated using Receiver-operating characteristics (ROC) curve **(Figure**Error! Reference source not found. **5)**.

Assessment of serum sST-2 levels as a potential predictor of complications after acute MI:

ROC curve was plotted for serum sST-2 to indicate the development of complications after MI sets a threshold value of 3100 pg/ml with 90% sensitivity and 96.15% specificity (p<0.001) **(Figure**Error! Reference source not found. **6)**.

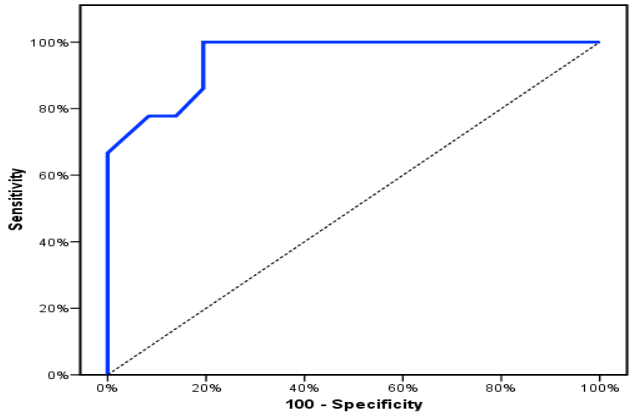


Figure (5): ROC curve for serum sST-2 (Day 1) for prediction of MI.

	Cut off	AUC	95% CI	Sensitivity	Specificity	P-value	PPV	NPV
sST-2 (Day 1)	**>150 pg/ml**	0.954	0.914 – 0.995	86.11%	80.56%	<0.001*	81.6	85.3

Symbols and abbreviation:

AUC: Area under a Curve P value: Probability value

CI: Confidence Intervals
PPV: positive predictive value
NPV: negative predictive value

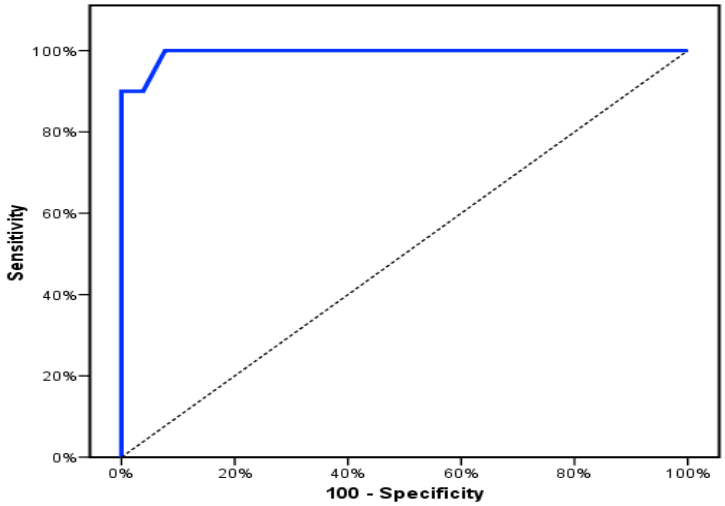


Figure (6): Roc curve for serum sST-2 (day 1) for prediction of complications after MI

	Cut off	AUC	95% CI	Sensitivity	Specificity	P-value	PPV	NPV
sST-2 (Day 1)	**>3100 pg/ml**	0.994	0.978 – 1.010	90.0%	96.15%	<0.001*	90.0	96.2

AUC= Area under a Curve
P value= Probability value
CI= Confidence Intervals
PPV= positive predictive value
NPV= negative predictive value

DISCUSSION

Among all the cardiac emergencies, acute myocardial infarction (AMI) is the most common and serious condition. It is still one of the worst diseases in the world. Therefore, precise risk classification is crucial for better clinical treatment, management, and decision-making. The prognosis of MI patients depends on a number of clinical characteristics and laboratory findings. Soluble ST-2, a member of the interleukin (IL)-1 receptor family, has been related to the fibrosis and remodeling of myocardium. An excess of soluble circulating sST-2, which is expressed by cardiomyocytes and cardiac fibroblasts, binds to the circulating cardioprotective ligand IL-33, reducing its bioavailability, which reduces myocardial fibrosis, prevents cardiomyocyte hypertrophy, prevents apoptosis, and enhances myocardial function [(14)]. Besides the competitive inhibitory effect on the IL-33/ST-2L signaling pathway, sST2 itself participates in the regulation of extracellular matrix remodeling and inflammation and leads to arrhythmia and other adverse cardiac events [(15)]. It is also recognized that by binding to ST-2L, IL-33 induces T-helper 2 (Th2) cells to produce cytokines that inhibit inflammation and myocardial hypertrophy [(16)]. In animal models, high levels of sST-2 are linked to myocardial hypertrophy, ventricular chamber dilation, and a decrease in ejection fraction when left ventricular pressure and volume overload are [(5)].

The results of the current study showed that patients between the age 52 and 64 years had a higher risk of myocardial infarction. The risk of myocardial infarction was higher in men than in women. MI was more likely to occur in patients with diabetes mellitus (DM), hypertension, and heavy smoking. These results are in agreement with results obtained by **Suryadevara *et al.*** [(17)].

It was found that serum sST-2 concentrations did not differ between patients with classical MI risk factors as DM, Dyslipidemia, previous history of ischemic heart disease, smoking or family history and those without. Meanwhile, serum sST-2 concentrations were significantly higher among patients suffering from hypertension than those not suffering. The current study data agree with the data from Framingham Heart Study by **Coglianese *et al.*** [(18)] who reported that sST-2 concentrations were related to systolic blood pressure, antihypertensive medication use, and diabetes. However

Wojtczak-Soska *et al.* [19] and **Demyanets *et al.*** [11] revealed that there was no association between sST-2 concentrations and classical risk factors.

In the present study, serum level of sST-2 and cardiac necrosis markers were positively correlated: serum CK, CK-MB, and LDH and negatively correlated with ventricular ejection fraction. This shows an association between soluble ST-2 in the circulation and the severity of myocardial damage or biomechanical load. An explanation for this is that when soluble ST-2 is bound to IL-33 rather than myocardial transmembrane ST-2, cardiomyocytes are less protected from apoptosis, which risks the function of the left ventricle [20]. It can be concluded that the release of sST-2 may indicate continued left ventricle stretching and predict the onset of left ventricle dysfunction in the initial stage when clinical signs and symptoms of left ventricle dysfunction have not yet manifested. In MI patients, there is myocardial damage, extra stretching of the left ventricular myocardium, and release of biomarkers such as sST-2 from myocardia and cardiac fibroblasts [16]. The current study's data are consistent with another study's findings reported by **Weinberg *et al.*** [20] who observed that the levels of circulating ST-2 were inversely correlated with left ventricular ejection fraction and positively with peak creatine kinase. On the other hand, **Suryadevara *et al.*** [17] reported that there was no correlation found between soluble ST-2 and CPK, CPK-MB, HDL, LDL, VLDL, TG and cholesterol. Only a correlation between soluble ST-2 and left ventricular ejection fraction was significantly negative. The authors concluded that patients with poor ventricular ejection fraction had higher serum sST-2 than controls. Also **Perez-Martinez *et al.*** [21] studied all clinical correlations of sST-2, and the only correlation that was significant was that decreased left ventricular ejection fraction that was related to a higher sST-2 concentration.

ST-2 is a receptor protein which is initially identified as an orphan protein that controls inflammation [16]. The ST-2 protein and Toll/IL-1 receptor have similar intracellular domain structures because they are both members of the IL-1 family [22]. This protein receptor serves as a transmembrane receptor for a number of interleukins and controls the leukocyte response to cytokine activation [22]. In the systemic inflammation and/or infection, sST-2 is markedly rising and is a strong predictor of a worse outcome [23]. Acute MI is characterized by activation of inflammatory cytokines and leukocytes due to continuous tissue necrosis, which stimulates sST-2 release [24].

It was observed that on the first day of hospitalization for MI, serum sST-2 levels increased by 16.6-fold compared to normal controls. This indicated that sST-2 plays a crucial part in the pathophysiologic process in the early stage of AMI and has an assistant diagnostic value for AMI. This is consistent with the research by **Suryadevara *et al.*** [17] who reported that the test group's sST-2 levels were higher than those of the control group. Moreover, **Barbarash *et al.*** [25] reported that on day 1, sST-2 concentrations were 4.5 times higher than controls. In addition, **Hartopo *et al.*** [26] demonstrated that participants with MI had median sST-2 levels that were considerably greater than controls (152.1 ng/mL versus 28.5 ng/mL). Furthermore, **Zhang *et al***. [27] observed that serum sST-2 levels are significantly elevated early after AMI. Another study conducted by **Timothy *et al.*** [28] suggested that the high sST2 levels can only be produced for a short period of time after infarct, within 12–18 hours of onset, they also studied whether the location of the infarct is associated with soluble ST2 and found that the type of infarct location had no effect on the high sST2 levels upon admission.

According to the current study, the median concentration of soluble ST-2 at day 1 in the test group was 2050 pg/ml, compared to 120 pg/ml in the control group. Perhaps the release of soluble form of ST-2 by injured cardiomyocytes is what causes the concentration of sST-2 to rise in MI cases. Our results are in line with a study conducted by **Zhang *et al.*** [28] who reported that serum of 59 acute MI Chinese patients had a median level of sST-2 of 2906 pg/ml. In the other hand, a study by **Suryadevara *et al***. [17] noted that the median of sST-2 in the test group was 213.46 pg/ml, while its median in the control group was 124.53 pg/ml. In a research from UK by **Weir *et al.*** [29] on 100 acute MI patients, the median sST-2 level was 263.3 pg/ml. **Shimpo *et al.*** [8] conducted a study in the USA where sST-2 levels were assessed in the serum of 810 patients with acute MI, the median sST-2 level was 235 pg/ml. A study by **Demyanets *et al.*** [11] performed in 98 patients with AMI, median sST-2 level was 453 pg/ml. One explanation for these discrepancies would be that the earlier studies were conducted on Caucasian populations while **Zhang *et al.*** [27] study was conducted on the Chinese population. The current data are similar to those that were in the Chinese population. Another explanation for the high sST-2 concentration seen in both our work and in the study by **Zhang *et al.*** [27] could also be the impact of the small sample size. In the previously mentioned studies, the timing of the samples that were taken varied

considerably. In our study, blood samples were taken within 24 hours following the onset of MI. While, **Shimpo *et al.*** [8] who took the samples within 12 hours of AMI, found that the median obtained was comparable to that seen with **Weir *et al.*** [29] who collected samples even as late as 14 days after MI. It seems that the sST-2 concentration remains steady in the first 14 days following MI and that the time of the sample had no direct effect on it, nevertheless this has to be investigated in future research.

In the current study, by day 30, the levels of serum sST-2 significantly decreased by 20.6-fold with no difference between day 30 and control group. This comes in agreement with **Barbarash *et al.*** [26] who measured sST-2 at day 1 & day 12 of hospitalization for MI and noted that sST2 concentration on day 12 revealed a considerable decline. Also, **Weir *et al.*** [29] examined serum samples from 69 research participants for sST-2 level on days 1, 14, and 90 following MI. On day 1 (3.8 0.4 ng/mL), circulating ST2 was higher than it was on day 14 (0.98 0.06 ng/mL) or on day 90 (0.79 0.07 ng/mL).

We followed up the patients after acute MI for 30 days and divided them into favorable and unfavorable outcome groups based on whether complications developed or not. Twenty-six patients (72.2%) did not develop any complications, while ten patients (27.7%) developed unfavorable outcome. Four patients (11.1%) developed heart failure, three patients (8.3%) developed arrhythmia, three (8.3%) developed another MI attack, and only one case (2.8%) developed cardiomyopathy. The present study results demonstrated that on day 1 the level of serum sST-2 was 4.6 times greater in the group with a poor outcome than in the group with a good outcome, but on day 30 following the MI, there was no difference in the levels between the two groups. On day 1, the sST-2 serum levels in the group with a poor outcome was 38.4 times more than that in the control group. We also found that patients who were complicated by heart failure showed the highest sST-2 levels among the poor outcome group. Similarly, **Barbarash *et al.*** [26] discovered that on day 1, the level of sST-2 in the group with a poor outcome was two times higher than that in the group with a good outcome. The authors also found that when compared to the control group, the levels of sST-2 in the groups with the sST-2 levels in the groups with good and poor outcome elevated by 1.9- and 3.7-fold, respectively. Moreover, **Zhang *et al.*** [27] in their study divided all the AMI patients into two groups according to the prognosis of AMI within 6-months: outcome events occurred and outcome events not occurred. They found that the first group's sST-2 concentration was 42.54 ng/ml, whereas the second group's was 18.01 ng/ml. Furthermore, **Hartopo *et al.*** [26] divided MI patients according their sST-2 level into supramedian and inframedian groups. They observed that the supramedian group had greater incidence of unfavorable cardiac events compared to the inframedian group. They noticed that the most common adverse cardiac event was acute heart failure. According to **Shimpo *et al.*** [8] the highest quintiles of sST-2 were linked to an increase in significant adverse cardiovascular events both during and 30 days following intensive hospitalization. Additionally, **Sabatine *et al.*** [30] who assessed sST-2 in 1,239 MI patients at baseline, found that increased sST-2 value was a strong predictor of in-hospital death and future severe cardiovascular events up to 30 days. The similar findings were reported by **Kohli *et al.*** [31] who assessed sST-2 in 6,560 MI patients and came to the conclusion that an elevated sST-2 value was highly related with worse outcomes at 30 days and one year. Another study by **Liu *et al.*** [32] showed that when the patients were followed up for a year, sST-2 was strongly linked to serious cardiac adverse events. While, a research made by **Dieplinger *et al.*** [33] noticed that the risk of cardiovascular death was two times higher in patients with sST-2 levels over the cut-off value of 24.6 ng/mL at baseline. **Dhillon *et al.*** [34] who measured sST-2 in 677 patients admitted to the coronary care unit, found that increased sST-2 values were strongly associated with higher mortality at the 30-day. **Christina *et al.*** [35] observed that high sST2 levels predict a higher risk of death from chronic heart failure and stable coronary artery disease.

In the current study, ROC curve was plotted to investigate the best cut-off value of 150 pg/ml of serum sST-2 that indicated the presence of MI with 86.11% sensitivity and 80.56% specificity. Also a ROC curve was done by **Zhang *et al***. [28] and determined the 36.415 ng/ml as a cut-off value for sST2, with sensitivity and specificity 77.4% and 89.7% respectively. These results indicated good validity of sST-2 as a diagnostic marker for acute MI.

We plotted another ROC curve for serum sST-2 for prediction of complications after MI and it sets a threshold value of 3100 pg/ml with 90% sensitivity and 96.15% specificity. A ROC curve analysis was done by **Liu *et al.*** [33] to assess the prognostic efficiency of sST-2 in predicting major adverse cardiac events, set a cut-off value of 58.7 ng/mL with AUC 73%, sensitivity 57.9% and specificity 73.9%.

Conclusions:

According to this study, soluble ST-2 is a cardiovascular biomarker that is higher in AMI patients. Its early measurement after AMI aids in the prediction of short-term complications.

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