Al-Azhar International Medical Journal

Volume 4 | Issue 11 Article 13

2023
Section: Cardiovascular

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How to Cite This Article

Mohamed, Ahmed Shehata; Hassan, Mohamed Hesham; Ahmed, Mohamed Abdelhady Abu; and Alzohery, Yousri Zaki Ali (2023) "The Prognostic Value of serum ST2 in Patients with non-ST segment elevation acute coronary syndrome," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 11, Article 13.
DOI: https://doi.org/10.58675/2682-339X.2100

ORIGINAL ARTICLE

The Prognostic Value of Serum ST2 in Patients With Non-ST Segment Elevation Acute Coronary Syndrome

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Abstract

Background: **Myocardial necrosis improved while cardiac biomarkers were reduced among individuals with non-ST-segment elevation myocardial infarction (NSTEMI), which was identified as the lack of ST-segment elevation. Myocardial ischemia at rest or during mild activity without cardiac myocyte necrosis characterizes unstable angina. Myocardial ischemia is characterized by an increase in the soluble form of ST2 and the inflammatory cytokine IL-1β in cardiac myocytes.**

Aim: **The goal of this study was to asses and determine whether or not serum ST2 levels were predictive of six-month mortality in cases with non-ST segment elevation ACS (by comparing plasma ST2 levels among survivors and non-survivors of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) emergency department diagnoses).**

Subjects & methods: **The research is a prospective cross-sectional observational study that involved 50 participants who presented to the specialized Damietta Cardiac Centre with symptoms and signs of NSTE-ACS within the period of February 2022 to November 2022.**

Result: **A high prevalence of serum ST2 levels was found in patients presenting with NSTEMI more than in patients presenting with unstable angina. The connection between Serum ST2 levels and the short-term outcome was statistically significant. The correlation among Serum ST2 levels and dyspnea was statistically significant. Serum ST2 levels had a significant association with arrhythmias. High levels of Serum ST2 were linked to hospital readmission in a statistically meaningful way. The correlation among Serum ST2 concentrations and coronary artery disease detected by angiography was statistically significant. High ST2 levels were more predictive of mortality and rehospitalization, dyspnea, arrhythmias, and obstructive coronary artery disease on receiver operating characteristic (ROC) curve analysis.**

Conclusion: **In the current investigation, individuals who died within 6 months had higher ST2 values. ST2 cutoff value of 150 ng/mL was determined to have a sensitivity of 97.2 % and specificity of 91.3 %. In conclusion, serum ST2 levels are positively correlated with 6-month mortality in NSTE-ACS patients. Our research results need to be confirmed by other investigations.**

Keywords: Coronary syndrome, Non-ST segment, Serum ST2

1. Introduction

STEMI, non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UA) constitute acute coronary syndrome.[1]

NSTEMI is characterized by myocardial necrosis accompanied by a rise in biomarkers in the absence of ST-segment elevation.[2] Myocardial ischemia at rest or during mild activity without cardio-myocyte necrosis is the diagnostic criteria for UA.[3]

The treatment plan may be adjusted at any point up until the time of hospital discharge based on the results of ongoing risk assessments. Care for individuals with ACS can benefit from specialized

Accepted 15 June 2023.
Available online 22 January 2024

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https://doi.org/10.58675/2682-339X.2100

chest pain units or coronary care units. The NSTE-ACS patient is at increased risk even after discharge and requires specialized care.[4]

The death rate from ACS is extremely high. Individuals diagnosed with ACS have had their mortality predicted using many different recommendations, clinical grading techniques, and biomarkers. Only thirty to fifty percent of individuals with NSTEMI will show electrocardiographic (ECG) abnormalities as ST depression and T wave inversion.[5]

Biomarkers are the backbone of the diagnostic process for these cases. Biomarkers that signal myocardial necrosis and myocardial dysfunction [cardiac troponin I-T, B-type natriuretic peptide (BNP)] have proven valuable not only for selecting the right medication but also for cardiac risk assessment, and are thus acknowledged as significant clinical diagnostics.[6]

The tumor-suppressing biomarker suppression of tumorigenicity-2 (ST2), which has its origins in the inflammatory system, has been demonstrated to have predictive value in cases with ACS. As an IL-1 receptor, ST2 binds to interleukin-33 and plays a critical role in the control of immunological and inflammatory responses. There is a soluble version of ST2 (sST2) that lacks trans-membrane and intracellular domains. Individuals who died of acute cardiac failure had increased levels of ST2.[7]

Numerous investigations have examined ST2's role in acute/chronic heart failure and contrasted it with BNP as a prognostic marker in computer aided design (CAD).[8]

The goal of this study was to determine whether or not serum ST2 levels were predictive of 6-month mortality in cases with non-ST segment elevation ACS (by comparing plasma ST2 levels among survivors and nonsurvivors of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) emergency department diagnoses).

2. Patients and methods

2.1. Place and duration of research

Cardiovascular Department of Damietta Cardiac Center, patients presented with symptoms and signs of NSTE-ACS within the time period of February 2022 to November 2022. The research was a Prospective cross-sectional observational study that included 50 participants who were presented with symptoms and signs of NSTE-ACS and done according to the research plan of our cardiovascular department in Damietta cardiac center.

2.2. Ethical consideration

Fully informed consent was taken from all cases. The study was not funded. The candidate and all supervisors have no conflict of interest. The patients and controls were treated according to the principles of the declaration of Helsinki.

2.3. Inclusion criteria

All hospitalized individuals with NSTE-ACS presented with either: Unstable Angina. Myocardial infarction with no ST segment elevation.

2.4. Exclusion criteria

Patients were diagnosed with STEMI. Patients who presented with cardiogenic shock. History of major surgery or trauma within the last 4 weeks. Refusal of participation.

2.5. Methods

Fifteen patients were subjected to history taking of sex, age, diabetes mellitus (DM), ischemic heart disease, hypertension, previous PCI, history suggestive fatal arrhythmias, or aborted sudden cardiac death, history of chronic pulmonary, chronic liver failure, chronic kidney disease, chronic hematological disorders, or other chronic illness, symptoms of shortness of breath, palpitation chest pain.

2.6. Full clinical examination

2.6.1. General examination

With an emphasis on blood pressure, pulse, respiratory rate, neck veins, and lower limbs.

2.6.2. Local examination

Contains previous cardiac surgery scarring, heart sounds, heart murmurs, galloping sounds as well as lung base crackles.

2.7. Investigations

2.7.1. Laboratory investigation

On admission, before any drugs were given, every individual had a venous blood sample taken: Serum ST2: Suppression of tumorigenicity 2 (ST2) assay. To determine plasma ST2 levels, the nurse in the emergency room extracted ~2 mL of blood. The antecubital vein was utilized to capture blood samples immediately after the ECG was obtained. Blood samples that were hemolytic, icteric, or lipemic were not included. To isolate the serum,

the samples were spun in a centrifuge for ten minutes at 4000 rpm. Blood samples were deposited in Eppendorf containers and frozen until analysis. Prior to analysis, the samples were defrosted at ambient temperature. ST2 concentrations were determined utilizing an automated Eti-Max 3000 (Diasorin SpA, Italy) micro-ELISA (Enzyme-Linked Immunosorbent Assay) system employing the sandwich ELISA methodology. As regard the manufacturer's instructions, a commercially available interleukin 1 receptor-like 1 (IL1RL-1) human Elisa reagent (Cusabio and Cusab Elisa kit) was utilized. The sensitivity of these kits is (0.436 ng/ml) the range of detecting ST2 levels is (0.5:250 ng/ml) and the normal level was (8:40 ng/ml).

Troponin I: Normal level was 0–0.04 ng/ml.

2.7.2. Serum creatinine level

The normal level of serum creatinine was 0.3–1.3 mg/dl. Evaluation of short-term clinical outcome of all patients within 30 days for major adverse cardiac events (MACE) as cardiovascular mortality, increase in New York Heart Association (NYHA) class, readmission for the acute coronary syndrome, readmission for heart failure, and readmission for arrhythmia. Any hospitalization lasting more than 24 h was considered readmission. Emergency room visits are categorized as those made because of symptoms and indications of ACS.

Short-term mortality constituted mortality throughout 30 days of NSTE-ACS presentation, either during admission or after hospital discharge. Discharged patients were followed up by telephone contact until 6 months after hospital discharge. Patients suspected of having NSTE-ACS might benefit from biomarkers in the following ways: diagnosis, risk stratification, and therapy. All individuals suspected of having NSTEACS must have a biomarker of cardiomyocyte damage measured; hs-cTn is the gold standard.[9]

In comparison with creatine kinase (CK), its myocardial band isoenzyme (CK-MB) & myoglobin, and cardiac troponins are more sensitive and specific indicators of cardiomyocyte damage.[9]

High-sensitivity cardiac troponin tests allow for a faster 'rule-in' and 'rule-out' of MI at the time of presentation compared with traditional assays, especially in individuals presenting soon after the beginning of chest pain9.

Electrocardiography: 12 lead ECGs were done for all patients in our study group to detect Arrhythmia. ST-T wave changes of Non-ST segment elevation acute coronary syndrome.

2.7.3. Echocardiography

Transthoracic echocardiography was carried out on all patients to assess: Dimensions of different chambers and great vessels, sex-specific normal ranges for LV size and function measured by two-dimensional echocardiography, Ejection fraction was calculated by Simpson's formula in case of regional wall motion abnormalities.

2.7.4. Coronary angiography

Diagnostic Coronary Angiography was performed for all the participants (50 patients) to assess obstructive and non-obstructive coronary artery disease, number of vessels has significant lesions, percent of significant atherosclerotic lesions, and PCI for significant atherosclerotic lesions was done for all of the patients.

2.7.5. Statistical analysis of the data

IBM's statistical analysis program, SPSS, version 22.0, was utilized to process the data. Quantitative (frequency) and percentage descriptions were used to characterize the qualitative data. The Kolmogorov-Smirnov test was utilized for evaluating the normality of the quantitative data, and if so, the mean, standard deviation, median, and range were used to characterize the data. The acquired findings were deemed significant at the five percent level. All tests were two-tailed.

Analysis of the association amongst the serum level of ST2 and the outcomes of the study (death, and rehospitalization) was done using a logistic regression model and ROC (receiver operator curve) with the area under the curve representing the sensitivity of the marker. Continuous variables were compared using the Mann-Whitney *U* test (among two groups) [expressed as z] because data is not normally distributed. All tests were considered significant if the *P* value less than 0.05.

3. Results

Two (4 %) patients had atrial fibrillation, 34 (68 %) patients had ischemic changes, and 16 (32 %)

Table 1. Electrocardiogram presentation in studied population.

Data	Number (50) (Percentage (100 %))
Atrial fibrillation	
Yes	2 (4 %)
No	48 (96 %)
Ischemic Changes	
Yes	34 (68 %)
No	16 (32 %)
Conduction Abnormalities	
Yes	16 (32 %)
No	34 (68 %)

Table 2. Morbidity and Mortality Data in studied population. (6 months follow up).

Data	*N* (50) (Percentage (100 %))
Chest pain	27 (54 %)
Dyspnea	20 (40 %)
Arrhythmia	10 (20 %)
Re-hospitalization	20 (40 %)
6 months mortality	4 (8 %)

patients had ECG conduction abnormalities, Table 1.

Four (8 %) patients of the study group died due to cardiovascular causes during follow-up time, and 27 (54 %) patients of the study group had recurrent chest pain and 20 (40 %) patients of the study group had dyspnea and 10 (20 %) patients had arrhythmias and 20 (40 %) readmitted to hospital after discharge, Table 2.

There is no significant difference between NSTEMI and UA patients regarding ST2, Table 3.

There is significant decrease among survival than nonsurvival group regarding ST2 while there is no significant variance between survival and non-survival groups regarding HTN, DM, Table 4.

Table 3. Serum ST2 in NSTACS categories.

Data	NSTEMI Mean ± SD	UA Mean ± SD	T-test	*P*.value
ST2	83.57 ± 55.9	60.07 ± 52.4	1.394	0.169

Table 4. Echocardiographic data in studied population.

Data	Mean ± SD	
EF	48.8 ± 9.6	
RWMA		
Yes	35	70 %
No	15	30 %

Abbreviations: EF, ejection fraction; **RWMA**, number; **SD**, standard Deviation.

3.1. Echocardiographic data on examination (Ejection fraction RWMA)

Mean of Left ventricular ejection fraction (EF) was (48.8 ± 9.6 SD). Resting wall motion abnormalities were observed in 35 (70 %) patients, Table 4, Fig. 1.

3.2. Coronary angiographic data in studied population

In our study group, coronary angiography was done for all patients 26 (52 %) had Obstructive CAD, 19.23 % had multivessel disease for coronary artery bypass graft surgery (CABG), 50 % had PCI to LAD, 11.5 % had PCI to RCA, 19.23%had PCI to LCX (Table 5, Fig. 2).

Correlation analysis between serum ST2 and dyspnea during follow-up time showed a significant relationship between elevated plasma ST2 and dyspnea, arrhythmia and rehospitalization. In emergency room visits for dyspneic patients, both those with and without acute unstabilized HF have had sST2 examined as a potential biomarker. Correlation analysis between serum ST2 and 6 months mortality during follow-up time had significant value, Tables 6–8.

4. Discussion

In our study group, among of all patient there was 16 (32 %) had normal ECG and it was correlated

Table 5. Coronary angiographic data in obstructive coronary artery disease.

Coronary angiographic data	*N* (26) (Percentage (100 %))
PCI to LAD	13 (50 %)
PCI to LCX	5 (19.23 %)
PCI to RCA	3 (11.5 %)
CABG	5 (19.23 %)

Abbreviations: N: number.

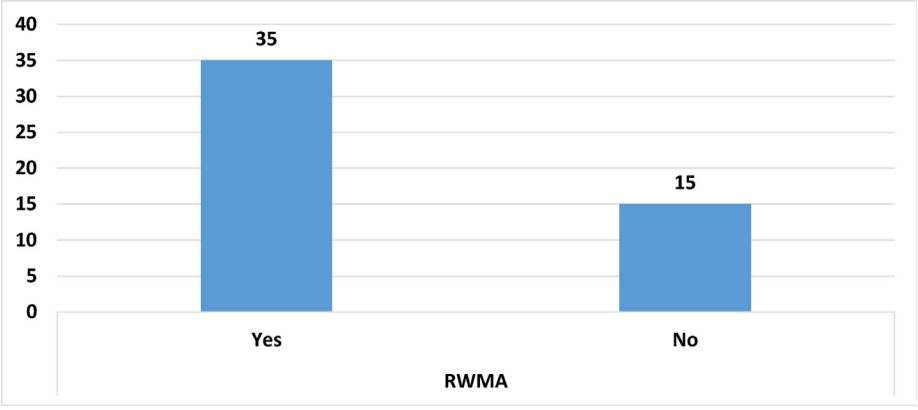

Fig. 1. Shows RWMA of echocardiographic data in studied population.

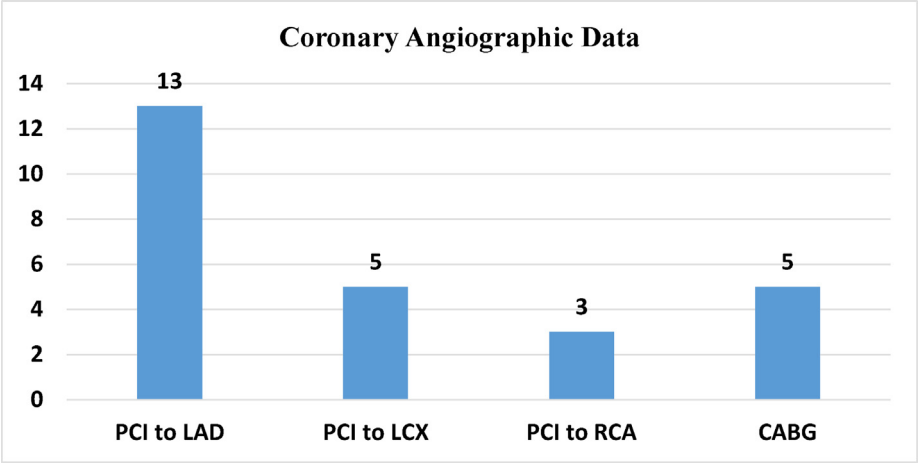

Fig. 2. Coronary Angiographic Data in Obstructive Coronary artery disease in studied population.

Table 6. Variable risk factors in survival and non-survival groups.

Data	Survival ($n = 46$)	Non-survival ($n = 4$)	*P*.value
ST2 (Mean ± SD)	48.4 ± 48.41	152.43 ± 27.29	0.0001*
HTN (n)	26	4	0.332
DM (n)	20	3	0.674

Table 7. Correlation between Serum ST2 and Morbidity and Mortality data in studied population. (6 months follow up).

Data	ST2	
	R	*P*-value
Chest pain	0.13	0.93
Dyspnea	0.317	0.025[a]
Arrhythmia	0.461	0.001[a]
Re-Hospitalization	0.237	0.046[a]
6 months mortality	0.575	0.0001[b]

R: Correlation factor.
[a] Significant correlation.
[b] Highly significant correlation.

Table 8. Receiver operating characteristic curve of Serum ST2 as a predictor for Mortality. (6 months follow up).

	Sig	Sensitivity	Specificity	AUC	Cutoff value
ST2	0.0003*	97.2 %	91.3 %	0.95	≥150 ng

AUC: Area under Curve.

with another study that showed while the patients in the setting of NSTE-ACS ECG may be normal in greater than 30 % of individuals.[10]

In our study population, 4 (8 %) patients were died due to cardiovascular causes during follow up time, and 27 (54 %) patients of the study group had recurrent chest pain and 20 (40 %) patients of the study group had dyspnea and 10 (20 %) patients had arrhythmias and 20 (40 %) readmitted to hospital after discharge and these findings correlated with the study of another study reported In a study of 88 patients diagnosed with NSTEMI, 18 (20 %) individuals were found to have died by the end of the 28-day follow-up period, suggesting that ST2 level is a credible biomarker for prediction of death.[11] Also these findings correlated with another study that demonstrated that sST2 levels were increased in cases with NSTE-ACS and also strongly predictive for mortality at one year.[12]

Comparative analysis between serum ST2 and dyspnea, arrhythmia, rehospitalization during follow-up time showed significant relation and it was correlated with another study that showed serum ST2 was strongly associated with measures of heart failure severity and poor outcomes.[13]

While in receiver operating characteristic (ROC) Curve Analysis, we found that the most sensitive test to predict cardiovascular mortality was serum ST2 with sensitivity of 97.2 % and specificity 91.3 and significant *P* value 0.0003.

Our findings may differ from those of other research since our sample size is too small to be representative of the general population. Large ongoing studies in the future are necessary to confirm this debate. The predictive significance of plasma ST2 in ACS has only been evaluated in a small number of trials.

4.1. Conclusion

Participants who ultimately passed away had higher ST2 readings, and an increase in ST2 was found to be a risk factor for death. With a sensitivity of 97.2 % and specificity of 91.3 %, a cutoff value of 150 ng/mL for ST2 was determined. In conclusion,

elevated blood ST2 levels are associated with an increased risk of dying within 6 months in individuals with NS-ACS.

Conflicts of interest

There is no any conflict of interest.

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