Levels of Some Biomarkers in Ischemic Heart Disease Patients

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Abstract

The present study is an attempt to investigate the changes in serum soluble suppression of tumorigenicity 2 (sST2) and Interleukin-33 (IL-33) biomarkers levels in Iraqi ischemic heart disease(IHD) patients including stable angina (SA), unstable angina (UA) and myocardial infarction (MI) compared to the healthy controls (HC), and to evaluate the differences in these levels between these diseases combination groups. The IHD'smortality surpass that of every major disease, so it is important that to get such research especially among Iraqi patients. These biomarkers are expressed by myocardial cells, the sST2 is released when there is a myocardial stress while the IL-33 has a cardio protective role, and both are expressed on atherosclerotic plaque which is the most common cause of IHD. Collecting the blood samples from one hundred thirty IHD patients with ages ranged (30-80) years, of both genders, excluding the patient with any autoimmune disease, investigated for sST2 and IL-33 by ELISA technique. This study revealed that the sST2 was highly significantly decreased in all IHD groups compared with HC; the 5% trimmed mean (ng/ml) was 8.48, 8.37, 9.31 versus 23.88 in SA, UA, MI and HC respectively; while the IL-33 was highly significantly decreased in SA and UA groups while not significantly different in MI patients;the 5% trimmed mean (ng/L) was 969.93, 762.21, 1279.45 versus 2110 in SA, UA, MI and HC respectively. Also there was a significant direct correlation between these biomarkers levels in all IHD groups.

Keywords: *sST2, IL-33, IHD, Stable angina, Unstable angina, Myocardial infarction.*

Introduction

The ischemic heart disease (IHD) is a disease of coronary arteries, so it is also called coronary heart disease (CHD) or coronary artery disease (CAD), in which there is a blood supply reduction to the myocardium, mostly due to atherosclerosis in the coronary arteries. It is the main cause of death worldwide, so it is important in many studies nowadays[(1)]. IHD can be classified into chronic stable angina (SA) and acute coronary syndrome (ACS) that include unstable angina (UA) and myocardial infarction (MI)[(2)]. The primary prevention of CAD is dependent upon the ability to identify high risk individuals[(3)]and by studying the novel biomarkerslong before the development of overt major adverse cardiac events (MACEs) [(4)]. The ST2 is known as interleukin-1 receptor-like-1 (IL1RL1) protein, it has two isoforms; ST2L and sST2, the later can act as a decoy receptor by binding freeIL-33,and it reflects the myocardial stress. It provides prognostic information especially in the MI[(5)]. The IL-33 is a cytokine,is a functional ligand for ST2L, is expressed by myocardial cells, it has a cardioprotective role and inhibits the atherosclerotic plaques development;it predicts the mortality andMACEs in the MI patients[(6)]. The present study aimed to investigate the changes in the serumsoluble suppression of tumorigenicity 2 (sST2) and Interleukin-33 (IL-33) biomarkers levels, as well as the risk factors such as age, gender, smoking and serum cholesterol level in Iraqi IHD patientswho are with SA, UA and MI compared to apparently healthy controls (HC) group.

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Patients and Method

Collecting the blood samples from one hundred thirty patients with ages ranged (30-80) years, of both genders, newly admitted to different Iraqi hospitals(Ibn Al- Betar Teaching Hospital, Baghdad Teaching Hospital and The Iraqi Center for Heart Disease), classifying them into fifty patients with MI, fifty patients with SA and thirty patients with UA according to the clinical manifestations, electrocardiogram findings and laboratory investigations.

Patients with diabetes mellitus [confirmed by blood sugar and hemoglobin A1c levels (bychemistry autoanalyzer (AU480, Beckman))]and with any other autoimmune disease were excluded from this study[7]. Thirty five apparently HC were enrolled in this study with the same age range of both genders. A form of questionnaire was applied for both the patients and HC groups. This questionnaire listed some informations especially the age, gender,presence of the medical history (especially of any autoimmune disease) and whether smoker with its grading or not. Most of the patients serum samples were collected within about (24-48 hours) of the symptom onset and investigated for blood cholesterol level(by chemistry autoanalyzer (AU480, Beckman)), sST2 and IL-33 by enzyme linked immune sorbent assay (ELISA) technique [(sandwichkit) (Human)].

Statistical analyzing: Analysis of data was carried out by using the available statistical package of SPSS-22 . The significance of the differences of different means (quantitative data) was tested by using Mann – Whitney U test for the differences between two independent means, while Pearson's Correlation Coefficients was calculated for the correlation between two quantitative variables. The correlation coefficient value (r) was either positive (direct correlation) or negative (inverse correlation);in addition to the graphical presentation by using Stem-Leaf Plots and Receiver Operation Characteristic (ROC) curve charts.

Results

Table (1): Studied (sST2 and IL-33) biomarkers in all combinations of studied groups.

Biomarkers	Groups / Statistics	Stable Angina	Unstable Angina	Myocardial Infarction	Healthy Controls	Combinations Groups	Z-value	P value
sST2 (ng/ml)	5% Trimmed Mean	8.48	8.37	9.31	23.88	SA x UA	-0.666	0.505 NS
	Median	7.90	7.65	7.90	15.40	SA x MI	-0.179	0.858 NS
	Range (minimum-maximum)	(3.70-20.20)	(2.10-26.00)	(2.40-46.20)	(6.40-53.90)	SA x HC	-5.316	0.000HS
	Interquartile Range	2.63	4.30	1.63	30.10	UA x MI	-0.726	0.468 NS
						UA x HC	-4.567	0.000HS
						MI x HC	-5.021	0.000HS
IL-33 (ng/L)	5% Trimmed Mean	969.93	762.21	1279.45	2110	SA x UA	-0.925	0.355 NS
	Median	756.40	756.45	912.40	1340.9	SA x MI	-3.864	0.000HS
	Range (minimum-maximum)	(309.90-3731.50)	(173.60-3574.10)	(705.00-4553.90)	(457.50-4383.2)	SA x HC	-2.796	0.005 S
	Interquartile Range	281.73	528.13	491.03	3395.3	UA x MI	-3.225	0.001HS
						UA x HC	-3.429	0.001HS
						MI x HC	-0.671	0.503 NS

Data presented as 5% Trimmed Mean, median, Interquartile Range and P value tested by Mann-Whitney U Test.SA: Stable angina;UA: Unstable angina; MI: Myocardial infarction; HC: Healthy controls; HS: Highly significant at P value <0.01;S: Significant at P value <0.05;NS: Non significant at P value >0.05; sST2: soluble suppression of tumorigenicity 2;IL-33: Interleukin-33.

In the table (1), the results of the sST2 and IL-33 biomarkers test had reported low levels of estimates compared with HC group. The 5% trimmed mean (ng/ml) concerning the sST2 was 8.48, 8.37, 9.31 versus 23.88 in SA, UA, MI and HC respectively; the IL-33 was highly significantly decreased in SA and UA groups while not significantly different in MI patients; the 5% trimmed mean (ng/L) concerning the IL-33 was 969.93, 762.21, 1279.45 versus 2110 in SA, UA, MI and HC respectively. Also this table shows that Mann-Whitney-U test statistic for testing distribution of sST2 and IL-33 biomarker's readings in each pair of probable combinations among studied groups. Regarding to sST2

biomarker, the significant differences are accounted at P <0.01 among the morbidity groups against the HC, while no significant differences at P >0.05 among diseases combinations groups such as between SA group and each UA and MI groups, and between UA and MI groups. Regarding to IL-33 biomarker, the significant differences are accounted at P <0.05, except between SA and UA groups, and between MI and HC groups, since no significant differences at P >0.05.

Table (2): Statistics of ROC Curve for studied (sST2 and IL-33) biomarkers responding according to (diseases and healthy) groups.

Groups	Biomarkers	Cutoff Point	Sensitivity	Specificity	Area	Standard Error	A. S.	Asymptotic 95% C. I.	
								L. b.	U. b.
Stable Angina	sST2 (ng/ml)	3.850	0.960	0.000	0.160	0.046	0.000 HS	0.070	0.250
	IL-33 (ng/L)	588.25	0.880	0.171	0.321	0.065	0.005 HS	0.194	0.448
Unstable Angina	sST2 (ng/ml)	2.250	0.967	0.000	0.170	0.049	0.000 HS	0.073	0.266
	IL33 (ng/L)	188.35	0.967	0.000	0.252	0.060	0.001 HS	0.134	0.370
Myocardial Infarction	sST2 (ng/ml)	4.350	0.960	0.000	0.179	0.052	0.000 HS	0.077	0.281
	IL33 (ng/L)	730.75	0.960	0.314	0.457	0.073	0.503 NS	0.315	0.599

HS: Highly significant at P value <0.01; NS: Non significant at P value >0.05; A. S.: Asymptotic significant;C. I.: Confidence interval; U. b.: Upper bound; L. b.: Lower bound; sST2: soluble suppression of tumorigenicity 2; IL-33: Interleukin-33. The positive actual state is Positive.

In the table (2), the results recorded significant area by Receiver Operation Characteristic (ROC) curve under the guideline of HC group in all IHD groups, with 95% confidence interval (C. I.) of all diseases with HC groups in light of studied sST2 and IL-33 biomarkers. In both SA and UA patients, the results show that the recorded significant area at P <0.01 concerning both biomarkers, with more accurate concerning sST2 compared with the IL-33, and accordingly indicating that both biomarkers could be reported good indicators for SA and UA diagnosis; while in MI patients, the results show that the recorded significant area at P <0.01 concerning sST2 biomarker, and accordingly indicating that the sST2 biomarkercould be reported very good indicator for patient's diagnosis with MI, while IL-33 biomarker illustrated weak or non-reliable indicator for MI diagnosis, since significant level was not achieved.

Figures (1,2 and 3) show that the ROC curve distribution concerning the sST2 and IL-33 biomarkers responding according to compare SA, UA and MI patients under the guideline of HC group respectively.

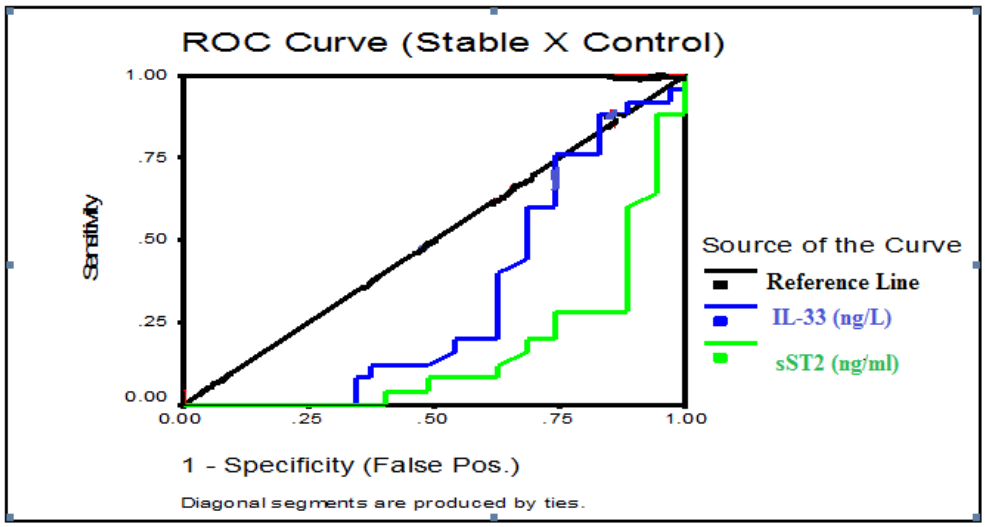

Figure (1): ROC Curve distribution for studied (sST2 and IL-33) biomarkers distributed according to (stable and healthy) groups. IL-33: Interleukin-33; sST2: soluble suppression of tumorigenicity 2.

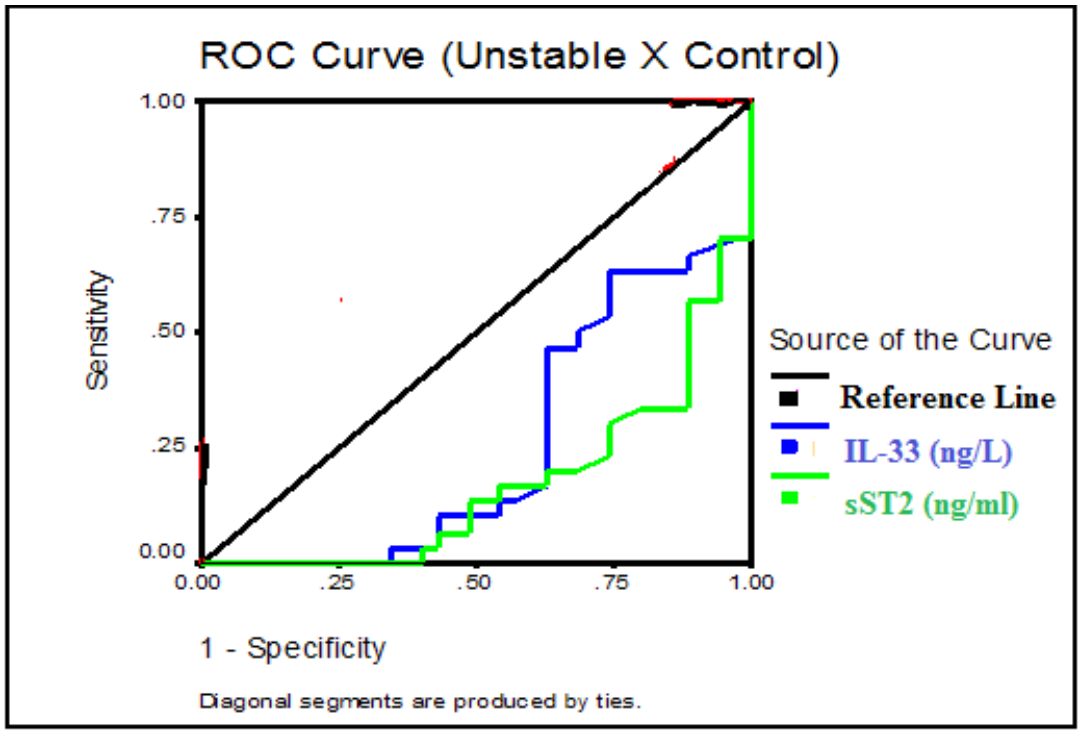

Figure (2): ROC Curve distribution for studied (sST2 and IL-33) biomarkers distributed according to (unstable and healthy) groups.IL-33: Interleukin-33; sST2: soluble suppression of tumorigenicity 2.

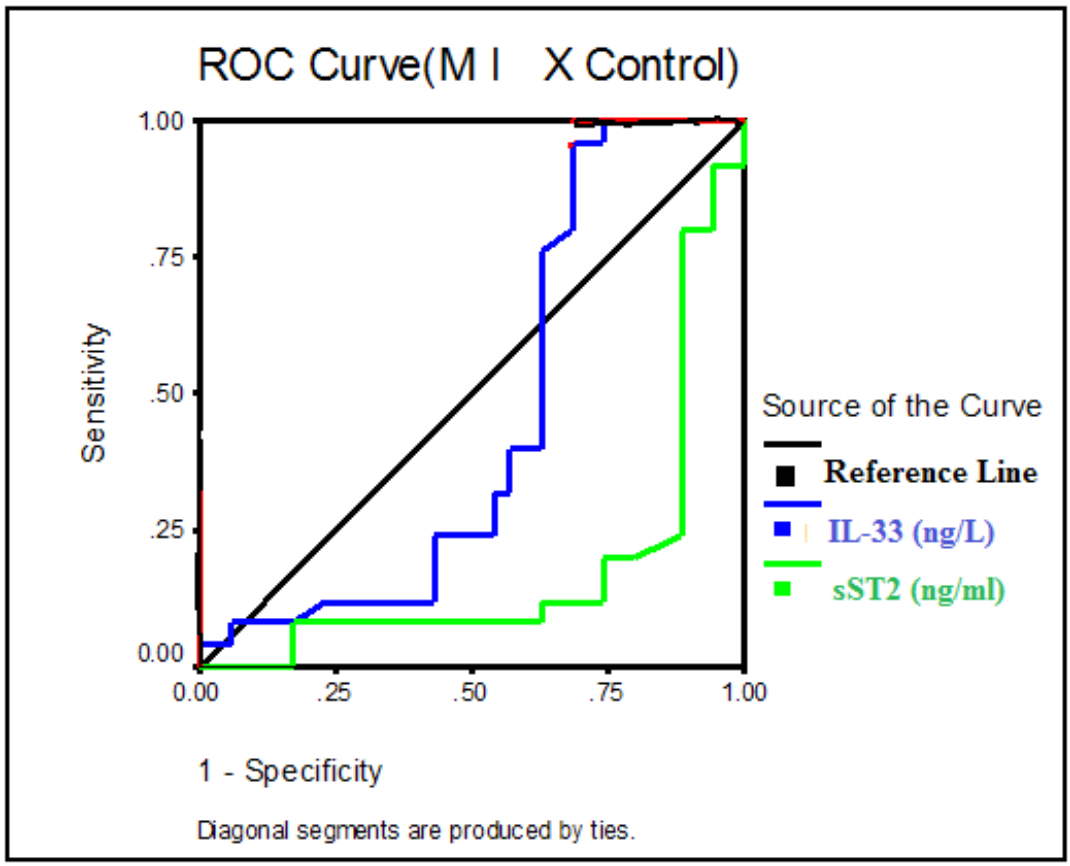

Figure (3): ROC Curve distribution for studied (sST2 and IL-33) biomarkers distributed according to (myocardial infarction and healthy) groups. IL-33: Interleukin-33; MI: Myocardial infarction;sST2: soluble suppression of tumorigenicity 2.

Table (3) shows that there is a perfect positive correlation and a direct proportion between the sST2 and IL-33 biomarkers levels in all disease groups by using Person'sCorrelations Coefficients, with highly significant at P <0.01.

Table (3): Using Person's Correlations Coefficientsfor (sST2 and IL-33) biomarkers responding according to stable angina, unstable angina and myocardial infarction groups.

Morbidity Groups	Marker (ng/ml)	Statistics	IL33 (ng/L)
Stable Angina	sST2	Correlation Coefficient	0.862
		Significant (1-tailed)	0.000HS
		No.	50
Unstable Angina	sST2	Correlation Coefficient	0.469
		Significant (1-tailed)	0.004HS
		No.	30
Myocardial Infarction	sST2	Correlation Coefficient	0.505
		Significant (1-tailed)	0.000 HS
		No.	50

HS: Highly significant at P value <0.01; No.: Number; sST2: soluble suppression of tumorigenicity 2; IL-33: Interleukin-33.

Discussion

The atherosclerosis formation tends to increase with age[8] and most of the IHD cases occur after the age of 65 years[9]. The male gender is one of the risk factors for IHD[10], so the present study results were compatible with the results of many studies regarding to the age and gender[11, 12].

Tobacco smoking is the most avoidable and strongest IHD risk factor [13]. It causes the death in IHD cases[14], the present study smoking results are exactly compatible with Radovanovic *et al*[8] and agree with Mohammad *et al*[15] studies results. Blood cholesterol is a predictive risk factors for CAD[16], and it play a role in the atherosclerosis development[17], so the present study cholesterol test results are agree with Chauhan and Trivedi[13], and Oommen*et al*[18] studies results.

The ST2 is released when myocytes are under stress or injuried [19], it plays a role in inflammatory signaling[20], cardiac fibrosis [21], and is involved in cardiac function and dysfunction [22]. In the extra cellular environment, the sST2 can act as a decoy receptor by binding free IL-33 [6].

The IL-33 is a functional ligand for ST2L, is expressed by myocardial cells, it has a cardioprotective role and inhibits the atherosclerotic plaques development[23]. IL-33 is expressed by myocardial and coronary arterial smooth muscle cells[24]. Both IL-33 and sST2 are expressed in atherosclerotic plaques, when sST2 is binding the free IL-33, the IL-33 level that is available for ST2L binding will be decreased, inhibiting the effects of IL-33/ST2L signaling which has a myocardioprotective function[25]. This IL-33/ ST2L signaling may be triggered by IL-33 or increased by inhibiting sST2 [26], so by the measurement of sST2 level, we can understand the role of IL-33 in IHD [27], so it is very important to study them together. Some results suggest that the ST2 concentrations may be elevated in some MI patients [28,29], while some studies revealed that its level may be not elevated in the MI patients [30]. It was found that the IL-33 levels were not different between the patients with the MI and the control group [31], while other study showed that the patients with heart failure with non-ischemic etiology had higher IL-33 levels than those with ischemic etiology [32]. The presence of the IHD risk factorssuch as age, gender or smokingdoes not influence the serum levels of both sST2 [31,33] and IL-33 biomarkers [27].

Regarding to the sST2 biomarker level, this study recorded that there was some elevation of sST2 level in the HC group in comparison with the lower levels in the morbidity groups; in the HC group, the minimum level was (6.4 ng/ml) and the maximum level was (53.9 ng/ml),

while the minimum level in the morbidity groups was in the UA group (2.1 ng/ml) and the maximum level was in the MI group (46.2 ng/ml). Some studiesrecorded that there were low levels of sST2 (6.2 ng/ml) in MI[30, 34,35]. The sST2 is also elevated in the asthma and autoimmune disease[7]; it reflects a non-specific inflammatory response thus limits its specificity and diagnosis for any disorder including IHD[5, 36]. The sST2 peak level occurred at 12 hours[37](6-18 hours of symptom onset) then is followed by a significant decreasing to a stable level by (24-42 hours) after the onset[21, 33].

Early post infarction sST2 values (i.e., < 24 hours after symptom onset) have the greatest significant prognosis [33], as it has been found that the baseline sST2 levels were significantly higher (the cutoff value of 58.7 ng/mL) in those patients who died or developed new MACEs such as heart failure or recurrent MI either in MI, in stable IHD or even in subjects without known IHD, during short-term follow-up (30 days) than those patients without MACEs[7,21,29,31,35]. Sothe importance of early sST2 levels is for the best prognostic information[33], so that we can prevent morbidity and mortality of the IHD by providing rapid and appropriate therapy[37]. in addition to that the most of Iraqi patients are too late to come to the hospital or physician after the beginning of symptom onset, the Iraqi patient may come after 24 hours of his first complain, so the sST2 peak level could not be detected in such situation as we knew that the peak level is 12 hours after the symptom onset.

In comparison with HC group, one of the studies stated that the ST2 baseline level had a clinical significant in SA patients[33] and it was reported that there was a significant difference in both UA and MI patients[31]. In diseases combination groups, it was showed that there was no significant difference between SA and MI groups, and confirmed that the sST2 has no significant distribution value for combination of UA and MI groups[34]. The study of Karimzadeh *et al* [38] observed that there was a significant correlation between the serum sST2 and IL-33 biomarkers levels in all the IHD.

In diseases combination groups, concerning to IL-33, it was showed that there was no significant difference between SA and UA groups [31, 35]; some studies showed that there was a significant difference between SA and MI groups and suggested that in SA patients, the IL-33 has a protective role against progression to UA or MI stage[41], while it was demonstrated that there was a significant difference between UA and MI groups regarding to IL-33[27].

Conflict of Interest: None

Source of Findings: None

Ethical Clearance: None

References

1. Kanu, J. S., Gu, Y., Zhi, S., Yu, M., Lu, Y., Cong, Y., Liu, Y., Li, Y., Yu, Y., Cheng, Y. and Liu, Y. Single nucleotide polymorphism rs3774261 in the AdipoQ gene is associated with the risk of coronary heart disease (CHD) in Northeast Han Chinese population: a case-control study. Lipids in health and disease,2016.15(1), 6.
2. Bashore, T. M., Granger, C. B., Jackson, K. P., and Patel, M. R. Chapter 10 Heart disease. In Papadakis, M. A., and McPhee, S.J. Current medical diagnosis and treatment .2019, 58thed.,pp. 365-392. McGraw-Hill.
3. Jakovljevic, V., and Djordjevic, D. Physical activity for the prevention of cardiovascular diseases. Serbian Journal of Experimental and Clinical Research, 2017.18(2), 99-109.
4. Wang, J., Tan, G. J., Han, L. N., Bai, Y. Y., He, M., and Liu, H. B. Novel biomarkers for cardiovascular risk prediction. Journal of geriatric cardiology: JGC,2017. 14(2), 135-150.
5. Pusceddu, I., Dieplinger, B., & Mueller, T. ST2 and the ST2/IL-33 signalling pathway–biochemistry and pathophysiology in animal models and humans. Clinica Chimica Acta,2019. 495, 493-500.
6. Chen, S., Chen, B., Wen, Z., Huang, Z., and Ye, L. IL-33/ST2-mediated inflammation in macrophages is directly abrogated by IL-10 during rheumatoid arthritis. Oncotarget,2017. 8(20), 32407-32418.
7. Guria, R. T., Marandi, S., and Srivastava, M. Relationship between serum concentration of the soluble interleukin-1 receptor family member ST-2 and serial change in left ventricular function after acute myocardial infarction. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), 2018.17(5), Ver. 6, 11-15.
8. Radovanovic, D., Pilgrim, T., Seifert, B., Urban, P., Pedrazzini, G., and Erne, P. Type 2 myocardial infarction: incidence, presentation, treatment and outcome in routine clinical practice. Journal of

Cardiovascular Medicine, 2017.18(5), 341-347.

9. Eljedi, A., and Mushtaha, M. Risk Factors of Coronary Artery Disease in Palestinian Patients Undergoing Coronary Angiography: A Case–Control Study. Journal of Advances in Medicine and Medical Research, 2015.5(1), 88-97.
10. Shen, J., Zhang, J., Wen, J., Ming, Q., Zhang, J., and Xu, Y. Correlation of serum alanine aminotransferase and aspartate aminotransferase with coronary heart disease. International journal of clinical and experimental medicine, 2015.8(3), 4399-4404.
11. Venkatesh K., Deepak D. C., and Venkatesha, V. T. Escalation of coronary atherosclerosis in younger people by comparison of two autopsy studies conducted a decade apart. Heart views: the official journal of the Gulf Heart Association, 2018.19(4), 128-136.
12. Chauhan, P. A., and Trivedi, A. Study of perception and behaviour in patients with coronary heart disease about risk factors and life style modification in tertiary care hospital, Bhavnagar. International Journal of Community Medicine and Public Health, 2019.6(4), 1549-1553.
13. Ciapponi, A., and World Health Organization (WHO).Systematic review of the link between tobacco and poverty.2014.
14. World Health Organization.WHO report on the global tobacco epidemic, 2017: monitoring tobacco use and prevention policies. World Health Organization.
15. Mohammad, A. M., Sheikho, S. K., and Tayib, J. M.Relation of cardiovascular risk factors with coronary angiographic findings in Iraqi patients with ischemic heart disease. American Journal of Cardiovascular disease research, 2013.1(1), 25-29.
16. Borland, M. (2018). Exercise-based cardiac rehabilitation, physical fitness, and physical activity in cardiac disease. Sahlgrenska Academy, University of Gothenburg.
17. Yang, N., Feng, J. P., Chen, G., Kou, L., Li, Y., Ren, P., Zhao, L. L., and Qin, Q.Variability in lipid profile among patients presented with acute myocardial infarction, unstable angina and stable angina pectoris. Eur Rev Med Pharmacol Sci,2014. 18(24), 3761-3766.
18. Oommen, A. M., Abraham, V. J., George, K., and Jose, V. J. Prevalence of coronary heart disease in rural and urban Vellore: a repeat cross-sectional survey. Indian heart journal,2016. 68(4), 473-479.
19. Villacorta, H., and Maisel, A. S.Soluble ST2 testing: a promising biomarker in the management of heart failure. Arquivos brasileiros de cardiologia, 2016.106(2), 145-152.
20. Pfetsch, V., Sanin, V., Jaensch, A., Dallmeier, D., Mons, U., Brenner, H., ... and Koenig, W.Increased concentrations of soluble ST2 independently predict cardiac and total mortality but not non-fatal cardiovascular events in stable coronary heart disease patients. Atherosclerosis, 2017.263, e46-e47.
21. Aleksova, A., Paldino, A., Beltrami, A. P., Padoan, L., Iacoviello, M., Sinagra, G., and Maisel, A. S.Cardiac Biomarkers in the Emergency Department: The Role of Soluble ST2 (sST2) in Acute Heart Failure and Acute Coronary Syndrome—There is Meat on the Bone. Journal of clinical medicine, 2019.8(2), 270.
22. Barnett, O., Polyetayeva, K., Halkevych, M., Lutsiv, N., Hrytsak, R., Blazhivska, I., and Kumurzhi, S. Novel marker of myocardial remodeling ST2 and the influence of aldosterone antagonist in patients with heart failure caused by hypertension and ischemic heart disease. Journal of Hypertension, 2018.36, e163.
23. Van Vark, L. C., Lesman-Leegte, I., Baart, S. J., Postmus, D., Pinto, Y. M., Orsel, J. G., and Hillege, H. L.Prognostic value of serial ST2 measurements in patients with acute heart failure. Journal of the American College of Cardiology,2017, 70(19), 2378-2388.
24. Demyanets, S., Kaun, C., Pentz, R., Krychtiuk, K. A., Rauscher, S., Pfaffenberger, S.,and Huber, K. Components of the interleukin-33/ST2 system are differentially expressed and regulated in human cardiac cells and in cells of the cardiac vasculature. Journal of molecular and cellular cardiology,2013.60,16-26.
25. Vianello, E., Dozio, E., Tacchini, L., Frati, L., and Romanelli, M. M. C. ST2/IL-33 signaling in cardiac fibrosis. The International Journal of Biochemistry & Cell Biology, 2019.116, 105619.
26. Caselli, C.Inflammation in cardiac disease: focus on Interleukin-33/ST2 pathway. Inflammation and Cell Signaling,2014.
27. Jafarinia, M., Firuzsalari, F. G., and Zaringol, M.

Serum levels of interleukin (IL)-33 in patients with ischemic heart disease. MOJ Immunol, 2018,6(2), 29-32

28. Snider, J. V., and Jacobson, S.Interleukin-33 (IL-33) for the diagnosis and prognosis of cardiovascular disease. U.S. Patent Application 2011,No. 12/943,676.
29. Jenkins, W. S., Roger, V. L., Jaffe, A. S., Weston, S. A., AbouEzzeddine, O. F., Jiang, R., ... and Enriquez-Sarano, M. Prognostic value of soluble ST2 after myocardial infarction: a community perspective. The American journal of medicine, 2017,130(9), 1112-e9-1112-e15.
30. Parenica, J., Malaska, J., Jarkovsky, J., Lipkova, J., Dastych, M., Helanova, K., ... and Gal, R.Soluble ST2 levels in patients with cardiogenic and septic shock are not predictors of mortality. Experimental & Clinical Cardiology,2012, 17(4), 205-209.
31. Demyanets, S., Speidl, W. S., Tentzeris, I., Jarai, R., Katsaros, K. M., Farhan, S., ... and Wojta, J. Soluble ST2 and interleukin-33 levels in coronary artery disease: relation to disease activity and adverse outcome. PLoS One,2014, 9(4), e95055.
32. Segiet, O. A., Romuk, E., Nowalany-Kozielska, E., Wojciechowska, C., Piecuch, A., and Wojnicz, R. The concentration of interleukin-33 in heart failure with reduced ejection fraction. Anatolian journal of cardiology,2019, 21(6), 305-313.
33. Richards, A. M., Di Somma, S., and Mueller, T. ST2 in stable and unstable ischemic heart diseases. The American journal of cardiology, 2015,115(7), 48B-58B.
34. Marino, R., Magrini, L., Orsini, F., Russo, V., Cardelli, P., Salerno, G., ... and NETWORK, G. Comparison between soluble ST2 and high-sensitivity troponin I in predicting short-term mortality for patients presenting to the emergency department with chest pain. Annals of laboratory medicine, 2017.37(2), 137-146.
35. Liu, X., Hu, Y., Huang, W., Zhang, G., Cao, S., Yan, X.,and Zheng, X. (2019). Soluble ST2 for prediction of clinical outcomes in patients with ST-segment elevation myocardial infarction receiving primary PCI. International heart journal, 2019.18-20.
36. Wang, Y., and Wang, B. Research Progress of IL-33/ ST2 Signaling Pathway in Cardiovascular Disease. 8th International Conference on Management, Education and Information . Advances in Intelligent Systems Research, 2018,163, 495-499. Atlantis Press.
37. Ardhana, T., Aminuddin, M., and Nugraha, J. Relationship between N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) level and protein ST2 level in acute coronary syndrome patient. Folia Medica Indonesiana,2013. 49(4), 202-207.
38. Karimzadeh, S., Zamani, S., Amirzade-Fard, F., Ardekani, A. A., & Doroudchi, M. Correlation between IL-33 and sST2 levels in sera of patients with acute myocardial infarction. Biomedical Research, 2017,28 (16), 7027-7034.