Journal for ReAttach Therapy and Developmental Diversities
eISSN: 2589-7799
2022 December; 5 (2s): 506-511

Utility of C - Reactive Protein and Troponin-I in Combination as Biomarkers for Early Diagnosis of STEMI Patients: A Case-Control Study

Samir S. Hammoud[1*], Shahlaa Kh. Chabuk[2], Dheyaa Kadhim Hassoon Al-Khafaji[3]

1Ass. Prof., (Med. Physiology), College of Medicine, University of Babylon, Babylon, Iraq.
2Ass. Prof., (Med. Physiology), Hammurabi College of Medicine, University of Babylon, Babylon, Iraq.
3Internist, Merjan Medical Teaching City, Babil Health Directorate, Babylon, Iraq. dheyaakadhim274@gmail.com

Received: 11-September-2022
Revised: 13-November-2022
Accepted: 15-December-2022

Abstract

Background: Acute myocardial infarction (AMI) had known as the principal source of death globally and the gravest type of coronary vascular disease. Early diagnosis of AMI is the cornerstone of the management to customize further lines of treatment and best outcomes. Cardiac troponin-I (cT-I), is the "gold standard" indicator for myocardial ischemia. Nevertheless, cT-I is not sensitive for the diagnosis of AMI during the early stages due to late release which is thus, termed the "troponin-blind period". C-reactive protein-namely the highly sensitive (HS-CRP)-is an acute inflammatory peptide synthesized in the liver. Some surveys have shown an increase in serum HS-CRP in patients with AMI and reported it as an independent prognostic factor for atherosclerotic events.

Aim of the study: The current study was designed to investigate the usefulness of combining cT-I and HS-CRP levels for the diagnoses of AMI on the day of presentation had investigated.

Methodology: It was a case-control, observational study to estimate the diagnostic value of HS-CRP in establishing STEMI analysis among admitted patients who revealed positive cT-I tests.The healthy (Non-AMI) group was selected from patients' companions when they have no heart problems. Information had descriptively examined to describe the variations of the two groups. Changes incT-I and HS-CRP between groups had been statistically studied with the independent-samples test and Spearman'-correlation.To find the predictability of both biomarkers (whether individual or combined) to distinguish STEMI from healthy, the receiver operating curve (ROC) analyses had decided.All statistical data had completed using SPSS-IBM software (version-25) compatible with Windows.

Results: Significantly high levels of cT-I and HS-CRP had observed in STEMI patients compared to the non-MI group (p-0.001). **R**isk factors in this study have significant differences between STEMI and Non-MI groups (p-0.001). Patients with levels higher than the HS-CRP cutoff (6.3 mg/L) have more than 5-folds a higher level of cT-I (> 0.19ng/ml). I.e., the higher CPR levels associated with 5-times more extent of cardiac necrosis [p-0.00, *OR* 5.4, and 3.01-962] reflected by higher cT-I (>0.19 ng/ml). The HS-CRP showed sensitivity (75.1), specificity (67.6), and significant-high accuracy of 75.4% with a 95% CI of 0.915-0.992. Meanwhile, the cT-I showed higher sensitivity and specificity (87.5 and 76.2) and significantly higher accuracy 76.5% and 95% CI of 0.929-1.0. The higher diagnostic and predictive capability of cT-I and HS-CRP for STEMI increased significantly when both markers were combined.

Conclusion: There were significantly higher levels of cT-I and HS-CRP in STEMI patients compared to the non-MI group. The higher CPR levels had associated with a 5-times higher extent of cardiac necrosis reflected by higher cT-I. The higher diagnostic and predictive capability of cT-I and HS-CRP for STEMI increased significantly when both markers were combined compared to their abilities alone.

Keywords: troponin-I, hypersensitive CRP, STEMI, AMI. inflammation.

1. INTRODUCTION

Acute myocardial infarction (AMI) had known as the principal source of death globally, and also as the gravest type of coro-nary vascular disease[1-3]. Acute coronary syndrome (ACS) is a cardiac emergency condition manifested as chest distress or symptoms due to MI. Electrocardiography (ECG) is a known diagnostic tool, for the management of subjects presenting with acute chest aches. ECG findings form the basis on which ACS has involved "unstable angina, and AMI" that is classified ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI)" a classification that provides data about the extent of myocardial risk and guides early therapy[4]. Early diagnosis of AMI is the cornerstone of the management to

customize the patient's further lines of treatment and best outcomes. Cardiac troponin-I (cT-I), is the "gold standard" indicator for myocardial ischemia [5, 6]. Nevertheless, owing to the late release, cT-I is not sensitive for diagnosis duringthe early stages of AMI which is thus being termed the "troponin-blind period"[7]. The initial inflammatory response is avital step in the evolution of AMI (4).C-reactive protein, -especially the highly sensitive (HS-CRP)- is an acute inflammatory peptidesynthesized in the liver[8-11]and reported as an independent prognostic factor foratherosclerotic events[12]. Some surveys have shown an increase in serum HS-CRP in patients with AMI [5, 12, 13].

The high mortality rates of AMI recommended the inevitable an earlier diagnosis for urgent management and to avoid mortality, especially in the Iraqi state. At present, in Iraqi hospitals, mainly in the three central hospitals in Babylon, the HS-CRP tests have not yet been routinely measured for AMI patients. As yet, only a scarce scholar has evaluated the combined variations of cT-I and HS-CRP in patients with AMI in IRAQ.

In the current work, the usefulness of combining cT-I and HS-CRP levels in the diagnoses of AMI on the day of presentation had been investigated in a case-control study.

2. METHODOLOGY

Study Plan and Subjects Recruitment

This research had conducted on patients from the ED and cardiac care unit of Al-Imam Al-Sadiq hospital during the period from June-August 2018. It was a case-control, observational study to estimate the diagnostic value of HS-CRP in establishing STEMI analysis among admitted patients who revealed positive cT-I tests. The patients labeled as "STEMI" had based on the diagnosis of the hospital cardiologists. The healthy (Non-AMI) group was selected from patients' companions when they have no heart problems.

Data and Sample Collections

After signing conversant permission, a proper medical history had achieved. The study had directed consistent with the "Helsinki Declaration", and our protocol had permitted by the ethical committee of local authorities. Then venous samples were collected for urea, creatinine, WBCs, R/FBS assessments using local obtainable procedures. As well, the blood samples had quantified for cT-I and HS-CRP with enzyme-linked fluorescent immunoassay by VIDAS® Troponin-I ultra-assay from BioMérieux (France) and HS-CRP from Elabscience® Human ELISA kit (Netherland). The time between the onset of chest pain and the blood sample was < 24 hours.

Statistical Analysis

Information had descriptively examined to describe the appearances and the risk factors of the two groups. Changes incT-I and HS-CRP between groups had been statistically studied with the independent-samples test and Spearman'-correlation. To realize which marker value has the highest AUC to STEMI, the cutoff point for each value, and the predictability of both biomarkers (whether individual or combined) to distinguish STEMI from healthy, the receiver operating curve (ROC) analyses had decided. All statistical data had completed using SPSS-IBM software (version-25) compatible with Windows.

3. RESULTS

Significant high levels of cT-I and HS-CRP had observed in STEMI patients, compared to the non-MI group (p-0.001). Troponin-I was >0.1 ng/ml in 89%, and HS-CRP was >10 mg/L in 30% of the STEMI patients (table-1).

Table 1. The Comparison of cT-I and Hs-CRP Levels between STEMI and Non-MI Groups

Biomarker (Mean ± SD)	Groups			Significance
	Total	STEMI	Non-MI	
HS-CRP	4.89±3.7	8.4±0.9	1.1±0.1	0.001
Troponin-I	6.05±6.3	8.1±1.1	0.01±0.05	0.001

The clinical and biochemical characteristics in STEMI and Non-MI groups were parallel other than significantly higher levels (p-0.05) of WBCs among STEMI patients (table-2).

Table 2: Clinical and biochemical characteristics in STEMI and Non-MI groups

Characteristics	Groups			Significance
	Total	STEMI	Non-MI	
SBP	131±13.7	131.7±38.3	121.9±18.3	> 0.05
DBP	88.05±26.3	91.5±11.6	73.6±36.5	> 0.05
R/FBS	5.4±2.4	6.6±4.2	5.4±2.4	> 0.05
Urea	60	14.3±5.2	13.6±6.1	> 0.05
Creatinine	58	84.4±32.1	91.4±11.6	> 0.05
WBCs	9.7±3.1	10.4±3.9	7.7±2.6	0.05

The risk factorsin this study varied significantly between STEMI and Non-MI groups (p-0.001). The excepted issue is the parallel weight of the participants of the two groups (table-3).

Table 3. Characteristics of Classic Risk Factor between STEMI and Non-MI Groups

Characteristics	Groups			Significance
	Total (N=168)	STEMI (N=118)	Non-MI (N=50)	
Age	4.89±3.7	64.4±7.9	38.5±11.7	0.001
BMI	28.05±6.3	27.1±7.1	28.1±5.05	> 0.05
DM	54	50	4	0.001
HT	60	57	3	0.001
Smoking	59	48	11	0.001

ROC curve analyses of HS-CRP, cT-I, and their combination for the prediction of AMI were scrutinized. The HS-CRP showed sensitivity (75.1), specificity (67.6), and significant-high accuracy of 75.4% with a 95% CI of 0.915-0.992. While the cT-I showed higher sensitivity and specificity (87.5 and 76.2) and significantly higher accuracy 76.5% and 95% CI of 0.929-1.0. The diagnostic and predictive values for STEMI increased significantly when both markers were combined (table-4).

Table-4: ROC curve analyses of HS-CRP, cT-I, and their combination for prediction of AMI

Biomarker	Sensitivity	Specificity	Accuracy	Significance	95% Confidence Interval
HS-CRP	75.1	67.6	0.754	0	*0.915 - 0.992*
Troponin-I	87.5	76.2	0.765	0	*0.929 - 1.000*
HS-CRP & Troponin-I	92.1	82.2	0.885	0	*0.962 - 1.000*

Patients with levels higher than the HS-CRP cutoff (6.3 mg/L) have more than 5-folds a higher level of cT-I (> 0.19ng/ml). I.e., the high CPR levels associated with 5-times more extent of cardiac necrosis [p-0.00, *OR* 5.4, and 3.01-962] reflected by higher cT-I (>0.19 ng/ml) (table-5). The association of high HS-CRP and cT-I in STEMI patients was independent of age, sex, and BMI in this study (results not shown).

Table-5: Chi-square correlation of HS-CRP with Troponin-I based on cut-off point among STEMI patients

Variables Cutoff	**Troponin-I ng/ml**					
HS-CRP mg/L	< 0.19	> 0.19	Total	P-value	*OR*	*95% CI*
HS-CRP <6.3	39 (86.8%)	6 (13.2%)	45	0	5.4	*3.01 - 9.62*

HS-CRP >6.3	11 (16.1%)	52 (83.9%)	63

Subjects with levels of HS-CRP and cT-I higher than their matching detected cutoff were significantly (0.000) distributed among STEMI patients (table-6).

4. DISCUSSION

In this study, the question under discussion is the predictive effects of combining HS-CRP as an inflammatory marker with cT-I in the diagnosis of AMI patients at presentation time. Our results displayed that the detection of these two biomarkers can afford high sensitivity, specificity, and accurate results for the diagnosis of STEMI patients. The estimation of cT-I levels is more sensitive and specific than HS-CRP. Still, at the time of cT-I detection, it will be STEMI late stage, and the myocardium has suffered necrotic or irreversible changes. In the meantime, HS-CRP could be measured earlier. Thus, it could provide earlier STEMI diagnosis and treatment. [1, 5, 12, 14].

Several investigations itemized the vital role of inflammation in the progression of atherosclerosis even a few years before AMI becomes evident [14]. Raised inflammatory biomarkers mirror "acute phase response".

The capacity of macrophages to release several cytokines like interleukins, chemokines like MCP-1 [15], and growthfactors like TGF-β superfamily that has a pleiotropic effect [16, 17] and PDGF that has a mitogenic effect [18, 19], further promote activity and proliferationof smooth muscle cells, the evolution of the lesion, andwaning of susceptible plaques by fibrotic-cap destruction. Thus far, arteriosclerosis and its sequelaeare categorized as local and systemic [15] inflammatory pathology.

The concentrations of HS-CRP were correlated to the severity of arteriosclerosis and the inflammatory process besides thrombogenesis through complement activation. As well, CRP is directly linked to expressed tissue factors over the monocytic surface[20]. CRP prevents endothelial NOsynthesis and subsidizes plaque vulnerability by enhancing adhesion molecules expression of the endothelium, by recruiting monocytes into the intimal plaque, and by enzymaticbinding into the low-density lipoproteins [3, 12, 13, 20].

The cells of tissue inflammation are accountable for plaque instability by altering "anti-adhesive and anti-coagulants" into pro-coagulant factors in monocyte that induce plaque dislodgment [3, 20].Consequently, evidence of leukocytosis and raised HS-CRP levels to indicate AMI, consistent with our results increased WBCs among STEMI patients.

Elevated ST points out transmural ischemia and detects those who necessitate urgent revascularization. The relation between ST-segment elevation on the ECG and the occluded coronary artery had been established in multiple clinical studies in patients with AMI. Cardiac troponin-I has not only analytic worth but harvests predictive information as well. People presenting with signs of AMI and high cT-I have worse consequences than those who lack measurable cT-I in the blood. Measures of cT-I had reported being about 100% sensitive > 12 hours after the possible onset of chest pain [21]. But still, compared toHS-CRP levels, cT-I analyses are markedly sensitive in the detection of cardiac injury[7, 21].

The data yielded by this study provides convincing evidence that combining HS-CRP and cT-I will increases the predictive ability of these biomarkers for AMI. This result is in line with more than few results published last year [5]. Wang et al. (2020) compared cT-I and HS-CRP before and after treatment of AMI. They proposed this may have enhanced value for evaluating the early therapeutic efficacy of AMI treatment[22]conducted this year in patients with non-ischemic cardiac failure that revealed raised CRP, cT-I, and GLS had been linked to cardiac inflammation[23]. Contrarily, combining various AMI biomarkers does not support risk stratification compared to cT-I alone reported in Sweden subjects presented with acute chest pain[24].

Koskinaset al.(2016) described that in STEMI patients, HS-CRP significantly declined after thorough statin administration compared to their initial levelsbeforestatin [25]. The second proposed explanation for the prior conflicting results might the bloodvalues of HS-CRP and cT-I were significantly inferior in the "treatment-effective"compared with the "treatment-ineffective" group of patients [22].The fluctuations of the serum levels of CRP have not been expected with cT-I assays as they had not influenced by thrombolytic agents[26].

Additionally, as the existing data specifies, cutoff points for cT-I and HS-CRP appear to be higher concerning myocardial inflammation compared with cutoff values used for diagnosis of AMI. Accordingly, there is an actual trick of how test-positive patients should manage in medical practice. Supplementary studies are desirable to verify cutoff points in STEMI patients with myocardial inflammation in particular.

Nevertheless, to the best of our knowledge, no preceding study has straight compared the predictive value of combined cT-I and HS-CRP together compared to cT-I alone, and then, further studies are warranted.

5. CONCLUSION

There were significantly higher levels of cT-I and HS-CRP in STEMI patients compared to the non-MI group. The higher CPR levels had associated with a 5-times higher extent of cardiac necrosis reflected by higher cT-I. The higher diagnostic and predictive capability of cT-I and HS-CRP for STEMI increased significantly when both markers were combined compared to their ability alone.

6. LIMITATION

Certain limitations in this study need to be declared: First, our study was single-center based, thus it should be substantiatedby prospective trials. Second, generally,the lack of a valid definition of myocardial inflammation makes the interpretation of elevated HS-CRP difficult to adopt as a marker specific for AMI-related inflammation, but creating more data about the ongoing myocardial inflammation was one of the main goals of our study.The collection time of cT-I and HS-CRP samples in certain patients did not fit the necessities of the study design, resulting in data loss. Anyway, work like our study will be improved much if the included sample was larger.

Financial support and sponsorship: Nil.

7. CONFLICTS OF INTEREST

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

REFERENCES

[1] Abed, D.A., Jasim, Raad, Al-Hindy, Hayder Abdul-Amir, Obaid, Ammar Waheeb, *Cystatin-C in patients with acute coronary syndrome: Correlation with ventricular dysfunction, and affected coronary vessels.* Journal of Contemporary Medical Sciences, 2020. **6**(1): p. 26-31.

[2] Amir Al-Mumin, A.-H.H.A., *Hyperuricemia has a Deleterious Role in Patients with Acute Coronary Syndrome Presented with Poor Oral Hygiene.* International Journal of Pharmaceutical Research, 2020. **SP1.193**: p. 1196-1202.

[3] Hajir K. Abdul-Husseein, F.S.D., Ameera J. Al-Aaraji, Hayder A. Makki Al-Hindy, Mazin J. Mousa, *Biochemical causal-effect of circulatory uric acid, and HSCRP and their diagnostic correlation in admitted patients with ischemic heart diseases.* Journal of Cardiovascular Disease Research 2020. **11**(2): p. 25-31

[4] Kristian Joseph S., A.A.S.J., Bernard R. Chaitman, Jeroen J. Bax, David A. Morrow, Harvey D. White, *ESC/ACC/AHA/WHF Expert Consensus Document. Fourth Universal Definition of Myocardial Infarction (2018).* Circulation, 2018. **138**: p. e618–e651.

[5] Amir Al-Mumin, H.A.M., Mazin JM., *Combined Assessments of Multi-panel Biomarkers for Diagnostic Performance in Coronary Artery Disease: Case-Control Analysis.* Sys Rev Pharm, 2020. **11**(6): p. 665-61.

[6] Hayder Abdul-Amir Maki Al-Hindi, M.J.M., Thekra Abid Jaber Al-Kashwan, Ahmed Sudan, Saja Ahmed Abdul-Razzaq, *Correlation of on Admission Levels of Serum Uric Acid with Acute Myocardial Infarction: Case-Control Study.* Journal of Global Pharma Technology, 2019. **11**(7): p. 289-94.

[7] Wang L, L.B., Yu J, Chen L, Cai X, Liu L, Hou K, Zhang M., *Changes of cardiac troponin I and hypersensitive C-reactive protein prior to and after treatment for evaluating the early therapeutic efficacy of acute myocardial infarction treatment.* Exp Ther Med, 2020. **19**(2): p. 1121-1128.

[8] Raghdan Z., A.K.S., Dleikh F., Al-Hindy H., *Is There any Association Between Highly Sensitive C-Reactive Protein and Dental-Status in Ischemic Heart Diseases? A Comparative Stud.* Biochemical and Cellular Archives, 2020. **20**(2): p. 6069-6075.

[9] Samer MM., A.S., Hayder AA., Mazin JM., *C-Reactive Protein is Associated with the Severity of Periodontal Disease — An Observational Study Among Acute Myocardial Infarction Patients.* Sys Rev Pharm 2020. **11**(10): p. 252-257.

[10] Qasim J., H.S., Ghada H., Hayder AA., *High-Sensitivity C-reactive protein Assessment in Bronchial Asthma: Impact of Exhaled Nitric Oxide and Body Mass Index.* Systematic Reviews in Pharmacy, 2020. **11**(3): p. 705-711.

[11] Al-Agam A, O.A., Alzughaibi M, Makki H, Alhaideri AF., *The Association of Depressive Symptoms With Plasma C-Reactive Protein in Patients With Major Depressive Disorder Under Treatment.* Iranian Rehabilitation Journal, 2021. **19**(4): p. 425-432.
[12] Hayder Abdul-Amir Maki Al-Hindi, M.J.M., Thekra Abid Jaber Al-kashwan, Ahmed Sudan, Saja Ahmed Abdul-Razzaq, *On Admission Levels of High Sensitive C- Reactive Protein as A Biomarker in Acute Myocardial Infarction: A Case-Control Study.* Indian Journal of Public Health Research & Development 2019. **10**(4): p. 1480-84.
[13] Asseel K. Shaker, R.A.-S., Raad Jasim, Hayder Abdul-Amir Makki Al-Hindy, *Biochemical Significance of Cystatin-C and High Sensitive CRP in Patients with Acute Coronary Syndrome; any Clinical Correlation with Diagnosis and Ejection Fraction.* Sys Rev Pharm, 2020. **11**(3): p. 301-9.
[14] Haidari, M., et al., *Evaluation of C-reactive protein, a sensitive marker of inflammation, as a risk factor for stable coronary artery disease.* Clin Biochem, 2001. **34**(4): p. 309-15.
[15] Wann, W.K.a.C., *C-reactive protein and coronary artery disease —what is the link? Editorial Comments.* . Nephrol Dial Transplant 1999. **14**: p. 2798–2800.
[16] Hanna, A. and N.G. Frangogiannis, *The Role of the TGF-β Superfamily in Myocardial Infarction.* Frontiers in cardiovascular medicine, 2019. **6**: p. 140-140.
[17] Hayder AA. Al-Hindy, M.J.M.A.K., Raghdan Z. Al-Saad, Widad HD., *Relationship of levels of transforming growth factorbeta1 (TGF-β1) to the levels of ferritin in blood of transfusion dependent β-thalassemia major patients with growth retardation: A case-control study* EurAsian J Biosci., 2020. **14**(1): p. 521-552.
[18] Hayder Abdul-Amir Maki Al-Hindy, M.J.M., Asseel K. Shaker, *No Significant Relationship of Ferritin Levels to the Levels of Platelet-derived Growth Factor (PDGF) in the Peripheral Blood of Transfusion-dependent ß-Thalassemia Major Patients with Growth Retardation.* International Journal of Pharmaceutical Research, 2020. **12**(3): p. 567-575.
[19] Fouad Shareef Dleikh, A.J.A.-A., Rebee Mohin, Mazin Jaafar Mousa, Hayder Abdul-Amir Makki Al-Hindy, Basim Abd Al-Ka'abi, *Possible cause-and-effect linkage of transforming growth factor-beta1 and platelets derived growth factor-AB with delayed anthropometric parameters in adolescent patients with Cooley's anemia: Cases vis control research strategy.* EurAsian Journal of BioSciences, 2020. **14**(1): p. 1119-25.
[20] Badimon, L., et al., *C-Reactive Protein in Atherothrombosis and Angiogenesis.* 2018. **9**(430).
[21] Stark M, K.C., Sharma S., *Troponin. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507805/.* In: StatPearls, 2021.
[22] Wang, L., et al., *Changes of cardiac troponin I and hypersensitive C-reactive protein prior to and after treatment for evaluating the early therapeutic efficacy of acute myocardial infarction treatment.* Experimental and therapeutic medicine, 2020. **19**(2): p. 1121-1128.
[23] Schwuchow-Thonke, S., et al., *Increased C reactive protein, cardiac troponin I, and GLS are associated with myocardial inflammation in patients with non-ischemic heart failure.* Scientific Reports, 2021. **11**(1): p. 3008.
[24] Eggers, K.M., et al., *Combining different biochemical markers of myocardial ischemia does not improve risk stratification in chest pain patients compared to troponin I alone.* Coron Artery Dis, 2005. **16**(5): p. 315-9.
[25] Koskinas, K.C., et al., *Changes of coronary plaque composition correlate with C-reactive protein levels in patients with ST-elevation myocardial infarction following high-intensity statin therapy.* Atherosclerosis, 2016. **247**: p. 154-60.
[26] Vogiatzis, I., et al., *A Comparison of Prognostic Value of the Levels of ProBNP and Troponin T in Patients with Acute Coronary Syndrome (ACS).* Med Arch, 2016. **70**(4): p. 269-273.