

Original Research Article

Highly Sensitive C Reactive Protein as a Predictor of in Hospital Outcome in Patients with Acute Coronary Syndrome

Abstract

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Background: C-reactive (CRP) protein is an extensively studied inflammatory factor whose prognostic value in cardiovascular diseases in recent years has become increasingly important 3-8. The aim of this work was to assess prognostic value of highly sensitive C-reactive protein in patients with acute coronary syndrome (ACS).

Methods: This observational study was carried out on 50 patients with ACS admitted to CCU and indicated for invasive coronary angiography. Patients were divided in two groups according to hs-CRP level: group A included (14) patients with $hs-CRP < 2$ and group B included (36) patients with $hs-CRP \geq 2$. All patients were subjected to: laboratory investigations (urea, creatinine, alanine amino transferase (ALT), aspartate aminotransferase (AST), creatine kinase myocardial band (CKMB), troponin, high-sensitivity C-Reactive protein (hs-CRP), HbA1C, lipid profile, twelve lead surface ECG, echocardiography and coronary angiography.

Results: Total cholesterol, LDL, HDL and triglyceride were significantly higher in group B compared to group A ($P=0.001$). Stent implantation was significantly higher in group 2 compared to group 1 ($P=0.040$)

Conclusions: There were correlation between hs CRP and lipid profile as a risk factor and there was no correlation between hs CRP and in hospital outcome in patients with ACS due to small sized study.

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Keywords: Highly Sensitive, C Reactive Protein, Hospital Outcome, Acute Coronary Syndrome.

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UNDER PEER REVIEW

Introduction:

Inflammatory biomarkers provide useful information on the inflammatory process of atherosclerosis; they act as a window into the process of cell activation, recruitment of inflammatory cells and proliferation ^[1].

Despite great progress in pharmacotherapy and interventional treatment, acute coronary syndrome (ACS) remains the major cause of mortality and morbidity in the modern world ^[2]. Inflammation plays a key role in the initiation and promotion of atherosclerotic lesions and can trigger ACS by the induction of plaque instability. C-reactive (CRP) protein is an extensively studied inflammatory factor whose prognostic value in cardiovascular diseases in recent years has become increasingly important ^[3-8]. Additionally, CRP is no longer merely considered a marker but also emerges as a mediator of atherosclerosis ^[9, 10].

A high level of highly sensitive CRP (hs-CRP) earlier in ACS, before development of myocardial necrosis, is an important indicator of poor prognosis with cardiovascular comorbidities. Its assessment during the time course of ACS may assist in risk stratification for myocardial dysfunction ^[11].

A scientific statement issued by Centre for Disease Control (CDC) and American Heart Association (AHA) has mentioned hs-CRP as the only inflammatory marker that can be used for risk prediction both for primary and secondary prevention of cardiovascular events ^[7]. The aim of this work was to assess prognostic value of highly sensitive C-reactive protein in patients with acute coronary syndrome.

Patients and Methods:

This observational study was carried out on 50 patients with acute coronary syndrome admitted to CCU and indicated for invasive coronary angiography, who had ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and

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✓ General and specific objectives
✓ Statement of the problems (rationales)
✓ Hypothesis/research questions
✓ Significance of the research

unstable angina. The study was done after approval from the Ethical Committee Tanta University Hospitals. An informed written consent was obtained from the patient.

Patients with chronic renal disease, chronic liver diseases, acute or chronic inflammation, pregnancy, malignancy, previous PCI and CABG were excluded.

All patients were subjected to: full history taking, clinical examination (vital signs, signs of inflammation, autoimmune diseases as systemic lupus and rheumatoid arthritis), laboratory investigations (urea, creatinine, alanine amino transferase (ALT), aspartate aminotransferase (AST), creatine kinase myocardial band (CKMB), troponin, high-sensitivity C-Reactive protein (HS CRP), HbA1C, lipid profile (total cholesterol, triglyceride, HDL-C and LDL-C), twelve lead surface ECG, echocardiography and coronary angiography.

Twelve lead surface ECG: ST-segment elevation is considered suggestive of ongoing coronary artery acute occlusion in the following cases: at least two contiguous leads with ST-segment elevation ≥ 2.5 mm in men < 40 years, ≥ 2 mm in men ≥ 40 years, or ≥ 1.5 mm in women in leads V2–V3 and/or ≥ 1 mm in the other leads. In patients with inferior MI, it is recommended to record right precordial leads (V3R and V4R) seeking ST-segment elevation, to identify concomitant right ventricular (RV) infarction. ST-segment depression in leads V1–V3 suggests myocardial ischaemia, especially when the terminal T-wave is positive (ST-segment elevation equivalent), and confirmation by concomitant ST-segment elevation ≥ 0.5 mm recorded in leads V7–V9 should be considered as a means to identify posterior MI. Non-ST-segment elevation ACS exhibit ECG changes that may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves or pseudo-normalization of T waves or the ECG may be normal.

Echocardiography: Transthoracic Echocardiography will be performed to assess the presence or absence of mechanical complications and the overall systolic function. The ejection fraction is measured using modified Simpson's method in apical 4,2.

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✓ Research sites and periods
✓ Research design
✓ Method of data collection
✓ Inclusion and exclusion criteria
✓ Sampling techniques
✓ Method of analysis

Coronary angiography: According to American Heart Association (AHA), The procedure is done in a hospital cardiac catheterization lab: a local anaesthetic is usually given to numb the needle puncture site. we will make a needle puncture through your skin and into a large blood vessel. A small straw-sized tube (called a sheath) will be inserted into the vessel. The doctor will gently guide a catheter (a long, thin tube) into your vessel through the sheath. A video screen will show the position of the catheter as it is threaded through the major blood vessels and to the heart. When a catheter is used to inject a dye that can be seen on X-rays, the procedure is called angiography. When a catheter is used to clear a narrowed or blocked artery, the procedure is called angioplasty or a percutaneous coronary intervention (PCI).

Criteria of STEMI, NSTEMI and unstable angina

Chest pain: is the hallmark of myocardial ischemia and it especially pronounced in patients with acute STEMI, the reason symptoms are more severe in patients with STEMI as compared with NSTEMI and unstable angina.

ECG: STEMI is defined by the presence of significant ST segment elevation, pathological Q waves and reciprocal ST segment depression. NSTEMI is defined by the absence of ST segment elevation, presence of ST segment depressions and/or T wave inversions such as unstable angina.

Cardiac enzymes: STEMI, NSTEMI will exhibit elevated troponin levels. Those who do not display elevated troponin levels are classified as unstable angina.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. The comparison between two groups with qualitative data were done by using Chi-square test and/or Fisher exact test was used instead of Chi-square test

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when the expected count in any cell was found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent t-test.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant if $P < 0.05$.

Results:

Gensini score was significantly higher in group B compared to group A ($P=0.001$). Demographic data, smoking, HTN and diabetes was insignificantly different between two groups. [Table 1]

Table 1: comparison between two groups according to demographic data, Gensini score, smoking, HTN, diabetes

	Group A(n=14)	Group B(n=36)	t. test	p. value
Age	48.07±4.81	46.08±6.59	1.025	0.311
Sex	Male			
	7(50%)	19(52.8%)	0.031	0.860
Weight	72.79±9.16	70.25±8.34	0.939	0.352
Height	1.60±0.12	1.60±0.10	0.002	0.998
BMI	28.69±4.99	27.51±3.57	0.932	0.356
Gensini score	30.29±18.62	80.28±52.35	3.470	0.001*
			X ²	P-value
Smoking	8 (57.1)	15(41.7)	0.972	0.324
HTN	11 (78.6)	22 (61.1)	1.369	0.242
Diabetes	7(50.0)	26 (72.2)	2.218	0.136

Data are presented as mean ± SD or frequency (%), BMI: Body mass index, HTN: hypertension

Total cholesterol, LDL, HDL and triglyceride were significantly higher in group B compared to group A ($P=0.001$). Urea, creatinine, ALT, AST, HbA1c and LVEF were insignificant difference between the two groups. [Table 2]

Table 2: Shows comparison between two groups according to demographic data of Urea, Creatinine, ALT, AST, total cholesterol, LDL, HDL, triglyceride, HbA1c and LVEF.

	Group A	Group B	t. test	p. value
Urea	20.07±7.26	22.03±6.91	0.886	0.380
Creatinine	0.94±0.15	0.93±0.19	0.312	0.756
ALT	15.93±2.92	17.00±3.94	0.921	0.362
AST	16.93±2.56	16.56±3.18	0.392	0.697
Total cholesterol (mg/dL)	87.77±47.34	174.04±40.90	6.409	0.001*
LDL-C, (mg/dL)	51.20±27.71	112.22±29.00	6.760	0.001*
HDL-C, (mg/dL)	27.74±17.93	53.61±20.54	4.134	0.001*

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Triglyceride, (mg/dL)	86.25±49.52	166.56±78.44	3.552	0.001*
HbA1c (NGSP), %	7.34±1.47	7.56±1.56	0.451	0.654
LVEF, %	60.57±13.78	57.69±15.31	0.614	0.542

Alt: Alanine transaminase, AST: Aspartate aminotransferase, LDL: Low density protein, HDL: High density protein, HbA1c: Hemoglobin A1c, LVEF: Left ventricular ejection fraction, *: significant P value

Stent implantation was significantly higher in group 2 compared to group 1 (P=0.040).

Incidence of unstable angina, NSTEMI, STEMI, death, cardiogenic shock, acute pulmonary edema, atrial fibrillation, mechanical ventilation, ventricular fibrillation and ventricular tachycardia were insignificantly different between the two groups. [Table 3]

Table 3: comparison between two groups according to the incidence of unstable angina, NSTEMI, STEMI, death, cardiogenic shock, acute pulmonary edema, atrial fibrillation, mechanical ventilation, ventricular fibrillation, ventricular tachycardia and stent implantation

	Group A	Group B	X²	P-value
Unstable angina	5(35.7%)	14(38.9%)	0.043	0.836
NSTEMI	2(14.3%)	9(25.0%)	0.674	0.412
STEMI	6(42.8%)	14(38.9%)	0.511	0.066
Death	3(21.4%)	2(5.6%)	2.822	0.093
Cardiogenic shock	5(35.7%)	7(19.4%)	1.463	0.226
Acute pulmonary edema	5(35.7%)	7(19.4%)	1.463	0.226
Atrial fibrillation	2(14.3%)	8(22.2%)	0.397	0.529
Mechanical ventilation.	3(21.4%)	4(11.1%)	0.891	0.345
Ventricular fibrillation	6(42.8%)	9(25.0%)	1.531	0.216
Ventricular tachycardia	4(28.6%)	9(25.0%)	0.067	0.796
Stent implantation	1(7.2%)	13(36.2%)	4.196	0.040*

X²: Chi square test, *: significant P value, STEMI: ST-elevation myocardial infarction.

Discussion

Many biomarkers were associated with the development and progression of coronary heart disease. In the past, the role of hs-CRP in cardiovascular disease was controversial as a risk marker ^[12].

The present study results are comparable to the studies by Cavusoglu Y, et al ^[13] And Tomoda N, et al ^[14] who demonstrated that the CRP concentrations in patients presenting with acute coronary syndromes, within 6 hours of onset of symptoms were significantly higher as compared to the Control Group. The inflammatory process has been shown to be

one of the mechanisms causing plaque rupture leading to elevated CRP levels in less than 6 hours in patients with acute coronary syndrome. In patients presenting with ACS, hsCRP concentrations are more than 10-fold higher than in patients with stable coronary disease or no known coronary disease.

A study by Vasan et al.^[15] compared between hsCRP and heart failure in patients with STEMI and Mega et al 103. Study that confirmed the presence of an association between hsCRP and heart failure when these variables were used as a part of a composite endpoint in patients with ACS as in Sabatine et al.,^[16] and Varo et al.,^[17] studies.

While Mach et al.,^[18] showed that among patients with acute ischemic heart disease and no biological markers of myocardial necrosis, the CRP concentration at the time of admission was significantly higher in patients in whom an acute myocardial infarction was ultimately diagnosed, while in patients with unstable angina the CRP levels were low.

On the other hand, Bogaty et al.,^[19] reported that assessment of severity of atherosclerosis through using only the Gensini score as grading tool showed that hsCRP levels correlated with the severity of atherosclerosis.

Elevated CRP concentration in patients who presented to hospital with chest pain due to ACS was previously demonstrated by others Niccol et al.,^[20] and Arroyo et al.,^[21].

Ray et al.,^[22] concluded that the addition of hsCRP to lipid-based measurements significantly improved risk prediction, in contrast, other studies showed lower discriminative usefulness of CRP 111. Also, hsCRP levels after AMI predicted emergence of heart failure in a study by Stumpf et al.,^[23] and also found that peak CRP is also a strong predictor of global and cardiovascular mortality during the following year after STEMI.

Bursi et al.,^[24] reported in a recent study that CRP at admission to hospital is useful for predicting the time course of heart failure in patients with AMI. The study by Kavsak et

al.,^[25] indicated that high CRP titers, independent of the subjects' age, gender, and cTnI concentrations, predict long-term heart failure and mortality.

Morrow et al.,^[26] that study used a cut off of 1.5 mg/dl (similar to ours) and observed that elevated CRP at admission was associated with higher mortality at 14 days. Schoos et al.,^[27] demonstrated that pre-procedures CRP is an independent and strong predictor of a composite endpoint of death, nonfatal recurrent myocardial infarction, and stent thrombosis after percutaneous intervention with coronary stent implantation^[28] confirmed the prognostic value of CRP in predicting short- and long-term outcomes after ACS.

Limitations: Its small sized study and done in one centre, a large study on a large number of populations in multiple centres is needed to validate the results.

Conclusions:

There was a correlation between hs CRP and lipid profile as a risk factor and there was no correlation between hs CRP and in hospital outcome in patients with ACS due to small sized study.

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COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the

advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References:

1. Kinlay S, Selwyn AP. Effects of statins on inflammation in patients with acute and chronic coronary syndromes. *Am J Cardiol.* 2003;91:9b-13b.
2. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive Summary: Heart Disease and Stroke Statistics—2012 Update. *Circulation.* 2012;125:188-97.
3. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet.* 2010;375:132-40.
4. Swiatkiewicz I, Kozinski M, Magielski P, Gierach J, Fabiszak T, Kubica A, et al. Usefulness of C-reactive protein as a marker of early post-infarct left ventricular systolic dysfunction. *Inflamm Res.* 2012;61:725-34.
5. Swiatkiewicz I, Kozinski M, Magielski P, Fabiszak T, Sukiennik A, Navarese EP, et al. Value of C-reactive protein in predicting left ventricular remodelling in patients with a first ST-segment elevation myocardial infarction. *Mediators Inflamm.* 2012;2012:250867.
6. Kubica J, Koziński M, Krzewina-Kowalska A, Zbikowska-Gotz M, Dymek G, Sukiennik A, et al. Combined periprocedural evaluation of CRP and TNF-alpha enhances the prediction of clinical restenosis and major adverse cardiac events in patients undergoing percutaneous coronary interventions. *International journal of molecular medicine.* 2005;16:173-80.
7. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.* 2003;107:499-511.

8. Wensley F, Gao P, Burgess S, Kaptoge S, Angelantonio E, Shah T, et al. Association between C reactive protein and coronary heart disease: Mendelian randomisation analysis based on individual participant data. *BMJ (Clinical research ed)*. 2011;342:d548.
9. Bisoendial RJ, Boekholdt SM, Vergeer M, Stroes ESG, Kastelein JJP. C-reactive protein is a mediator of cardiovascular disease. *European Heart Journal*. 2010;31:2087-91.
10. Pepys MB, Hirschfield GM, Tennent GA, Ruth Gallimore J, Kahan MC, Bellotti V, et al. Targeting C-reactive protein for the treatment of cardiovascular disease. *Nature*. 2006;440:1217-21.
11. Habib SS, Kurdi MI, Al Aseri Z, Suriya MO. CRP levels are higher in patients with ST elevation than non-ST elevation acute coronary syndrome. *Arq Bras Cardiol*. 2011;96:13-7.
12. Wang D, Juonala M, Viikari JSA, Wu F, Hutri-Kähönen N, Raitakari OT, et al. Exposure to Parental Smoking in Childhood is Associated with High C-Reactive Protein in Adulthood: The Cardiovascular Risk in Young Finns Study. *J Atheroscler Thromb*. 2017;24:1231-41.
13. Cavusoglu Y, Gorenek B, Alpsoy S, Unalir A, Ata N, Timuralp B. Evaluation of C-reactive protein, fibrinogen and antithrombin-III as risk factors for coronary artery disease. *Isr Med Assoc J*. 2001;3:13-6.
14. Tomoda H, Aoki N. Prognostic value of C-reactive protein levels within six hours after the onset of acute myocardial infarction. *American Heart Journal*. 2000;140:324-8.
15. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation*. 2003;107:1486-91.
16. Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation*. 2002;105:1760-3.

17. Varo N, de Lemos JA, Libby P, Morrow DA, Murphy SA, Nuzzo R, et al. Soluble CD40L: risk prediction after acute coronary syndromes. *Circulation*. 2003;108:1049-52.
18. Mach F, Lovis C, Gaspoz JM, Unger PF, Bouillie M, Urban P, et al. C-reactive protein as a marker for acute coronary syndromes. *Eur Heart J*. 1997;18:1897-902.
19. Bogaty P, Boyer L, Simard S, Dauwe F, Dupuis R, Verret B, et al. Clinical utility of C-reactive protein measured at admission, hospital discharge, and 1 month later to predict outcome in patients with acute coronary disease. The RISCA (recurrence and inflammation in the acute coronary syndromes) study. *J Am Coll Cardiol*. 2008;51:2339-46.
20. Niccoli G, Biasucci LM, Biscione C, Fusco B, Porto I, Leone AM, et al. Independent prognostic value of C-reactive protein and coronary artery disease extent in patients affected by unstable angina. *Atherosclerosis*. 2008;196:779-85.
21. Arroyo-Espliguero R, Avanzas P, Cosín-Sales J, Aldama G, Pizzi C, Kaski JC. C-reactive protein elevation and disease activity in patients with coronary artery disease. *Eur Heart J*. 2004;25:401-8.
22. Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. Prognostic Utility of ApoB/AI, Total Cholesterol/HDL, Non-HDL Cholesterol, or hs-CRP as Predictors of Clinical Risk in Patients Receiving Statin Therapy After Acute Coronary Syndromes. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2009;29:424-30.
23. Stumpf C, Sheriff A, Zimmermann S, Schaefauer L, Schlundt C, Raaz D, et al. C-reactive protein levels predict systolic heart failure and outcome in patients with first ST-elevation myocardial infarction treated with coronary angioplasty. *Arch Med Sci*. 2017;13:1086-93.
24. Bursi F, Weston SA, Killian JM, Gabriel SE, Jacobsen SJ, Roger VL. C-reactive protein and heart failure after myocardial infarction in the community. *Am J Med*. 2007;120:616-22.

25. Kavsak PA, MacRae AR, Newman AM, Lustig V, Palomaki GE, Ko DT, et al. Elevated C-reactive protein in acute coronary syndrome presentation is an independent predictor of long-term mortality and heart failure. *Clin Biochem.* 2007;40:326-9.
26. Morrow DA, de Lemos JA, Sabatine MS, Wiviott SD, Blazing MA, Shui A, et al. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation.* 2006;114:281-8.
27. Schoos MM, Kelbæk H, Kofoed KF, Køber L, Kløvgaard L, Helqvist S, et al. Usefulness of preprocedure high-sensitivity C-reactive protein to predict death, recurrent myocardial infarction, and stent thrombosis according to stent type in patients with ST-segment elevation myocardial infarction randomized to bare metal or drug-eluting stenting during primary percutaneous coronary intervention. *Am J Cardiol.* 2011;107:1597-603.
28. Abbate A, Biondi-Zoccai GG, Brugaletta S, Liuzzo G, Biasucci LM, editors. C-reactive protein and other inflammatory biomarkers as predictors of outcome following acute coronary syndromes. *Seminars in vascular medicine*; 2003: Copyright© 2003 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New

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