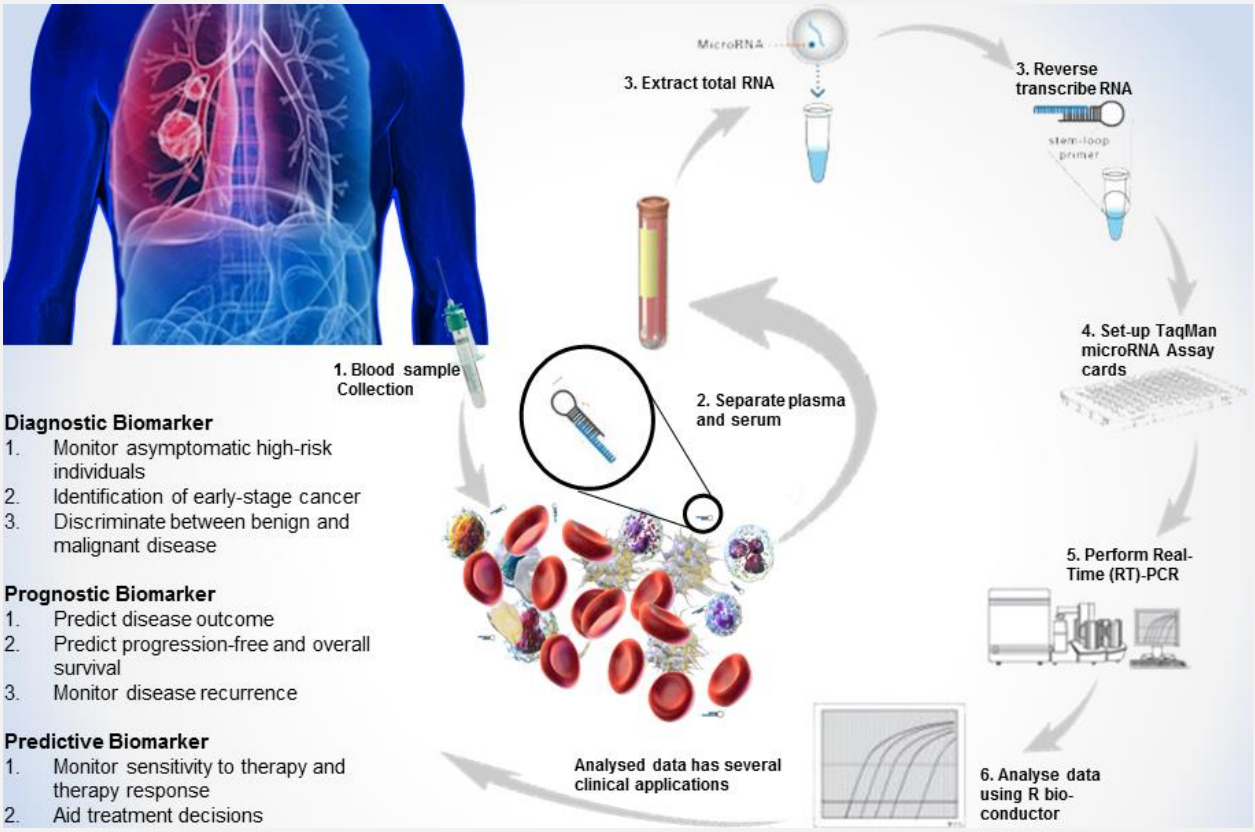
A study on Role of circulating hsCRP as a biomarker of clinical significance in acute Myocardial infarction (MI) and identification of extent of involvement, risk assessment and post MI complications.

N.Hemalatha[1], Narasinga Rao Siddanathi[* 1], K.Indira Devi[1], B.V.Chandrakala[1] and G.V.Hari Krishna[1]
Department of Medicine, Andhra Medical College, Visakhapatnam, AP, India.

Corresponding author: Dr.Narasinga Rao Siddanathi, M.D;e-mail: snrnaveen007@gmail.com Phone No: +919848136704



Abstract

Introduction: Myocardial infarction (MI) due to coronary artery disease (CAD) has become a leading cause of death worldwide surpassing malnutrition and infectious diseases especially in a developing country like India. There is a need for studies involving a single biomarker of detection as well as for identification of the extension of involvement to decide on effective management of patient. In the present study variations in serum high sensitive C reactive protein (hsCRP) concentration and its correlation with the extent of lesion involvement in MI is presented.. Keeping in view the significance of this aspect of role of hsCRP estimation, we studied 50 cases presenting with acute coronary syndrome (ACS) to King George Hospital, Visakhapatnam, India from December 2012 to September 2014. We measured hsCRP level in each patient to determine the association between hsCRP and ACS and its significance in the prognosis.

Results: Acute Coronary syndrome was observed to be highest among the age group of 41 to 50 years and chest pain was the most common presenting complaint with smoking as the most common risk factor. Out of 50 patients with acute coronary syndromes, 34(68%) patients had STEMI, 8 (16%) had UA and 8 (16%) had NSTEMI. Out of 34 patients who had STEMI, extensive anterior wall involvement was the most common type. Left ventricular failure was the most common complication seen in 15(30%) patients. Serum hsCRP levels were significantly increased in 34 (68%) out of 50 patients of acute coronary syndrome and 30 (60%) patients with high hsCRP levels developed post MI complications with LVF being the most common. All the values showed statistical significance was ($P<0.01$).

Conclusion: Present study has shown a strong correlation not only in the various levels of serum hsCRP and ACS, but has also shown an association between the concentration of the hsCRP and the extent of myocardial involvement and post MI complications.The fact that more number of STEMI patients having increased levels of hs-CRP shows increased incidence of adverse cardiac outcomes, when compared with UA/NSTEMI, suggest that hs-CRP levels may be related to the severity of inflammatory processes associated with multiple plaque rupture or infarct expansion in the spectrum of acute coronary syndrome. Raised hs-CRP levels are independent markers of adverse outcomes. Hence hs-CRP levels obtained at admission in acute coronary syndromes can be used as a marker for identification of patients who are likely to develop significant complications in the immediate in-hospital course and to predict the prognosis.

However, the limitation of this study includes a small sample size and a single serum hsCRP measurement instead of serial estimations at intervals and this limitation can be overcome in our future studies.

Key words : ACS,hs CRP, stemi, NSTEMI and UA

Introduction

Coronary artery disease (CAD) is a leading cause of death worldwide even in a developing country like India. Despite progress in the prevention of cardiovascular diseases, a significant proportion of first cardiovascular event occurs among individuals without traditional risk factors. The advancements in understanding pathophysiological mechanisms of atherosclerotic vascular diseases have brought new insight regarding potential indicators of underlying hidden atherosclerosis and cardiovascular risk. Coronary plaque disruption, with consequent platelet aggregation and thrombosis, is the most important mechanism by which atherosclerosis leads to the acute ischemic syndromes of unstable angina, acute myocardial infarction, and sudden death[1].

With growing evidence that atherosclerosis is an inflammatory process, several plasma markers of inflammation have been evaluated as potential tools for the prediction of coronary events[2]. However, recent technological advances in diagnostic tools have led to the utilization of various blood biomarkers of clinical significance in detecting heart disease like myocardial infarction at an early stage. Various lipid, protein and enzymatic biomarkers like lipoproteins, CK-MB, troponin and inflammatory acute phase proteins have been studied extensively for the early detection and management. Inflammation releases inflammatory cytokines from the inflamed tissue, which stimulates liver to synthesize a number of acute phase proteins, including the prototypical acute phase reactant, CRP. There is a need for studies involving a single biomarker of detection as well as for identification of the extent of involvement to decide on effective management of patient. Hence we have focused on the study of variations in serum high sensitive C reactive protein (hs-CRP) concentration and its correlation with the extent of lesion involvement in MI. Some clinical studies have shown circulating levels of hs-CRP correlating with total infarct size in acute MI, post MI complications and with prognosis[3]. Thus hs-CRP is beginning to emerge as a marker of underlying coronary inflammation indicating an extent of myocardial necrosis. The present study is an observational and prospective estimation of hsCRP level to determine the association between hsCRP and ACS and its significance in the prognosis.

2. Material and Methods

Study design: The present study was conducted selecting fifty patients in age group ranging between 30 to 80 years with a male to female ratio of 4:1 with acute coronary syndromes [ST Elevation Acute myocardial Infarction (STEMI) or Unstable angina (UA) or Non ST Elevation Myocardial Infarction (NSTEMI)] who were admitted in Intensive Cardiac Care Unit of King George Hospital, Visakhapatnam, Andhra Pradesh, India from December 2012 to September 2014. Written consent was taken from each patient or closest relative.

Inclusion Criteria: Patients admitted to ICCU of King George Hospital with the diagnosis of STEMI , UA or NSTEMI. Diagnosis of Acute coronary syndrome was made based on history, physical examination and electrocardiogram.

Exclusion Criteria: (i). All cases of stable angina (ii) Presence of infectious diseases (iii) Patients with neoplastic diseases, (iv).Recent major trauma (v).Recent major surgery. (vi) Patients on immunosuppressive drugs (vii).Osteoarthritis, Rheumatoid arthritis, Psoriatic arthritis, gout (viii) Immunological disorders. (ix) .Patients on Statins, Fibrates, niacin and Aspirin.(x) Patients on oestrogen or progesterone pills.Detailed history, clinical examination and laboratory tests were the tools used to exclude these conditions.

Study patients underwent the following Investigations: Hb%, TC, DC, ESR, RBS, RFT,ECG,2D ECHO,CK-MB, Tropnin T, Fasting Lipid Profile & hsCRP levels measured within 6 hours of admission.

The present study was focussed on hsCRP levels and an association was studied with the extent of involvement and with post MI complications

Laboratory method of measuring hs C-reactive protein:: hs-CRP was measured on TURBILYTE-CRP using turbidimetric immunoassay for the determination of C-reactive protein in serum of the patient and is based on the principle of agglutination reaction. The test sample was mixed with TURBILYTE-CRP latex reagent and allowed to react. Presence of CRP in the test specimen results in the formation of an insoluble complex producing a turbidity, which is measured by spectrophotometer at 546 nm wavelength. The increase in turbidity corresponds to the concentration of CRP in the test specimen[4]. hs-CRP levels were measured on the day of admission within 6 hours. The hs-CRP detection limit of this test is 1 mg/L. Therefore, values of <1mg/L were taken as Low or no risk, 1-3mg/L as average risk, >3 mg/L as High risk as per AHA/CDC risk assessment guidelines[5]

All patients were followed up for 30 days and observed for the development of complications.

STATISTICAL ANALYSIS:

Statistical analysis was performed using Chi-square test. Results were considered significant if $P < 0.05$.

3. Results

After analysing the data out of fifty patients in age group ranging between 30 to 80 years with a mean age of 58.21 years where the highest incidence seen between 41 and 50 years with male to female ratio of 4:1 with acute coronary syndromes. Chest pain was the most common symptom accounting for 43(86%) patients, followed by sweating in 34(68%), Breathlessness in 18(36%), Vomiting in 12(24%) and Giddiness in 4 (8%) patients. In this study the most common risk factor was Smoking, accounting for 35 (70%) patients followed by Diabetes (32%) and Dyslipidaemias (50%). It is noted that out of 40 male patients who suffered acute coronary syndromes, 35 (87.5%) were smokers.

Out of 50 patients with acute coronary syndromes, 34 patients (68%) had STEMI and 16 patients had UA/NSTEMI, out of which 8 (16%) had UA and 8 (16%) had NSTEMI. Out of 34 patients who had STEMI, 15(44%) had Extensive anterior wall involvement (most common type) followed by Antero septal 10(29.4%), Inferior wall 7(20.5%) and Anterolateral walls 2(5.88%) in descending order of frequency.

In our hospital, pharmacological reperfusion performed to eligible patients was Streptokinase 1.5 million units infusion , Out of 34 patients with STEMI. Only 21 patients were eligible for Streptokinase therapy. Chest pain of more than 12 hrs duration and established Q waves (9 patients) was the most common cause to withhold thrombolysis followed by Hypotension (4 patients). LVF was the most common complication seen in 15(30%) patients, followed by Cardiogenic shock 6(12%),

AV block 6(12%), and 2(4%) had LBBB. 5(10%) patients had VT/ VF and died. Thus 34 (68%) patients suffered from complications whereas 16 (32%) patients did not have any complications.

Distribution of Post MI Complications with hs CRP levels among various types of Acute Coronary Syndromes : Of the 50 patients 15 had AWMI, out of which 13 had hs-CRP>3mg/L and met with complications ,Other complications in descending order of frequency.(Ref table 1)

TABLE 1: DISTRIBUTION OF POST MI COMPLICATIONS WITH hs-CRP LEVELS AMONG VARIOUS TYPES OF ACS

DIAGNOSIS	No of Cases	Post MI Complications	
		hs CRP <3 mg/L	hs CRP >3 mg/L
AWMI	15	0	13
IWMI	7	2	5
ASMI	10	1	6
ALMI	2	0	1
UA/NSTEMI	16	1	5
Total	50	4	30

Post MI Complications in relation to hs-CRP Levels: 15 patients had Left ventricular failure, out of which 13 had hs-CRP levels >3mg/L and 2 had hs-CRP levels <3mg/L (Ref table 2)

TABLE 2: POST MI COMPLICATIONS IN RELATION TO hs CRP LEVELS

Post MI Complications	Quartiles of hs-CRP (mg %)			Total
	<1	1-3	> 3	
Left ventricular failure	0	2	13	15
Cardiogenic shock	0	1	5	6
AV Block	0	1	5	6
LBBB	0	0	2	2
VT/VF & DEATH	0	0	5	5

Association between hs-CRP Level and Post MI Complications:

Out of 34 patients with complications, only 4 showed hsCRP levels <3mg/l and 30 showed hs CRP levels>3mg/L. And out of 16 without complications, 12 showed hsCRP levels<3mg/L and only 4 showed hsCRP levels>3mg/L.Chi Square value test value was 30.09 . At one degree of freedom, P value is statistically very significant ($p<0.01$). This indicates patients with hs-CRP levels, measured within 6hrs of admission are at high risk range according to AHA/CDC risk assessment guidelines and are prone to develop complications.

Other Investigations:

Raised blood glucose (RBG) RBG levels were found elevated in 16(32%) patients who were known diabetes mellitus patients. Diabetes mellitus is one of the risk factor for IHD and is considered as IHD equivalent. **Troponin T** was positive in 42 patients, out of which 34 patients had raised hs-CRP and 30 patients met with complications. **CK MB** was raised in 36 patients, out of that 34 patients had raised hs-CRP and 30 met with complications.

Discussion

Chest pain is the most common presenting symptom in 86% of cases. This is similar to PS Singh et al[6] showing the commonest presenting symptom as chest pain (90%), followed by sweating (75%) and breathlessness (60%). It is also comparable to Huggins et al[9] study.

Smoking is the most common risk factor, found in 35 (70%) patients, in contrast to other studies, Mohmoud Suleiman et al[8] study where smoking was observed in 40% of patients.

In Salim Yusuf et al[10] study, 65.19% of patients were smokers , In PS Singh et al[6] study, smoking was major risk factor (65%). In Foussas et al[7] study, smoking was observed in 57% of patients.

Abnormal lipid profile was seen in the Present study showing 25 (50%) patients with lipid abnormalities., this correlates with other studies .In Foussas et al[7] study, 64.6% of patients had lipid abnormalities. And in Mohmoud Suleiman et al[8] study, 41% of patients had dyslipidemias.

Diabetes Mellitus: In the present study 16 (32%) patients had diabetes as the risk factor, this correlates with other studies. In Foussas et al[7] study, diabetes mellitus was seen in 31% of patients and in Mohmoud Suleiman et al[8] study, diabetes was present in 30% of patients. In PS Singh et al[6] study, Diabetes was seen in 32%.

Hypertension: in the present study 7 (14%) patients had hypertension , this differs from many other studies like Foussas et al[7] study (51%) and Mohmoud Suleiman et al[8] study (53%) and PS Singh et al[6] study (33%). which correlates with Salim Yusuf et al[10] study, (19.3%)

Type of ACS: Out of 50 ACS patients in the present study, 34 (68%) had STEMI, 8 (16%) had UA and 8 (16%) had NSTEMI. This correlates with Schaan et al19 study where 71% patients had STEMI ,12% had NSTEMI and 17% with unstable angina. It differs from Magdalena Krintus et al11 study where out of 220 patients with ACS, 96(43.6%) had UA, 57(25.9%) with NSTEMI and 67(30.4%), had STEMI. Present study also differs with Sheikh et al21 study, where out of 963 patients, 187 are controls and Out of 776 patients with ACS, 232 had UA ie.,29.8%, 258 had STEMI ie.,33.2% and 286 had NSTEMI ie.,36.8%., Almost similar number of patients had STEMI in Mohmoud Suleiman et al 8 study.

Reperfusion Therapy in the present study only 14 (41%) patients with STEMI underwent reperfusion therapy in the form of pharmacological thrombolysis with streptokinase , It is comparable to 32% of patients thrombolysed in Mohmoud Suleiman et al[8] study.

Serum hs-CRP in the present study was estimated on the day of admission within 6 hours. This correlates with most studies (refer table 4).

As per the risk Categorisation of patients based on hs-CRP levels according to CDC/AHA Guidelines 2003 we considered values of < 1mg/L as normal concentration of CRP and low risk, values between 1-3mg/L were taken as average risk, values of > 3mg/L were taken as high risk. This correlates with most studies,(Refer table 3)

TABLE 3: CATEGORISATION BASED ON hs-CRP LEVELS IN VARIOUS STUDIES

Studies	Low Risk	Average Risk	High Risk
Present Study	<1mg/L	1-3mg/L	>3mg/L
David et al	<1mg/L	1-3mg/L	>3mg/L
Buckley DI et al	<1mg/L	1-3mg/L	>3mg/L
Morrow et al	<1mg/L	1-3mg/L	>3mg/L

Relation of Raised hs-CRP levels with Post MI complications in various studies: In this study of 50 patients with ACS, 34 (68%) had raised hs-CRP levels (>3mg/L), of which 30 (60%) patients met with complications. This is in correlation with most recent studies. Refer table 4.

TABLE 4: RELATION OF hs-CRP LEVELS WITH POST MI COMPLICATIONS IN VARIOUS STUDIES

Studies	Results
Present Study	34 (68%) patients had raised hs-CRP levels (>3mg/L). And 30 (60%) patients who had hsCRP levels>3mg/L met with complications
Morrow et al [13]	Patients with serum CRP levels 1–3mg/L had a greater mortality risk in comparison with those with levels <1mg/L. The mortality risk for patients >3mg/L was even higher.
Schiele et al [14]	Subjects with level >22mg/L (4th quartile) had 4 times greater mortality risk within 30 days
Schaan et al [15]	Patients with CRP levels >3 mg/L showed an almost 5-fold increase in the risk of death compared to patients with lower levels, and a 7-fold increase in the risk of adverse events

Relation of hs-CRP Levels with the type of ACS in various studies:

In the present study, 25 (68%) out of 34 STEMI patients, 3 (36%) out of 8 NSTEMI patients, 2 (12%) out of 8 UA patients had hs-CRP levels (>3mg/L) in high risk range, indicating more number of STEMI patients had severe inflammation and other groups (UA/NSTEMI) had lesser inflammation.In Magdalena Krintus et al[11] study, the highest CRP levels were observed in NSTEMI and STEMI patients and were considerably higher than in UA patients. Syed shahid et al [12], compared hs-CRP levels in STEMI and NSTEMI patients, STEMI patients with significant higher peak hs-CRP levels compared to NSTEMI. These data suggest that inflammatory process plays an independent role in the pathogenesis of myocardial infarction.

In Brunetti ND et al [20] study, CRP concentrations showed a different release curve in patients with STEMI in comparison with patients with NSTEMI and with patients with UA. The increase in hs-CRP levels during STEMI seems to be linked to the extension of myocardial damage.

In Sheikh et al study [16]**,** hs-CRP was elevated (>3 mg/L) among 27.6% patients with unstable angina; 70.9% with STEMI; 77.9% patients with NSTEMI and 5.3% in the control group. Among cases with elevated CRP, 92.1% had a cardiac event compared to 34.3% among patients with CRP >3 mg/L ($P < 0.0001$). The mortality was significantly higher ($P < 0.0001$) in STEMI patients (8.9%) and NSTEMI (11.9%) as compared to unstable angina (2.1%).

Relationship of hs-CRP levels with Post MI complications in the present study showed 34 (68%) patients had raised levels of hs-CRP >3mg/L. Among these 34 patients, 30(60%) patients had met with complications and 4 patients did not have any complications. A raised hs-CRP level >3mg/L was shown to be significantly associated with serious post MI complications such as left ventricular failure (26%), cardiogenic shock (10%), AV block 6(10%) and LBBB 2(4%), Ventricular Tachycardia/Ventricular Fibrillation and death (10%). This is in comparison with O Keskins et al [17] reported that high hs-CRP, collected once at admission was an independent predictor of 30 day recurrent cardiac events such as re-infarction, post MI angina and cardiac death. In this study, re-infarction and post MI angina were not noted but LV failure (30%) and mortality (10%) were observed as check..Suleiman et al [8] reported that a high CRP level obtained within 12-24 hours of symptom onset, was an independent predictor of 30 day mortality and heart failure, but not associated significantly with the development of post infarction angina or recurrent myocardial infarction in patients with acute myocardial infarction. Same cardiovascular outcomes were observed in this study also.

Benjamin et al [18] study was to evaluate hs-CRP across the spectrum of acute coronary syndrome. Patients with highest quartile of hs-CRP were at increased risk of death at 30 days and also with the development of heart failure. They concluded that increased baseline concentrations of hs-CRP are strongly associated with mortality and heart failure across acute coronary syndrome spectrum. This study also showed increased cardiac complications like LV failure, cardiogenic shock and mortality in the immediate hospital course.

Foussas et al[7] studied 1,846 patients with acute coronary syndromes and showed that elevated plasma CRP levels confer a significantly increased risk of future fatal or non- fatal ischemic complications. Mohmoud Suleiman et al[8] concluded that, plasma hs-CRP levels obtained within 12-24 hours of symptom onset is an independent marker of 30 day mortality and the development of heart failure in patients with acute myocardial infarction. S

Bhagat et al[20] compared 44 unstable angina patients with 40 age and sex matched healthy controls. They concluded that, the plasma CRP is an independent predictor of adverse cardiac outcomes in severe unstable angina, in short term follow-up and hence is useful for risk stratification of these patients. Pietila K O[21] showed that, high serum hs-CRP concentrations in acute myocardial infarction patients treated with thrombolytic drugs predict increased mortality up to 6 months following the myocardial infarction.

Haruo Tomada et al[22] studied a total of 234 patients with acute myocardial infarction, and concluded that hs-CRP levels within 6 hours after the onset of symptoms reflect the vulnerability of culprit coronary lesions and predict adverse coronary events after primary PTCA/stenting. P Mishra et al [19] studied 50 cases of acute myocardial infarction and observed that serum hs-CRP concentration on admission is significant prognostic indicator of their in hospital stay. Schiele et al [18] studied 1500 cases with acute coronary syndrome and observed hs-CRP improves risk prediction in patients with acute coronary syndrome.

He LPTX et al [23] study showed higher early blood hs-CRP moderately increases long-term risk of recurrent cardiovascular events or death, and may be a valuable prognostic predictor in patients after ACS. Schaan B.D. et al [15] showed hs-CRP levels adequately predicted increased long-term risk in a population of patients initially evaluated at admission due to acute coronary syndrome. This association was observed independent of lipid levels, and thus may add information for risk stratification and planning of effective interventions in this group of patients. Kompoti M et al[24] study showed hs-CRP at admission was a stronger predictor of in-hospital death. Serum hs-CRP at admission is an independent predictor of mortality in hospitalized patients, particularly in the elderly.

Admission CRP higher than 120 mg/l was associated with increased probability of in-hospital death compared with lower levels. Similar to these studies, our study also revealed that increased levels of plasma hs-CRP in the study group were associated with more adverse events.

LIMITATIONS OF THIS STUDY: To assess the role of hs-C-Reactive protein as prognostic indicator of acute coronary syndrome requires further studies with large sample size. The prediction of recurrent myocardial infarction, as part of prognosis could not be done since it required a longer follow-up. Serial hs-CRP determination could be a better prognostic predictor than isolated sample of CRP estimation, which was not done in this study.

Conclusion

Plasma CRP levels on admission serves to identify high risk patients in the setting of acute coronary syndromes. Among patients presenting with acute coronary syndromes with elevated hs-CRP (>3mg/L) level is associated with significant post MI complications (60%) with significant statistical value ($p<0.01$). Our study has shown a strong correlation not only in the various levels of serum hsCRP and ACS, but has also shown an association between the concentration of the hsCRP and the extent of myocardial involvement and post MI complications. The observed strong association establishes the role of inflammatory markers in atherosclerosis and progress to acute myocardial infarction and post MI complications. Hence hsCRP being an acute phase protein, a strong inflammatory marker with a longer half-life can be considered as a robust biomarker of clinical significance. The fact that more number of STEMI patients having increased levels of

hs-CRP has increased incidence of adverse cardiac outcomes, when compared with UA/NSTEMI, suggest that hs-CRP levels may be related to the severity of inflammatory processes associated with multiple plaque rupture or infarct expansion in the spectrum of acute coronary syndrome. Raised hs-CRP levels are independent markers of adverse outcomes. Hence hs-CRP levels obtained at admission in acute coronary syndromes can be used as a marker for identification of patients who are likely to develop significant complications in the immediate in-hospital course and to predict the prognosis.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

The authors thank faculty and residents of Department of Cardiology and General Medicine, Andhra Medical College and King George hospital, Visakhapatnam, India for their cooperation help for conducting this study.

References

1. Fuster V, Badimon L, Badimon J, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:242-50.
2. Ross R. Atherosclerosis- an inflammatory disease. N Engl J Med 1999;340:115-26.
3. Pietila¨ K, Harmoinen A, Hermens WT, Simoons ML, van de Werf F, Verstraete M. Serum C-reactive protein and infarct size in myocardial infarct patients with a closed versus an open infarct-related coronary artery after thrombolytic therapy. Eur Heart J. 1993;14:915
4. Bertran N[1], Camps J, Fernández-Ballart J, Murphy MM,et al. Evaluation of a high-sensitivity turbidimetric immunoassay for serum C-reactive protein: application to the study of longitudinal changes throughout normal pregnancy. Clin Chem Lab Med. 2005;43(3):308-313
5. Pearson TA, et al AHA/CDC Panel: Recommendations for Use of hs-CRP in Clinical Practice, Circulation. 2003; 107:499-511.
6. PS Singh, G.Singh,SK Singh et al., "Clinical profile and Risk factors in Acute Coronary Syndrome" Journal, Indian Academy of Clinical Medicine 2013; Vol.14 No.2:130-2
7. Foussas SG, Zairis MN, Lyras AG, Patsourakos NG, Tsirimpis VG, Katsaros K et al, Early prognostic usefulness of C reactive protein added to thrombolysis in myocardial infarction risk score in acute coronary syndromes, Am. J. Car, Aug 2005; 96; p 533-537.
8. Suleiman M, Aronson D, Reisner SA, Kapeliovich MR, Markiewicz W, Levy Y et al, Admission C reactive protein levels and 30-day mortality in patients with acute myocardial infarction. Am Jr of Med; Dec 2003, 115; 9 p 695-701
9. Huggins GS, O' Gara PT, Clinical presentation and diagnostic evaluation of atherosclerosis and coronary artery disease, Philadelphia, Lippincott-Raven, 1996.
10. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al, Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study), Am Heart J, June 1963, 65; p 749-757

11. Magdalena Krintus, Marek Kozinski, Anna Stefanska, et al., "Value of C-Reactive Protein as a Risk Factor for Acute Coronary Syndrome: A Comparison with Apolipoprotein Concentrations and Lipid Profile," Mediators of Inflammation, vol. 2012, Article ID 419804, 10 pages, 2012. doi:10.1155/2012/419804
12. Syed Shahid Habib, Mohammad Ibrahim Kurdi, Zohair Al Aseri, Mohammad Owais Suriya, CRP Levels are Higher in Patients with ST Elevation Than Non-ST Elevation Acute Coronary Syndrome Manuscript received April 18, 2009; revised manuscript received November 07,2009.
13. D. A. Morrow, J. A. de Lemos, M. S. Sabatine et al., "Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial," *Circulation*, vol. 114, no. 4, pp. 281–288, 2006
14. F. Schiele, N. Meneveau, M. F. Seronde et al., "C-reactive protein improves risk prediction in patients with acute coronary syndromes," *European Heart Journal 2010*, vol. 31, no. 3, pp. 290–29 .
15. SCHAAN, B.D. et al. C-reactive protein in acute coronary syndrome: association with 3-year outcomes. *Braz J Med Biol Res* [online]. 2009, vol.42, n.12 [cited 2014-10-20], pp. 1236-1241 .
16. Sheikh AS, Yahya S, Sheikh NS, Sheikh AA. C-reactive protein as a predictor of adverse outcome in patients with acute coronary syndrome. Heart Views 2012;13:7-12. © *Gulf Heart Association 201*
17. Keskin, R Eusoy, Kalemogulu, Yildirim "White blood cell count and c reactive protein predict short term prognosis in acute myocardialinfarction J Int Med Res 2004; 32(6):646-654.
18. Benjamin M.Scirica, David A. Morrow, Christopher P. Cannon, James A. de Lemos, Sabina Murphy, Marc S. Sabatine, Stephen D. Wiviott, Nader Rifai, Carolyn H. McCabe "Clinical Application of C-Reactive Protein across the spectrum of Acute Coronary Syndromes" Clinical Chemistry 53:10 1800-1807 (2007).
19. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-Reactive Proteinas a Risk Factor for Coronary Heart Disease: Ann Intern Med. 2009;151:483-495.
20. Bhagat S, Gaiha M, Sharma VK, Anuradha S, A comparative evaluation of C- reactve protein as a short term prognostic marker in sever unstable angina- A preliminary study, JAPI, April 2003; 51, p 349
21. Pietila KO, Harmonen AP, Jokinitty J, Pasternack AI, Serum C reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment, Eur Heart J, 1996;17;p 1345-1349.
22. Tomada H, Aoki N, Prognostic value of C reactive protein levels within six hours after the onset of acute myocardial infarction, Am Heart J, Aug 2000; 140; p 324-
23. He LPTX, Ling WH, Chen WQ, et al. Early C-reactive protein in the prediction of long-term outcomes after acute coronary syndromes: a meta-analysis of longitudinal studies. Heart 2010; 96:339e
24. Kompoti M, Drimis S, Papadaki A, Kotsomytis K, Poulopoulou C, Gianneli D, et al. Serum C-reactive protein at admission predicts in-hospital mortality in medical patients. *Eur J Intern Med* 2008; 19: 261-265.