Original Article

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Association of High Sensitivity C-Reactive Protein with In-Hospital Mortality in Patients with Acute ST-Segment Elevation Myocardial Infarction.

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Abstract

Background and Aims: Among the various biomarkers, high sensitivity C-Reactive Protein (hs-CRP) has been widely studied and is easy to use in the prognostication of patients with acute ST elevation myocardial infarction (STEMI). This study aimed to associate serum level of hs-CRP with in-hospital mortality in patients presented with acute STEMI.

Methods: This was a hospital-based prospective observational study conducted in Shahid Gangalal National Heart Centre among patients presented to the emergency department with chest pain of less than 24 hours duration, who were diagnosed subsequently to have STEMI. Patients who had known chronic inflammatory diseases, septic foci and chest pain of over 24 hours were excluded from the study. Blood sample for Hs-CRP was sent from the emergency department and was measured with Finecare ™ FIA system; Model number: FS-112. The study was conducted from April 2019 to March 2020. Patient outcomes were stratified as per the four groups of serum level of hs-CRP and among them the relationship between mortality and hs-CRP level was tested with chi-square test. The p-value across the groups was again tested for inter-group significance using the Bonferroni adjusted significance level.

Results: 140 patients (112 males and 28 females) with mean age of 58.1±14.86 years were enrolled in the study. There was no increased in-hospital mortality in acute STEMI patients who had serum level of hs-CRP below 3 mg/l. In-hospital mortality showed an increasing trend above this level but it reached statistical significance beyond 10 mg/l only. Thirty five percent of our patients of acute STEMI were found to have serum level of hs-CRP above this threshold. The total in-hospital mortality was 13 (9.28%).

Conclusion: The increased serum level of hs-CRP was associated with increased in-hospital mortality in patients with acute STEMI.

Keywords: Acute ST elevation myocardial infarction; in-hospital mortality; serum level of hs-CRP.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide accounting for more than 17.6 million deaths per year in 2016, which is expected to grow to more than 23.6 million by 2030.[1] The prevalence of CVD is also increasing in Nepal. A hospital-based prevalence study of non-communicable diseases (NCD) in 28 hospitals across the country found that 31% of the admissions were for NCDs, 40% of which was CVD and ischemic heart disease (IHD) accounted for 7%.[2] Myocardial infarction is associated with

an inflammatory reaction, which is a prerequisite for healing and scar formation.[3] Therefore, inflammatory biomarkers increase once the infarction process sets in. More the area of infarction involved, higher will be the level of biomarkers.

The inflammatory biomarkers have been found to be increased in acute coronary syndrome (ACS).[4] As of today, hs-CRP has been the most studied systemic marker of inflammation as a risk predictor in ACS.[5,6] The mean levels are progressively higher in patients with unstable angina, non-ST elevation myocardial infarction (NSTEMI) and STEMI.[7,8] In STEMI, serum level of hs-CRP is proportionately more with the area of infarction; therefore, hs-CRP level in the early phase, may be a potential prognostic factor regarding the risk of death.[9-11] hs-CRP evaluation may provide a simple and inexpensive method to improve global risk prediction.[12] A scientific statement issued jointly by Centre for Disease Control (CDC) and American Heart Association (AHA) about hs-CRP has mentioned it as the only inflammatory marker that can be used for risk prediction both for primary and secondary prevention of cardiovascular events.[13]

A study done by Sheikh AS et al. showed elevated CRP a predictor of adverse outcome in patients with acute coronary syndromes that could be useful in identifying patients at risk of cardiovascular complications.[14] Another study done by Milano et al showed a strong association between hs-CRP obtained on admission and in-hospital mortality after STEMI.[15] Such study has not been undertaken in tertiary care hospitals in Nepal. So, this study was done to risk-stratify acute STEMI patients presented to emergency department in a tertiary care cardiac centre in Nepal.

Methods

This study was a hospital based, prospective, observational study. It was conducted in Shahid Gangalal National Heart Center, Bansbari, Kathmandu through April 2019 to March 2020 for a period of 1 year. Ethical clearance was formally taken from Institute Review Board, National Academy of Medical Sciences, Mahabouddha, Kathmandu. The study included patients with acute ST Elevation myocardial infarction (STEMI) presented within 24 hours of symptoms onset. ST Elevation Myocardial Infarction was defined according to the European Society of cardiology/ACCF/AHA/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction.[16] Patients with chronic inflammatory and debilitating diseases, acute infection, HIV infection and those taking immunomodulators, were excluded from the study. The patients who presented after 24 hours of symptom onset were not enrolled in the study; the time frame was selected as per the positive correlation between hs-CRP and mortality up to the first 24 hours in a study done by Alferi Al Aseri et al.[17]

Written informed consent was taken from the patient or relative. Plan and purpose of the study was clearly explained. Confidentiality of all the collected information was maintained throughout the study.

Blood sample was taken in the Emergency department and it was sent to the laboratory for hs-CRP measurement. The test was done with Finecare™ FIA system; Model number: FS-112. The test report was collected.

American Heart Association and U.S. Centers for Disease Control and Prevention have defined the risk groups for hs-CRP level as low risk (less than 1.0 mg/L), moderate risk (1.0 to 3.0 mg/L) and high risk (above 3.0 mg/L).[13,18] The serum level of hs-CRP has been found to vary with ethnicity, and a study done in overtly healthy Asian Indians has shown higher hs-CRP levels than in Caucasians.[19] As we have many similarities with Indians in regard to genetic make-up, food habits, living standards and culture, the risk group for hs-CRP level was re-classified into four groups: Minimal risk (hs-CRP<1.0 mg/L), Low risk (hs-CRP: 1.0-3.0 mg/L), Moderate risk (hs-CRP: 3.1-10 mg/l), and High risk (hs-CRP>10mg/l). This was similar to the grouping done by Carrero JJ et al who used logistic regression analysis to identify clinical predictors of hs-CRP threshold and categorized patients into four groups in his study of hs-CRP and cardiovascular events in patients with myocardial infarction.[20]

Each patient was followed during the hospital stay. The outcomes of the treatment were recorded as discharge, in-hospital mortality and referral. In-hospital mortality was defined as the mortality of the patient during the index hospitalization.

Statistical Analysis

Data analysis was performed using Statistical Package for Social Sciences SPSS (IBM SPSS Statistics, version 23) for Mac-OS. Continuous variables were expressed as mean±SD whereas categorical data were expressed in frequency and percentages. Patient outcomes were stratified as per the four groups of serum level of hs-CRP and the relationship between mortality and hs-CRP level was tested with chi-square test. A value of $P<0.05$ was taken as statistically significant. The p-value across the four groups was again tested for inter-group significance using the Bonferroni adjusted significance level.

Results

Table 1: Baseline Characteristics of Patients

Variables		Number (%)/ Mean+SD
Age		58.1±14.86 years
Sex	Male	112 (80%)
	Female	28 (20%)
Hs-CRP		9.342±10.84 mg/l
Diabetes		21 (15%)
Smoking		63 (45%)
Hypertension		56 (40%)
Alcohol Use		37 (26.4%)
Clinical Heart Failure		10 (7.1%)
Intervention	Primary PCI	95 (67.9%)
	Thrombolysis	12 (8.6%)
	Medical Management	33 (23.6%)
In-Hospital Events	Ventricular Tachycardia	9 (6.4%)
	Ventricular Fibrillation	9 (6.4%)
	Complete heart block	2 (1.4%)
Duration of Hospital Stay		4.75±2.25 days
Outcome	Discharged	125 (89.3%)
	Mortality	13 (9.3%)
	Referred	2 (1.4%)

Baseline Characteristics of Study Population

A total of 140 patients presented with acute STEMI within 24 hours of symptom onset, who fulfilled the inclusion criteria, were included in the study. The study group comprised of 112 males (80%) and 28 females (20%). The mean age of study group was (58.1±14.86) years, the range being 30-97 years. The demographic and clinical characteristics of the study population are summarized in Table 1.

Most of the patients had anterior wall MI (21.43%) followed by extensive anterior wall MI (19.29%) [Figure: 1].

Patient outcomes were stratified as per the four groups of serum level of hs-CRP and among them the relationship between mortality and hs-CRP level was tested with chi-square test. The p-value across the groups was significant (p=0.007), which was again tested for inter-group significance using the Bonferroni adjusted significance level. The Bonferroni corrected p-value was calculated at 0.00417. The association between mortality and serum hs-CRP was statistically significant only above the level of 10mg/l (p=0.00010) [Table: 2].

Figure 1: Types of Myocardial Infarction in Study Sample

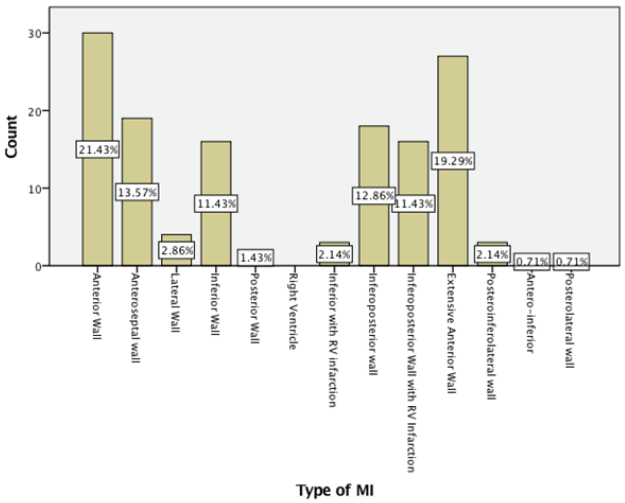


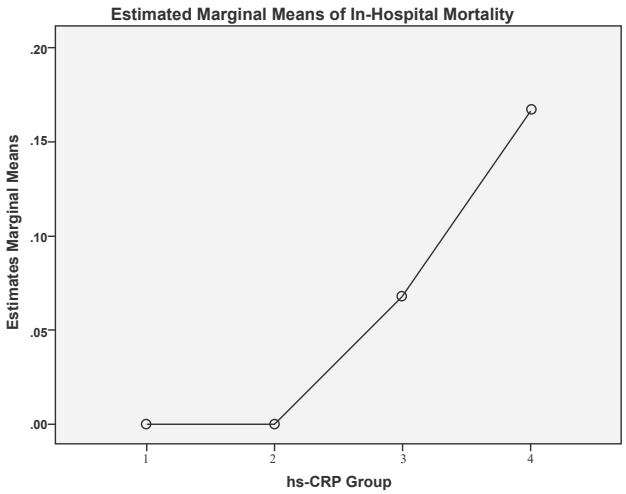
Table 2: Outcomes in Patients as per hs-CRP level

			Outcome			
			Discharged	**Mortality**	**Referred**	**Total**
hs-CRP Level (mg/l)	<1.00	Count	17	0	0	17
		% within hs-CRP Group	100.0%	0.0%	0.0%	100.0%
		Adjusted Residual	1.5	-1.4	-.5	
		P-Value	0.13361	0.16151	0.61708	
	1 to 3	Count	29	0	1	30
		% within hs-CRP Group	96.7%	0.0%	3.3%	100.0%
		Adjusted Residual	1.5	-2.0	1.0	
		P-Value	0.13361	0.04550	0.31731	
	3.1 to 10	Count	41	2	1	44
		Group % within hs-CRP	93.2%	4.5%	2.3%	100.0%
		Adjusted Residual	1.0	-1.3	.6	
		P-Value	0.31731	0.19360	0.54851	
	>10	Count	38	11	0	49
		% within hs-CRP Group	77.6%	22.4%	0.0%	100.0%
		Adjusted Residual	-3.3	3.9	-1.0	
		P-Value	0.00097	0.00010	0.31731	
Total	Count	125	13	2	140	
	% within hs-CRP Group	89.3%	9.3%	1.4%	100.0%	

Bonferroni corrected P-value = 0.00417.

The profile plot showing the relation between estimated marginal means of in-hospital mortality and hs-CRP level revealed the fact that there is no increased risk of mortality after acute STEMI at a serum level of hs-CRP<3mg/l; the risk increases beyond this level. However, it reaches statistical significance only above the serum level of 10mg/l [Figure: 2]. This means the in-hospital mortality in patients with acute STEMI is significantly associated with hs-CRP level above 10mg/L.

Figure 2: The Profile Plot Between Estimated Marginal Means of hs-CRP and In-Hospital mortality



Discussion

In our study, it was found that in-hospital mortality in acute STEMI patients was not increased below the serum level of 3mg/l of hs-CRP; mortality increased progressively beyond this level but it reached statistical significance above 10mg/l of hs-CRP. This finding corroborates with the finding in the study by Fonseca FA.[21] In another study it was found that higher the serum hs-CRP levels at the time of admission in patients with Acute Myocardial Infarction (AMI) greater the patients prone to develop a complication during their hospital stay.[22] Another study has shown association of serum hs-CRP level and mortality and heart failure beyond hospital stay as well. Also high hs-CRP level measured at first AMI would predict myocardial dysfunction and heart failure in follow up visits. The study highlighted the fact that measurement of hsCRP levels in patients earlier in AMI could help clinicians to discriminate those patients who are at increased risk of heart failure in the future. In clinical practice, different Risk Scoring Systems have been validated to predict the mortality after acute STEMI. Some of them are very cumbersome and need multiple factors for calculation. Serum hs-CRP could be an easy to use parameter to predict the future risk in patients presented to emergency department with acute STEMI. Moreover, it can add to the predictive value of conventional risk scoring systems. Most of the researches on hs-CRP and cardiovascular risks have been done on Caucasians, who have relatively lower baseline values; the risk categories being: Low risk (hs-CRP<1mg/l), Moderate risk (hs-CRP: 1-3mg/l) and high risk (hs-CRP>3mg/l).[23] In our study, we classified patients into four groups: Minimal risk (hs-CRP<1.0 mg/L), Low risk (hs-CRP: 1.0 - 3.0 mg/L), Moderate risk (hs-CRP: 3.0 - 10 mg/l), and High risk (hs-CRP>10mg/l). It was because of the higher baseline level of hs-CRP in south east Asians as suggested in the study by Carrero JJ et al.[20] This study may prove as a milestone for prognostication of mortality in acute STEMI patients in resource-limited countries like ours.

Limitations

- This study enrolled a relatively small sample size from a single center that may not be representative of the general population.
- This study was based exclusively on the accuracy of the lab test of hs-CRP from a single supplier, the reliability of the test could not be ascertained by cross-checking with other laboratory results because of logistic problems.
- As various inflammatory diseases that are usually present in older population at risk for STEMI confound the serum level of hs-CRP, it may overestimate the risk.
- Baseline level of hs-CRP should be established in our population prior to using it as a risk predictor. The level may vary with ethnicity and geographical region.

Conclusion

Besides identifying patients at high inflammatory risk, hs-CRP has a prognostic indication as well. The risk of mortality increases with higher level of this biomarker. Its level in isolation or in combination with the conventional risk scoring systems may add to the value of prognostication in patients with acute STEMI. In our study, the threshold for risk prediction was 10mg/l.

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Conflict of Interest: None declared

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